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CYTOKINE PROFILE IN BLOOD SERUM OF INFERTILE MEN WITH CONCOMITANT PATHOLOGIES

O.V. Melnyk[1], M.Z. Vorobets[2], A.S. Besedina[3], P.B. Pokotylo[3], R.V. Fafula[4], D.Z. Vorobets[2]

Danylo Halytsky Lviv National Medical University, Lviv, Ukraine:
[1]Microbiology Department, ORCID ID: 0000-0002-2097-596X, e-mail: viruszet8@gmail.com;
[2]Urology Department,
ORCID ID: 0000-0002-6104-5769,e-mail: vorobetsz@ukr.net;
ORCID ID: 0000-0002-8431-5151, e-mail: dv@ukr.net;
[3]Normal Anatomy Department,
ORCID ID: 0000-0001-5152-219X, e-mail: annabes@ukr.net;
ORCID ID: 0000-0003-2104-0100, e-mail: anatomp1@ukr.net;
[4]Biophysics Department, ORCID ID: 0000-0002-0121-9093, e-mail: roman_fafula@ukr.net

Abstract. The mechanisms of formation of male infertility are increasingly becoming immune-dependent. Immunological isolation of the testes is provided by the anatomical blood-testis barrier and the special tolerance of the immune system to antigens expressed on male gametes. For a better understanding of the immunopathogenetic mechanisms of infertility, a study of the role of various immune factors is required.

The aim: to study the role of pro-inflammatory and anti-inflammatory cytokines in blood serum to clarify their role in spermatogenesis.

Materials and Methods: 45 infertile men aged 22-48 were examined. They were divided into 2 groups: first group – 22 men with a systemic autoimmune disease - rheumatoid arthritis; second group – 23 somatically healthy patients with idiopathic infertility. The control group included 27 fertile healthy men aged 22-48 years. Determination of the cytokines concentration in blood serum was carried out by the immunoenzymatic method. Student's t-test was used to compare the significant difference in mean values between groups. $P < 0.05$ was considered significant.

Results. Patients with autoimmune diseases (rheumatoid arthritis) had the highest rate of leukocytospermia, indicating a possible long-term inflammatory process. In patients with idiopathic infertility, oligozoospermia was diagnosed in 3 patients (13.04%), oligoasthenozoospermia in 7 patients (30.36%), asthenozoospermia in 8 patients (34.78%) and leucocytospermia in 5 patients (21.82%). In patients with rheumatoid arthritis, the concentration of IL-18 (cytokine of the IL-1 family) in the blood serum of infertile men was 1.36 times higher than that of fertile men. The level of IL-6 was 6 times higher, and the concentration of IFN-γ exceeded the norm by more than three times. The level of IL-10 was 9,4 times higher than in control group. Significant changes in the serum cytokine profile were recorded in men with idiopathic infertility. The level of pro-inflammatory cytokines increased statistically significantly: IL-18 – 1.45 times, IL-6 – 2.85 times, IFN-γ – 2.65 times. Simultaneously, the level of anti-inflammatory cytokines increased: IL-10 – 3.0 times.

We also analyzed the ratio of serum levels of pro- and anti-inflammatory cytokines. Significant increase in IL-10/TNF-α ratio was recorded in men with idiopathic infertility and infertile men with rheumatoid arthritis. Specifically, in men with idiopathic infertility the IL-10/TNF-α ratio was 3.3 times higher and in patients with rheumatoid arthritis the IL-10/TNF-α ratio was 4.1 times higher than in control group. In patients with rheumatoid arthritis the IL-10/IFN-γ ratio was in 3 times higher than in control group. Significant positive correlations were found in healthy fertile men: TGF-β1 – IFN-γ, IL-10 – IL-18 and IL-10 – TNF-α. In men of the control group, the synthesis of IL-18 and TNF-α was balanced by the production of IL-10. The synthesis of IFN-γ was by balanced by the production of TGF-β1.

Conclusions. The development of infertility associated with various accompanying pathologies is related with by changes in both systemic and local immune reactivity. The pro-inflammatory cytokine profile of blood serum and a decrease in the concentration of IL-1β are observed in patients with idiopathic infertility. The largest number of deviations of immune reactivity was found in infertile men with concomitant autoimmune diseases.

Keywords: cytokines, male infertility, idiopathic infertility, rheumatoid arthritis.

