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DIAGNOSIS AND PREVALENCE OF IMMUNEINFERTILITY IN MEN WITH IMPAIRED FERTILITY

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ХУЛОСА

Тадқиқотда ёши 26 дан 45 гача бўлган 324 бепушт эркак иштирок этди. Барча иштирокчилар нормал спермограмма билан MAR-тестдан ўтказилди, бу антиспермал антитаналарни (АСАТ) аниқлаш учун қўлланилди. 15,6% пациентларда АСАТ аниқланди, бу иммун тизимига боғлиқ бепуштликни кўрсатади. Энг юқори АСАТ концентрацияси варикоцеле ва инфекцион генезга эга пациентларда кузатилди. Бу натижалар MAR-тестни эркаклар бепуштлигини ташҳислашга киритиш зарурлигини таъкидлайди. Тадқиқот бепуштликнинг сабабларини аниқлаш ва даволашни танлаш учун тўлиқ текширув ўтказиш аҳамиятини кўрсатади.

Калит сўзлар: *иммун тизимига боғлиқ бепуштлик, антиспермал антителалар, MAR-тест, спермограмма, варикоцеле.*

РЕЗЮМЕ

В исследовании приняли участие 324 мужчины с бесплодием в возрасте от 26 до 45 лет. Всем участникам с нормальной спермограммой был проведен MAR-тест для выявления антиспермальных антител (АСАТ). У 15,6% пациентов были обнаружены АСАТ, что свидетельствует о наличии иммунного фактора бесплодия. Наибольшие концентрации АСАТ наблюдались у пациентов с варикоцеле и инфекционным генезом. Эти результаты подчеркивают необходимость включения MAR-теста в диагностику мужского бесплодия. Проведенное исследование показывает важность комплексного обследования для уточнения причин бесплодия и выбора лечения.

Ключевые слова: *иммунное бесплодие, антиспермальные антитела, MAR-тест, спермограмма, варикоцеле.*

The frequency of infertility in marriage, according to epidemiological studies presented by the WHO, is 8-29% in various populations among married couples of childbearing age and has a tendency to increase [1, 5, 9, 15]. In addition, 10% of couples experience stillbirth, and 10-25% do not conceive more than one child [2, 6, 12, 16]. The current interest in male infertility is due to data indicating that in 40-50% of cases, the causes of infertility in marriage are associated with a disorder of the male reproductive system. Moreover, in recent years, a tendency towards a decrease in the activity of spermatogenic function has been noted [3, 7, 10, 13] and the presence of antisperm antibodies (ASAT) may be the cause of some of them. Their presence is associated with a reduction in natural conception and live births and affects the success of assisted reproductive technologies.Unfortunately, it is not always possible to suspect the presence of these antibodies based on spermogram data; the presence of sperm agglutination may indirectly indicate the presence of ASAT, but a number of other factors may lead to sperm sticking together, and the absence of agglutination does not exclude the presence of these antibodies. The relevance and importance of conducting research in this area were determined by a number of factors. Firstly, there is no generally accepted point of view on the role of ASAT in male infertility. Although most clinicians believe that ASAT affects spermatogenesis, sperm quality and the interaction of sperm with the egg, some deny the influence of ASAT on individual stages of the reproductive process. The diagnosis: “immunological factor of infertility”, according to the WHO recommendations (2022), is identified as a separate nosology, at the same time, it is absent from the ICD-10; three times over the past 30 years, WHO experts have changed the recommended normal limits (40, 10 and 50% of ASAT-positive motile sperm, respectively). In recent years, the improvement of examination methods in reproductive medicine has made it possible to develop modern diagnostics, which allows identifying immune factors of infertility [4, 8, 11, 14]. The antisperm immune response is the result of an imbalance of normal protective mechanisms, including the hematotesticular barrier, immunosuppressive factors

of seminal plasma in men and suppressor mechanisms of immunoregulation in men and women. Most often, ASAT is detected in the ejaculate and cervical mucus [6, 9, 12, 16]. There are different diagnostic methods: 1) study of general immunity; 2) a study of local immunity; 3) tests for compatibility and penetration ability of spermatozoa, which also includes the MAR test, using this test, recommended by WHO, it is possible to determine the percentage of spermatozoa covered with ASAT, as well as the amount of antibodies on their surface.

THE AIM OF THE WORK

The purpose of this study was to assess the level of IgG antibodies produced against one's own spermatozoa (ASAT) in men with normal spermogram parameters.

