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IMPACT OF COVID–19 ON SPERMATOGENESIS IN MEN

Summary. *According to scientific research, SARS-CoV-2 can hurt the male reproductive system. Of this study was to study the main indicators of semen fluid in men after COVID-19 infection. The study included male patients who had recovered from COVID-19. Between February 2020 and September 2021, semen analysis was performed on 48 men. 26 of them, had a history of COVID-19 and had laboratory confirmation of the last infection (IgG). The key indicators of the spermogram were studied: Volume of ejaculate, Total number of sperm, Concentration of sperm, Percentage of pathological forms, pH of semen fluid, and concentration of leukocytes. The spermogram indicators of patients who recovered from COVID-19 differed significantly from the indicators of patients who did not survive COVID-19 infection. Their ejaculate volume is 2 times less, and the total number of sperm is 3.6 times less. Accordingly, the concentration of spermatozoa is reduced by almost 2 times. An increase in the pH of semen fluid was detected. The percentage of pathological forms of sperm is 2 times higher. Men who have had COVID-19 and have elevated levels of IgG SARS-CoV-2 are characterized by significant quantitative and qualitative changes in fertility. Therefore, the COVID-19 coronavirus infection affects male reproductive function and may thus contribute to the aggravation of the already ongoing decline in male fertility in recent decades. These data indicate a possible decline in the birth rate in this region.*

Key words*: COVID-19, SARS-CoV-2, male fertility, male reproductive system.*

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ВЛИЯНИЕ COVID-19 НА СПЕРМАТОГЕНЕЗ У МУЖЧИН

Аннотация. *SARS-CoV-2 может оказывать негативное воздействие на репродуктивную систему мужчин. Изучение основных показателей спермальной жидкости мужчин после перенесенной инфекции COVID-19. В исследование включены пациенты-мужчины, выздоровевшие от COVID-19. В период с февраля 2020 года по сентябрь 2021 года проведен анализ спермальной жидкости 48 мужчин. Из них 26 мужчин, у которых в анамнезе переболели COVID-19 и имели лабораторное подтверждение перенесенной инфекции. Исследованы ключевые показатели спермограммы: объём эякулята, общее количество сперматозоидов, концентрация сперматозоидов, процент патологических форм, pH спермальной жидкости и концентрация лейкоцитов. Показатели спермограммы больных, переболевших COVID-19, существенно отличались от показателей пациентов, которые не перенесли инфекции COVID-19. У них в 2 раза снижен объём эякулята, в 3,6 раза меньше общее количество сперматозоидов. Соответственно этому, почти в 2 раза снижена и концентрация сперматозоидов. Обнаружено повышение pH спермальной жидкости. Процент патологических форм сперматозоидов оказался в 2 раза больше. Для мужчин, перенесших COVID-19 и у которых повышен уровень IgG SARS-CoV-2 в сыворотке крови, характерны достоверные количественные и качественные изменения фертильности. Следовательно, коронавирусная инфекция COVID-19 влияет на мужскую репродуктивную функцию и тем, самым может способствовать усугублению уже происходящему в последние десятилетия снижению мужской фертильности. Эти данные указывают на возможное снижение рождаемости в данном регионе.*

Ключевые слова: COVID-19, SARS-CoV-2, фертильность мужчин, репродуктивная система мужчин.