Introduction. The regulation of male reproductive function is realized through different levels, involving both the endocrine and immune systems. The mechanisms of formation of male infertility are increasingly becoming immune-dependent. Immunological isolation of the testes is provided by the anatomical blood-testis barrier and the special tolerance of the immune system to antigens expressed on male gametes. The seminal fluid ensures the microenvironment for differentiated gametes. It is a multicomponent solution and contains a range of active biological substances with immunomodulatory properties [7, 9].

Background of the research. In addition to hormones, cytokines TNF-α, IFN-γ, TGF-β2/β3 та IL-1α/1β та IL-12 play an important role in the regulation of spermatogenesis. They regulate the penetrability of the barrier in normal physiological state and pathological conditions [5, 8]. The cytokines TGF-β2 / β3, TNF-α and IL-1α perform a leading role in the regulation of the blood-testis barrier. These cytokines in the germinal epithelium are synthesized by Sertoli cells and germ cells (specifically spermatocytes and early spermatids, since elongated spermatids produce exclusively TNF-α, receptors to which are

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located mostly on Sertoli cells). The interaction between polar proteins is regulated by cytokines. This is important both for the regulation of endocytic processes of protein transport and for the synergization of actin- and steroid-mediated effects on the blood-testis barrier [2].

The effect of cytokines on sperm in the seminal fluid is a physiological phenomenon. IL-6, IL-10 levels and TNF-α level are positively correlated with sperm concentration, motility and normal morphology [12], and IL-6 level positively correlated with the ability of sperm to penetrate egg [13]. In the seminal fluid of a healthy man, in addition to a small number of leukocytes (about 1 million/ml), cytokines TGF-α/β and IL-1β and IL-6,8 and a soluble receptor for IL-2 were detected. Some of these molecules (IL-1 and TGF-β) are synthesized in the testes, others, probably, in the appendages or other male gonads. In the seminal fluid of healthy men except a small number of leukocytes (about 1 million/ml), cytokines TGF-α/β, IL-1β and IL-6,8 and a soluble IL-2 receptor were detected. Some of these molecules (IL-1 and TGF-β) are synthesized in the testes, others, probably, in the other male gonads [4]. For a better understanding of the immunopathogenetic mechanisms of infertility, a study of the role of various immune factors is required.The aim of the research: to study the role of pro-inflammatory and anti-inflammatory cytokines in blood serum to clarify their role in spermatogenesis.

Materials and Methods. Study population and semen collection. This research is carried out at department of medical biology of Danylo Halytsky Lviv National Medical University (Ukraine). Men underwent a thorough genitourinary examination to establish exclusion criteria. Individuals with normally developed urogenital organs were included in the study. The study included individuals with a diagnosis of rheumatoid arthritis without concomitant inflammatory diseases of the connective tissue, other inflammatory diseases and oncological pathology at the time of the study. The duration of the disease was from 6 to 360 months. All patients with rheumatoid arthritis were diagnosed with asthenozoospermia or leukocytospermia. The idiopathic form of infertility, characterized by an unstudied etiopathogenesis, was diagnosed by the lack of fertilization during the year of the couple's mortal life and the impossibility of finding out the cause of the disease. This form of infertility included men with oligozoospermia, oligoasthenozoospermia, asthenozoospermia, and leucospermia.

45 infertile men aged 22-48 were examined. They were divided into 2 groups: first group – 22 men with a systemic autoimmune disease - rheumatoid arthritis; second group – 23 somatically healthy patients with idiopathic infertility. The control group included 27 fertile healthy men aged 22-48 years.

Ethical approval was obtained from the Ethics Committee of Danylo Halytsky Lviv National Medical University and informed consent was obtained from all eligible, consenting participants.

Blood processing. Semen was collected, analyzed and classified according to the criteria of the WHO (2009) [3]. Semen was obtained by masturbation into sterile plastic containers following 3–5 days of abstinence. Semen analysis was performed within 30 min. of sample arrival in the laboratory.

Blood was collected by venipuncture (20 ml) from the elbow vein in the morning, under conditions of physiological rest, on an empty stomach, in test tubes stabilized with heparin (final dilution 1:100). Seminal fluid and blood serum were stored at -20°C until the beginning of the studies, mostly for two weeks.

Determination of the cytokines concentration in blood serum was carried out by the immunoenzymatic method. To determine the cytokines IL-1β, IL-6, IL-10, IL-18, IFN-γ, TNF-α in blood serum and seminal fluid, kits from DIACLONE (France) were used, TGF-β1 - kit from DRG Diagnostics (Germany). The study was carried out according to the manufacturer's instructions. The microplayphotometer SUNRISE TECAN (Austria) was used for the analysis.