MATERIALS AND METHODS OF RESEARCH

A multicenter study of the prevalence of immune infertility among men was conducted in 2 clinics of the Department of Urology and Andrology of the Center for the Development of Professional Qualifications of Medical Workers from 2022 to 2024. The results of an examination of 324 men aged 26 to 45 years with complaints of the absence of pregnancy in their spouse for 1 year or more were analyzed. The diagnosis was verified based on complaints, anamnesis and examination, clinical and instrumental research methods, general blood and urine tests, determination of hormone levels in the blood serum, examination for the presence of bacterial and viral infections, ultrasound of the scrotum, kidneys, prostate gland and Dopplerography of the veins of the spermatic cords (to exclude varicocele). Ejaculate was collected in accordance with WHO criteria (2022). Simultaneously with the analysis of ejaculate parameters, a MAR test was performed to detect antisperm antibodies (immunoglobulin G) in the ejaculate. This test determines the ratio of normal actively motile spermatozoa, but covered with antisperm antibodies, to the total number of spermatozoa with the same motility characteristics, expressed as %.

Our assessment of the level of IgG antibodies produced against one's own spermatozoa (ASAT) showed that in the ejaculate of the examined men (n=324) the frequency of all cases of ASAT detection was 15.6%, which amounted to 50 people, including the frequency of cases of detection of spermatozoa with a high concentration of ASAT was 20%. (Table 1). For comparative characteristics, patients with high MAR test values were divided into 3 groups, depending on the number of spermatozoa covered with ASAT. As a result of the examination of men with low MAR test values from 0 to 9% there were 28 people, which amounted to 56%, with average values from 10 to 39% 12 patients (24%), and with high values from 40% and above 10 men, which was the lowest percentage of 20%, out of the total number of those examined with a positive MAR test.

Table 1

ASAT levels in patients with a positive MAR test

ASAT	(n=50)
0 – 9%	56% (28)
10 – 39%	24% (12)
40 – 50% and more	20% (10)

It should be noted that in men with abnormalities in the immunological parameters of the ejaculate, statistically significant differences in the content of ASAT were noted when analyzing its level depending on the etiological factor.

Based on the data, the following groups were formed from 50 patients with positive results obtained during the MAR test:

- Group 1 - with idiopathic infertility - 12 men (24%) with unclear etiology.
- Group 2 - 24 men (48%) with unilateral or bilateral varicocele
- Group 3 - 14 men (28.0%) with infectious genesis. (Table 2)

Table 2

ASAT levels in patients by etiologic factor

	Idiopathic (n=12)	Varicocele (n=24)	Infection (n=14)
0 – 9%	66.6% (8)	16.7%(4)	21.5%(3)
10 – 39%	25% (3)	25% (6)	35.7%(5)
40 – 50% and more	8.4% (1)	58.3% (14)	42.8%(6)

Mathematical processing of the data was carried out using methods of variation statistics using standard mathematical packages of applied programs on a personal computer with the determination of the mean, its error, and the Student's t-criterion.

RESEARCH RESULTS AND THEIR DISCUSSION

It was found that in addition to the main complaint of reproductive disorders, the subjects complained of various diseases. Analysis of somatic diseases revealed that patients with infectious and idiopathic infertility had hypertension, which was more common (12.4% and 10.7%, respectively) compared to the varicocele group. Ischemic heart disease in the anamnesis of patients in group 3 was 8.6%, which is significantly higher than in groups with other pathologies (5.1% and 6.3%). The incidence of ENT diseases (allergic rhinitis, chronic tonsillitis and sinusitis) was higher in the idiopathic infertility group (11.4%),

as well as endocrine diseases. Gastrointestinal diseases (GERD, chronic gastritis, gastric ulcer and hepatobiliary diseases) were detected in 17.6% of patients in Group 1, which is more common than in Groups 2 (15.4%) and 3 (14.2%). While anemia was more common in the group with varicocele (Table 3).

Table 3

Assessment of somatic health and harmful effects habits of men with infertility (%)

Indicator	1 group (n=12)	2 group (n=24)	Group 3 (n=14)
Hypertensive heart disease	12.4%	7.6%	10.7%
Ischemic heart disease	5.1%	6.3%	8.6%
ENT diseases	11.4%	5.6%	9.8%
Gastrointestinal diseases	17.6%	15.4%	14.2%
Anemia	2.1%	7.6%	6.2%
Endocrine diseases	27.6%	12.6%	6.4%

Also, the analysis of alcohol consumption and smoking prevalence among men in the compared groups showed that alcohol consumption and heavy smoking were common among patients in the compared groups, however, no significant differences were found between the groups: patients with infertility and all comparison groups were equally susceptible to this toxic effect. (Fig. 1.)