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COVID 19 NING ERKAKLARDA SPERMATOGENEZGA TA'SIRI

Annotatsiya. *Ilmiy tadqiqotlarga ko‘ra, SARS-CoV-2 virusi erkaklarning reproduktiv tizimiga salbiy ta’sir ko‘rsatishi mumkin. Ushbu tadqiqotning maqsadi — COVID-19 infeksiyasidan keyin erkaklar urug‘ suyuqligining asosiy ko‘rsatkichlarini o‘rganishdan iborat bo‘ldi. Tadqiqotga COVID-19 dan sog‘aygan erkak bemorlar jalb etildi. 2020-yil fevralidan 2021-yil sentabriga qadar 48 nafar erkakning spermogrammasi tahlil qilindi. Ulardan 26 nafarida COVID-19 bilan kasallanish tarixi mavjud bo‘lib, ularning oxirgi infeksiyasi laboratoriya orqali (IgG) tasdiqlangan edi. Spermogrammaning asosiy ko‘rsatkichlari o‘rganildi: eyakulyat hajmi, spermatozoidlarning umumiy soni, ularning konsentratsiyasi, patologik shakllar foizi, urug‘ suyuqligining pH darajasi va leykotsitlar konsentratsiyasi. COVID-19 dan sog‘aygan bemorlarning spermogramma ko‘rsatkichlari ushbu infeksiyani boshdan kechirmagan bemorlarning ko‘rsatkichlaridan sezilarli darajada farq qildi. Ularning eyakulyat hajmi 2 baravar kam, spermatozoidlarning umumiy soni esa 3,6 baravar kam bo‘ldi. Mos ravishda spermatozoidlar konsentratsiyasi deyarli 2 baravar kamaygan. Urug‘ suyuqligining pH darajasida oshish kuzatildi. Spermatozoidlarning patologik shakllari foizi 2 baravar yuqori bo‘ldi. COVID-19 bilan kasallangan va SARS-CoV-2 IgG darajasi yuqori bo‘lgan erkaklarda fertilitetning miqdoriy va sifat jihatdan jiddiy o‘zgarishlari kuzatiladi. Shunday qilib, COVID-19 koronavirus infeksiyasi erkaklarning reproduktiv funksiyasiga salbiy ta’sir ko‘rsatib, so‘nggi o‘n yilliklarda kuzatilayotgan erkaklar bepushtligining ortishiga hissa qo‘shishi mumkin. Ushbu ma’lumotlar mintaqada tug‘ilish darajasining pasayishi ehtimoli borligini ko‘rsatadi.*

Kalit so‘zlar: *COVID-19, SARS-CoV-2, erkaklar fertiliteti, erkaklar reproduktiv tizimi.*

Relevance. Data from a meta-analysis published in 2017 indicate that over 4 decades (1973-2011), there was a decrease in key spermogram indicators by 50-60% [1]. WHO is constantly reviewing the Recommendations for the evaluation of spermograms. It should be noted that they also change in the direction of decreasing the values of these and other indicators. Consequently, there is a tendency to decrease the quality of sperm every year [2, 3].

According to a number of authors, these conclusions are erroneous and the reason for this, in their opinion, is the lack of high-quality data confirming the decrease in sperm parameters over time. Disputes exist due to poor-quality data and interpretations that have been used over the past century. More reliable modern data provide a more convincing signal that neither sperm parameters nor male fertility have changed over the last century [3].

Significant causes of the observed transformations are environmental changes. Exposure to chemicals and a sedentary lifestyle have a negative impact on spermatogenesis [4]. And this trend is likely to intensify among the general population, and future prospective studies should clarify the potential causes of this decline.

Due to the excesses that have occurred over the past 5 years, it is reasonable to expect deeper changes in male fertility indicators. In particular, this concerns the impact of coronavirus infection on men's health. According to recent scientific studies, SARS-CoV-2 can have a negative impact on the reproductive system, leading to a decrease in the number and motility of spermatozoa, affect erectile dysfunction, and a decrease in blood testosterone levels [5].

In light of reports of declining sperm quality and fertility rates in some regions of the world, as well as other changes, the question of whether male fertility is changing requires investigation. All this indicates the need (demand) for continued research on this issue [6].

The purpose of the study. To study the effects of COVID-19 on spermiological parameters in men of reproductive age.

Materials and methods. *Characteristics of patients.*

Male patients who had recovered from COVID-19 were recruited for the study. In the period from February 2020 to September 2021, the analysis of the sperm fluid of 48 men was carried out. Of these, 26 men had a history of COVID-19 and had laboratory confirmation of the infection (group 1) - increased IgG levels in the blood serum. The average age of patients in this group was 26.3±2.7 years. The following 22 men had no subjective or laboratory signs of COVID-19 infection (group 2). The average age of patients in this group was 29.9±0.6 years. By the time of the examination, none of the men from both groups had been vaccinated against COVID-19.

Laboratory tests.

All patients underwent tests according to standard generally accepted recommendations [7]. Semen analysis was performed on a SW-3700 analyzer (manufactured by MES, China). The analysis was carried out according to WHO recommendations [8].

Also, to ensure the accuracy of data collection, the patients' attention was focused on the following points:

- make sure that all semen gets into the collection cup;
- Do not use a condom to collect semen;
- Refrain from ejaculating for two to seven days before collecting a sample;
- collect a second sample no later than two weeks after the first one.
-Avoid using lubricants, as these products may affect sperm motility.