Statistical analysis. All quantitative variables were expressed as mean ± standard deviation, while qualitative data were shown in the form of number and percentage. Student's t-test was used to compare the significant difference in mean values between groups. $P < 0.05$ was considered significant. Correlation coefficients were established by using Spearman's correlation coefficients. SPSS 16.0 version for Windows was used for statistical analysis.

Results. Ejaculate analysis has of fundamental importance for diagnosis and determining the degree of severity of male factor in infertility. Although it is based on a quantitative change in parameters of ejaculate, functional defects are important. Spermatogenesis in humans lasts almost 3 months, and the influence of exogenous factors can persist for 2-3 months.

Analysis of ejaculate was done according to WHO 5th guideline. Reduced number of normal spermatozoa and their motility was detected in all examined groups (Table 1).

Table 1

Evaluation of the spermogram of infertile men with various accompanying pathologies

Parameters	Control group	Idiopathic infertility	Rheumatoid arthritis
Number of sperm in 1 ml (million)	58.27±7.51	38.42±4.73	49.37±6.82
Number of sperm in ejaculate (million)	195.69±24.32	107.9±12.64*	121.87±13.56
Sperm motility (%)	56.71±7.51	31.36±4.20*	42.16±5.42*
Morphologically normal sperm count (%)	68.83±8.95	38.11±5.23*	39.17±5.36*
Leukocytes (10^6/ml)	0.28±0.06	0.46±0.08	0.34±0.07

* *P* value between parameters is significant $P < 0.05$.

Patients with autoimmune diseases (rheumatoid arthritis) had the highest rate of leukocytospermia, indicating a possible long-term inflammatory process. When examining patients with autoimmune pathology,

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asthenozoospermia was found in 8 (36.36%) patients and leucocytospermia in 14 patients (63.64%). In patients with idiopathic infertility, oligozoospermia was diagnosed in 3 patients (13.04%), oligoasthenozoospermia in 7 patients (30.36%), asthenozoospermia in 8 patients (34.78%) and leucocytospermia in 5 patients (21.82%).

In general, quantitative and qualitative changes in spermatozoa were found: in men with autoimmune diseases - in 8 patients (36.36%); in men with idiopathic infertility - in 12 patients (52.17%). The frequency of changes in spermatozoa did not differ in the examined groups. At the same time, leukocytospermia was determined much more often in patients with autoimmune pathology, compared to patients with idiopathic infertility. In infertile men with concomitant autoimmune pathology, the number of leukocytes in sperm probably exceeded the values in all other groups.

The next task was to determine the main cytokines in blood serum of men with infertility. To analyze the cytokine profile in blood serum the levels of the following cytokines were determined: pro-inflammatory – interleukin 1β (IL-1β), interleukin 18 (IL-18), interleukin 6 (IL-6), tumor necrosis factor α (TNF- α), interferon γ (IFN-γ) and anti-inflammatory - interleukin 10 (IL-10), transforming growth factor β1 (TGF-β1). In patients with rheumatoid arthritis the concentration of IL-18 (cytokine of the IL-1 family) in the blood serum of infertile men was 1.36 times higher than that of fertile men (Table 2). The level of IL-6 was 6 times higher, and the concentration of IFN-γ exceeded the norm by more than three times. The level of IL-10 was 9,4 times higher than in control group.

Table 2

The level of the cytokines in blood serum of infertile men

Parameters, pg/ml	Control group	Idiopathic infertility	Rheumatoid arthritis
TGF-β1	479.23±78.75	548.23±58.17	539.72±77.51
TNF-α	3.36±0.35	2.99±0.17	7.46±0.64
IFN -γ	9.17±1.21	24.32±2.46***	27.77±3.29***
IL-1β	3.61±0.45	2.72±0.23	9.87±1.68*
IL-6	2.37±0.67	6.76±0.73***	14.29±2.52***
IL-10	1.24±0.75	3.71±0.49	11.66±2.47***
IL-18	196.79±23.71	287.69±24.15*	268.22±18.34*

* *P* value between parameters is significant * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Significant changes in the serum cytokine profile were recorded in men with idiopathic infertility. The level of pro-inflammatory cytokines increased statistically significantly: IL-18 – 1.45 times, IL-6 – 2.85 times, IFN-γ – 2.65 times. Simultaneously, the level of anti-inflammatory cytokines increased: IL-10 – 3.0 times.