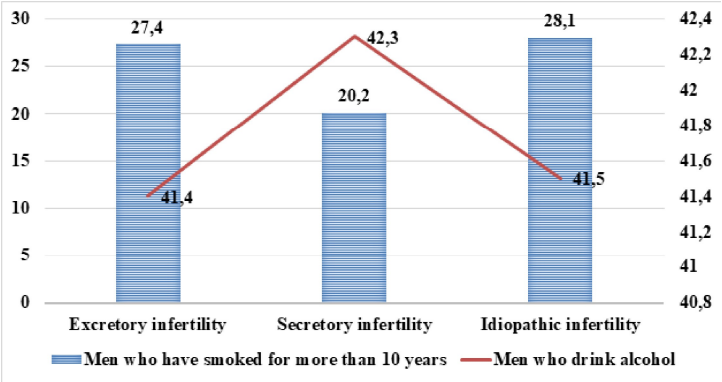

Fig. 1. Bad habits of the subjects (%)

When assessing the infectious status of the ejaculate of patients of the compared groups of bacterial and viral infections, the following was revealed. Bacterial microflora was isolated in an amount of less than 1.2×10^3 CFU/ml, which is not considered diagnostically significant, in the ejaculate of patients, representatives of the following families were typed: Staphylococcaceae, Streptococcaceae, Enterobacteriaceae. In the microbial landscape of the ejaculate of patients of the main groups, coccal flora dominated.

When counting the number of leukocytes in the ejaculate of patients, their level was significantly higher in 7 patients of group 3 with infertility of infectious genesis than in healthy patients ($P<0.01$).

The ELISA method in the blood serum of patients in the compared groups determined only IgG antibodies to the following types of pathogens: Ureaplasma urealitycum 13.3%, Mycoplasma hominis 10.4, Toxoplasmos 10.9, Herpes simplex virus type 2 47.6%, Chlamydia trachomatis 21.0%. IgM antibodies to these pathogens were not detected. (Fig. 2)

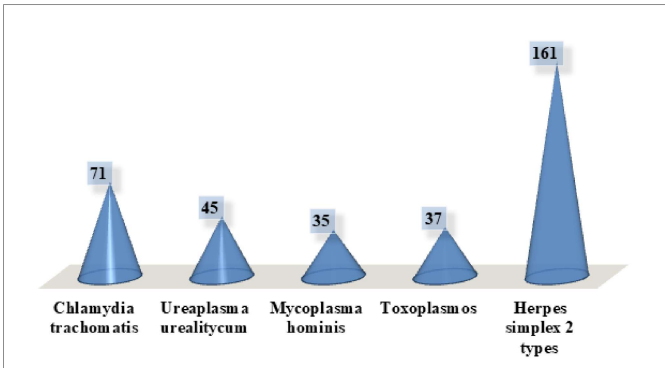

Fig. 2. Analysis of viral infection in the examined patients.

A man's hormonal background is one of the most important indicators of the normal functioning of his body. During its formation, a large number of different hormones are produced, which determine not only the physical but also the sexual health of a man.

Analysis of hormone levels in all 3 groups revealed the following - thyroid stimulating hormone, luteinizing hormone, follicle-stimulating hormone, prolactin - in the blood serum of patients in infertile men did not reveal statistically significant differences in the hormonal background (Table 4). The content of total testosterone in all patients was within the normal range and did not differ significantly.

Table 4

Evaluation of hormonal status in men with infertility

Indicator	Group 1 (n=12) with idiopathic infertility	Group 2 withvaricocele (n=24)	3 group of infectious genesis (n=14)
TSH, mIU/L	11.02 ±0.62	11.8 ±0.9	13.4 ±0.38
LH, mIU/L	5.63 ±0.73	6.6 ±0.19	5.5 ± 0.82
FSH, mIU/L	5.23 ± 0.23	7.1 ± 0.53	5.53 ± 0.23
Prolactin, mIU/L	9.3 ± 0.32	10.4 ± 0.35	10.1 ± 0.29
Testosterone, nmol/l	4.43 ±0.92	4.2 ±0.6	5.79 ±0.36

The assessment of the level of IgG antibodies produced against one's own spermatozoa showed that in the ejaculate of the examined men of all groups the indicators in % were different depending on the etiology of the antibodies. Thus, in patients of the 2nd and 3rd groups with varicocele and in the group with infectious genesis the level of ASAT over 40-50% was several times higher than the similar indicator in patients of the 1st group, in whom these parameters characterizing the organization of male germ cells did not differ from the normal values (Table 2).