The following were selected as key indicators for the analysis of the spermogram in this study:

Ejaculate volume,

Total number of spermatozoa,

Sperm concentration,

Percentage of pathological forms of spermatozoa,

sperm pH,

The concentration of leukocytes in the sperm fluid.

To exclude the presence of bacterial infection in the genitourinary tract, a Meares-Stamey portioned urine test was performed - microscopic and bacteriological (if necessary) examination of prostate secretions and urine samples obtained from various parts of the genitourinary tract. The presence of nitrite was monitored as an indirect sign of bacterial invasion.

Statistical analysis. All statistical analyses were performed on a personal computer using the Microsoft Excel 2013, Microsoft Access 2013 software, as well as the R for Windows 2.15.0 statistical software package. The arithmetic mean (M), mean square deviation (□), and relative values (frequency, %) were calculated. The statistical significance of the measurements obtained when comparing averages was determined by the Student's criterion (t) (with a normal distribution) and using the Wilcox test (when analyzing abnormally distributed and nonparametric data). The confidence intervals (CI) given in the work were constructed for a confidence probability of p=95% (the critical significance level in this study was assumed to be 0.05).

The results of the study. *Clinical characteristics of patients.*

This study included 48 male patients, residents of Surkhandarya region, who sought consultation at an outpatient andrological appointment. Of these, there are 26 patients with a confirmed diagnosis of COVID-19 in the anamnesis (1.5-2 months after the illness and no earlier than the 42nd day after the illness). The remaining 22 patients were examined for erectile dysfunction, without any concomitant chronic diseases.

Laboratory-confirmed COVID-19 was defined as a positive test result for the level of SARS-CoV-2 class G (IgG) antibodies to the RBD domain of the S protein. The method of determination was chemiluminescent immunoassay (Sperm Quality Analyzer SQA-iO, China). Quantitative measurement range: 2.9 - 5680 BAU/ml.

For randomization and purity of the results, the presence of other diseases in the subjects was excluded, which may be the cause of an increase in class G immunoglobulins. Autoimmune pathologies such as rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, as well as sarcoidosis, chronic liver diseases, chronic or recurrent infections, and parasitic diseases. Of the concomitant diseases, patients in the first group had residual effects after pneumonia, as well as mild erectile dysfunction and symptoms of category IV abacterial prostatitis in patients in both groups (Table 1).

Table 1.

Clinical characteristics of patients

Group	Age, Median (IQR)	Severity of COVID-19 disease, n (%)			Concomitant diseases, n (%)		IgG ≥ 10,0 BAU /мл, n (%)	
		Mild to moderate, Severe to severe	Mild to moderate, Severe to severe	Mild to moderate, Severe to severe	Yes	No	Yes	No
With confirmed COVID-19 (n = 26)	27,0 (21-44)	17 (65,4)	7(26,9)	2(7,7)	12 (46,2)	14 (53,8)	26 (100)	ND
No confirmation of COVID-19 (n = 22)	29,0 (19-45)	НД	НД	НД	6(27,3)	16 (72,7)	ND	22 (100)
Abbreviations: ND – no data/ not applicable.								

The results of laboratory studies of the ejaculate are shown in Table 2.

Table 2.

The results of laboratory studies of ejaculate

Criteria	Covid patients (n=26), M+m	Without covid (n=22), M±m	p
Ejaculate volume, ml	1,94±0,08	3,86±0,21	<0,05
Total number of spermatozoa, million	44,16±6,14	159,1±12,3	<0,05
Number of spermatozoa, million/ml	22,37±2,90	42,72±2,89	<0,05
pH of sperm fluid	8,41±0,12	7,61±0,02	<0,05
Pathological forms, %	27,72±1,29	12,73±0,88	<0,05
Concentration of leukocytes, million/ml	2,78±0,29	0,72±0,11	<0,05

As can be seen from the table, the spermogram indicators of patients who had COVID-19 significantly differed from those of patients who had not been infected with COVID-19 (Table 2). In patients of the first group, the volume of ejaculate was reduced by 2 times compared with the same results in patients of the second group. The total number of spermatozoa was also 3.6 times lower than in the second group. Accordingly, the concentration of spermatozoa is reduced by almost 2 times. The fact of increasing the pH of the ejaculate turned out to be particularly interesting. Thus, in men who had COVID-19 (group 1), the pH was significantly (<0.05) higher than in men in group 2. The percentage of pathological forms of spermatozoa was 2 times higher in patients in the first group. The white blood cell concentration indicator showed a similar ratio. The latter was 3.8 times higher in patients in the first group..