We also analyzed the ratio of serum levels of pro- and anti-inflammatory cytokines (Table 3). Significant increase in IL-10/TNF-α ratio was recorded in men with idiopathic infertility and infertile men with rheumatoid arthritis. Specifically, in men with idiopathic infertility the IL-10/TNF-α ratio was 3.3 times higher and in patients with rheumatoid arthritis the IL-10/TNF-α ratio was 4.1 times higher than in control group. In patients with rheumatoid arthritis the IL-10/IFN-γ ratio was in 3 times higher than in control group.

Table 3

The ratio of IL-10/IFN-γ and IL-10/TNF-α levels in blood serum of the examined men

Groups	IL-10/TNF-α	IL-10/IFN-γ
Control group	0.38±0.07	0.14±0.02
Idiopathic infertility	1.26±0.22***	0.16±0.02
Rheumatoid arthritis	1.56±0.24***	0.42±0.06***

* *P* value between parameters is significant *** $P < 0.001$

A significant positive correlations were found in healthy fertile men: TGF-β1 – IFN-γ, IL-10 – IL-18 and IL-10 – TNF-α. In men of the control group, the synthesis of IL-18 and TNF-α was balanced by the production of IL-10. The synthesis of IFN-γ was by balanced by the production of TGF-β1 (Table 4).

Discussion. Systemic diseases are indicated in the WHO classification and topical classification as a cause of infertility. Since about 15% genes in the male genome are associated with reproductive processes, it can be assumed that there may be other genetically determined diseases associated with fertility defects. The interdependence between fertility and health is exacerbated by many concomitant factors. Obesity, smoking, drug treatment negatively affects both ejaculate parameters and the health state in general. The lack of data on all components of the pathogenesis of many diseases makes it difficult to study the relationship between somatic and reproductive health.

The interaction of cells of the immune system with each other depends on their production many biologically active substances, in particular cytokines, which can have both pro-inflammatory and anti-inflammatory effect. A change in the cytokine profile is one of the immunopathogenetic mechanisms of many diseases, in particular the reproductive system [1]. Elevated serum levels of proinflammatory cytokines are a characteristic feature of impaired immune reactivity for autoimmune pathology [10].

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Table 4

Correlations (Spearman rank correlations) between blood serum cytokines of infertile men

Groups of cytokines	Control group	Idiopathic infertility	Rheumatoid arthritis
IL-10 – IL-1β	0.206628	0.272408	0.432838
IL-10 – IL-6	0.170343	0.259813	0.180408
IL-10 – IL-18	0.407734*	0.508948	0.270664
IL-10 – TNF-α	0.533632*	0.222228	0.004119
IL-10 – IFN-γ	0.149463	0.383951	0.370274
TGF-β1 – IL-1β	0.179902	0.637889*	0.172547
TGF-β1 – IL-6	0.207968	-0.586876*	-0.029026
TGF-β1 – IL-18	0.141260	-0.125248	0.104100
TGF-β1 – TNF-α	0.265217	0.695551*	0.220608
TGF-β1 – IFN-γ	0.450431*	0.184943	0.208828

* P value between parameters is significant $P < 0.05$.

Thus, an increase in the concentration of pro-inflammatory cytokines, especially IFN-γ was the general distinctive feature of the changes in the cytokine profile of infertile men with various accompanying pathologies. An increase in the serum level of this cytokine is evidence of systemic pro-inflammatory cytokines activation of the immune system. In addition, IFN-γ is involved in the process of isotype switching of antibodyogenesis before IgG synthesis. The key role in the formation of the cytokine profile of blood serum belongs to T-helpers. The population of T-helpers includes several subpopulations, the most important of which are T-helpers of types 1 and 2 (Tx1 and Tx2). Cytokines produced by Tx1 inhibit the cytokines production of Tx2 profile and inhibit the differentiation of naïve T-lymphocytes according to this profile. Conversely, Th1-profile cytokines are antagonists of the Th2-profile immune response [11].

T-helpers play an important role in the development of inflammation, as they are inducers of the adaptive immune response. The imbalance of T-helpers of types 1 and 2 and the cytokines produced by them cause the development of chronic inflammatory diseases. In addition, the balance of these cells during the activation of the immune response determines its subsequent form: primarily cellular or humoral. However, the ratio between cytokines does not completely reflect their production by T-helpers of types 1 and 2, since it is known that under conditions of inflammation, for example, TNF-α is produced not only by Tx1 lymphocytes, but also by monocytes/macrophages. In addition to Tx2 lymphocytes IL -10 is also produced by Tx3 lymphocytes and some other cells. The ratio between the total level of IL-10 and TNF-α in blood serum and, especially, in seminal fluid is used to assess the fertility of bulls in veterinary medicine [12].