Thus, the revealed tendency to increase the level of ASAT in patients with abnormal ejaculate parameters, in our opinion, depends on the severity of changes in the chromatin structure, which indicates the possibility of developing an autoimmune reaction against one's own spermatozoa. Analysis of the obtained data showed that an increase in the level of IgG antibodies against one's own spermatozoa is accompanied by a deterioration in the MAR test parameters, which is one of the leading mechanisms for reducing the fertilization capacity of the ejaculate and is consistent with the studies of a number of authors. The tendency to increase the level of ASAT in the ejaculate of patients in infertile couples allows us to assume the existence of disorders occurring at the level of the hematotesticular barrier, the basis of which is Sertoli cells. Consequently, pathological processes in the hematotesticular barrier can be caused by the "weakening" of intercellular contacts, which in turn leads to a disruption of the integrity of the barrier, and the failure of defense mechanisms entails the penetration of antigens of mature germ cells into the bloodstream, the production of specific antisperm antibodies and the development of an autoimmune inflammatory process.

CONCLUSIONS

A reliable increase in the level of ASAT was revealed in patients with infertility of various genesis, the highest rates of which were in the groups with varicocele and in the group with infectious genesis. Determination of antisperm antibodies to one's own spermatozoa by the MAR test (IgG) should be used in a comprehensive examination of men with infertility, to clarify the treatment and diagnostic tactics, which will allow identifying the causes of disturbances in ejaculate parameters.

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ОСОБЕННОСТИ ИММУНОЛОГИЧЕСКИХ ПОКАЗАТЕЛЕЙ У БОЛЬНЫХ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ НА ФОНЕ АЛЛЕРГИЧЕСКИХ ЗАБОЛЕВАНИЙ

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XULOSA

Tadqiqot maqsadi: *arterial gipertenziya bilan og'rigan bemorlarda allergiya bilan bog'liq holda sitokinlar darajasini o'rganish.*

Materiallar va usullar. *Toshkent shahar Tibbiyot xodimlarining kasb malakasini oshirish markazining ko'ptarmoqli klinikasida yotgan arterial gipertenziyali (AD) 65 nafar bemor klinik-immunologik tekshiruvdan o'tkazildi. Bemorlarning yoshi 45 yoshdan 65 yoshgacha bo'lgan va bemorlar 2 guruhga bo'lingan edi: 1-guruh gipertoniya bilan og'rigan 42 bemor va 2-guruh 23 gipertoniya + allergic kasalliklar (AK). Barcha bemorlar klinik, instrumental va laboratoriya tekshiruvidan o'tkazildi. Qon zardobida yallig'lanishga xos va yallig'lanishga qarshi sitokinlarning darajasini IFT usuli yordamida amalga oshirildi.*

Natijalar. *Gipertenziyada IL-1β, IL-6 va TNFα darajasining oshishi kuzatiladi. Shu bilan birga, yallig'lanishga qarshi IL-4 darajasi nazorat qiymatlari ichida qoladi. Gipertenziya va AK ning birgalikda kursida sitokin muvozanatining buzilishi IL-1β, IL-6, TNF-α yallig'lanishga qarshi sitokinlarning qon zardobida kontsentratsiyasining yanada sezilarli darajada oshishi va qon zardobida IL-4 kontsentratsiyasini sezilarli darajada oshishi bilan tavsiflanadi.*

Xulosa. *Gipertenziyada yallig'lanishning sitokin profilini va biomarkerlarini AK bilan birgalikda o'rganish qon tomir kasalliklarini erta tashhislash va arterial gipertenziya bilan og'rigan bemorlarda profilaktika choralarini optimallashtirish imkonini beradi.*

Kalit so'zlar: *arterial gipertenziya, allergiya, yallig'lanish, immune tizimi, sitokinlar.*

SUMMARY

The aim of the study: *to study the level of cytokines in patients with arterial hypertension in association with allergies.*

Materials and methods. *Clinical and immunological examination was conducted in 65 patients with arterial hypertension, who were in the multidisciplinary clinic of the center for the development of professional qualifications of medical workers, Tashkent. The age of the patients ranged from 45 to 65 years. The patients were divided into 2 groups: 42 patients with hypertension - group 1 and 23 patients with hypertension + allergic diseases. All patients underwent clinical, instrumental and laboratory examination. Immunological studies were conducted by studying the level of pro- and anti-inflammatory cytokines in the serum of peripheral blood by the ELISA method using the test systems of AO Vector Best (RF).*

Results. *In hypertension, an increased level of IL-1β, IL-6 and TNFα is observed. At the same time, the level of the anti-inflammatory cytokine IL-4 remains within the control values. In the combined course of hypertension and AZ, the cytokine imbalance is characterized by an even more significant increase in the serum concentration of proinflammatory cytokines IL-1β, ID-6, TNF-α and a reliable increase in the serum concentration of IL-4.*

Conclusion. *The study of the cytokine profile, biomarkers of inflammation in hypertension in combination with AZ will allow for early diagnosis of vascular disorders and optimize preventive measures in patients with arterial hypertension with a comorbid course.*

Keywords: *arterial hypertension, allergy, inflammation, immune system, cytokines.*