The ratio of cytokines that are antagonists: IL-10/IFN-γ, IL-10/NGF-α were evaluated. The analyzed indicators were characterized by significant individual variability. However, a tendency towards a decrease in the IL-10/IFN-γ ratio was found in almost all infertile men, which indicates pro-inflammatory activation of the immune system. The immune system functions as a single integrated mechanism, and under physiological conditions, the cytokines synthesis with multidirectional effects is usually interdependent. Therefore, the correlations between pro- and anti-inflammatory cytokines are important. In some cases, antagonistic cytokines inhibit each other's synthesis. In another case, the over synthesis of cytokines of one effect causes a homeostatic increase in the cytokines synthesis of the opposite effect [6]. As a rule, various pathological conditions are accompanied by changes in the number and nature of correlation relationships between different parameters of immune reactivity, including serum levels of cytokines of different effects in comparison with correlations in healthy persons.

Conclusions. The development of infertility associated with various accompanying pathologies is related with by changes in both systemic and local immune reactivity. The pro-inflammatory cytokine profile of blood serum and a decrease in the concentration of IL-1β are observed in patients with idiopathic infertility. The largest number of deviations of immune reactivity was found in infertile men with concomitant autoimmune diseases.

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ЦИТОКІНОВИЙ ПРОФІЛЬ У СИРОВАТЦІ КРОВІ НЕПЛІДНИХ ЧОЛОВІКІВ ІЗ СУПУТНЬОЮ ПАТОЛОГІЄЮ

О.В. Мельник[1], М.З. Воробець[2], А.С. Беседіна[3], П.Б. Покотило[3], Р.В. Фафула[4], Д.З. Воробець[2]

Львівський національний медичний університет імені Данила Галицького, м. Львів, Україна:
[1]кафедра мікробіології,
ORCID ID: 0000-0002-2097-596X,
e-mail: viruszet8@gmail.com;
[2]кафедра урології,
ORCID ID: 0000-0002-6104-5769,
e-mail: vorobetsz@ukr.net;
ORCID ID: 0000-0002-8431-5151,
e-mail: dv@ukr.net;
[3]кафедра нормальної анатомії,
ORCID ID: 0000-0001-5152-219X,
e-mail: annabes@ukr.net;
ORCID ID: 0000-0003-2104-0100,
e-mail: anatomp1@ukr.net;
[4]кафедра біофізики,
ORCID ID: 0000-0002-0121-9093,
e-mail: roman_fafula@ukr.net

Резюме. Відомо, що механізми формування чоловічого неплідддя є імунозалежними. Для кращого розуміння імунопатогенетичних механізмів неплідддя важливим є вивчення ролі різних ланок імунітету.

Мета. Вивчити роль прозапальних і протизапальних цитокінів у сироватці крові для з'ясування їх ролі в сперматогенезі.

Матеріали і методи. Обстежено 45 неплідних чоловіків віком 22-48 років. Їх розділили на 2 групи: перша група – 22 чоловіки з системним аутоімунним захворюванням – ревматоїдний артрит; друга група – 23 соматично здорових пацієнти з ідіопатичним неплідддям. Контрольну групу склали 27 фертильних здорових чоловіків віком 22-48 років.

Результати. У хворих на ревматоїдний артрит концентрація IL-18 у сироватці крові неплідних чоловіків була в 1,36 раза вищою, ніж у фертильних чоловіків. Рівень IL-6 був вищим у 6 разів, а концентрація IFN-γ перевищувала норму більш ніж у три рази. Рівень IL-10 був у 9,4 рази вищим, ніж у контрольній групі. У чоловіків з ідіопатичним неплідддям зареєстровані значні зміни сироваткового цитокінового профілю. Статистично достовірно підвищувався рівень прозапальних цитокінів: ІЛ-18 – у 1,45 раза, ІЛ-6 – у 2,85 раза, ІФН-γ – у 2,65 раза. Одночасно підвищувався рівень протизапальних цитокінів: IL-10 – у 3,0 рази.

Висновки. Розвиток неплідддя, пов'язаного з різними супутніми патологіями, пов'язаний зі змінами як системної, так і місцевої імунної реактивності. У пацієнтів з ідіопатичним безпліддям спостерігається прозапальний цитокіновий профіль сироватки крові та зниження концентрації IL-1β. Найбільшу кількість відхилень імунної реактивності виявлено в неплідних чоловіків із супутніми аутоімунними захворюваннями.

Ключові слова: цитокіни, чоловіче неплідддя, ідіопатичне неплідддя, ревматоїдний артрит.

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