Discussion of the results. In a number of publications in recent years, information can be found that despite the fact that SARS-CoV-2 could not be detected in semen, the coronavirus infection COVID-19 generally affects male reproductive function and thereby significantly contributes to the aggravation of the decline in male fertility that has already occurred in recent decades. However, in men who are ill and have recovered from COVID-19, these studies have contradictory data when analyzing the quality of sperm [2, 3, 17]. When the samples were re-examined after 2-2.5 months, these indicators changed, but not to the optimal level. For couples, assisted reproductive technology clinics, and sperm banks, special consideration should be given to evaluating the sperm of men infected with COVID-19. Consequently, there is no well-defined data for men with a positive history of SARS-CoV-2, both in terms of timing and normalization of their sperm quality.

It has been confirmed that the multi-organ effects of COVID-19 significantly alter the functional state of many body systems, including the heart, lungs, kidneys, skin, brain, and male reproductive function [18, 19]. It is well known that several viral infections, including mumps, are associated with decreased sperm quality and male infertility [20]. In addition, it has already been confirmed that all febrile conditions negatively affect the post-meiotic period, making significant changes in the concentration, morphology, and motility of spermatozoa [21].

A recent structural and functional study has shown that the angiotensin converting enzyme receptor 2 is a target for SARS-CoV-2 infection. The presence of enzyme expression in germ cells, Leydig cells, and Sertoli cells suggests that the testicles are a potential target for SARS-CoV-2 infection [22]. As confirmation of this, the results of the study by Yang and co-authors, who reported significant damage to the seminal tubules and a decrease in the number of Leydig cells, as well as the presence of mild lymphocytic inflammation in the testicles of patients with COVID-19 [23].

Some publications suggest that the adverse effects of COVID-19 on male reproductive function may be primarily due to a systemic inflammatory response and the induction of oxidative stress [24]. The changes revealed during the study confirmed the assumption of an expected deterioration in fertility in men after COVID-19. This is another confirmation of the expected decrease in fertility rates in the near future and, accordingly, an increase in the population's appeal to specialized specialists should be assumed [4].

Of course, it is important to analyze the causal relationship between the detected changes in spermograms. It is known that if the pH of the sperm fluid is higher than normal – 8.0 and is located in the alkaline range, then the presence of an inflammatory process or infection should be assumed. Scientific studies have confirmed that infections can reduce male fertility through various mechanisms. This may be a violation of local immune regulation, which thus causes the development of autoantibodies to spermatozoa, or a violation of the function of the male accessory glands. As a result, the quality or quantity of seminal fluid decreases. In addition, pathogens can damage spermatozoa directly or through inflammation caused by them [9, 10, 11].

In our observations, another confirmation of the presence of inflammation is an increase in the concentration of white blood cells in the sperm fluid. Although none of the patients reported having had epididymitis or orchitis in the acute period of COVID-19, their white blood cell concentration was 4 times

higher than in group 2. This corresponds to the results of observations and a literary review of the publication by D. Yenikeev et al. [5]. A negative nitrite test and the absence of microflora growth in urine and seminal fluid samples indicate the aseptic nature of inflammation in our patients.

The role of aseptic inflammation is generally recognized in the pathogenesis of infertility associated with oxidative stress, nitrosative stress, and hypoxia [12]. Under physiological conditions, sperm produces small amounts of reactive oxygen species (ROS), which are necessary for fertilization, acrosome reaction, and capacitation. In pathological conditions, the main source of free radicals (SR) in the ejaculate are spermatozoa with impaired morphology, as well as leukocytes. The latter produce CP up to 1000 times more than spermatozoa. On the one hand, such a high level of CP production is necessary for the realization of antimicrobial and anti-inflammatory functions. On the other hand, a large amount of CP, in turn, is associated with oxidative stress, which causes death or pathology of spermatozoa [13, 14, 15]. Consequently, if increased CP production is not associated with enhanced purification systems, peroxide damage to the plasma membrane of spermatozoa and loss of DNA integrity occur, which leads to cell death and, consequently, decreased fertility.

COVID-19 is capable of causing widespread endothelial dysfunction in organ systems outside of the lungs and kidneys. The virus can enter endothelial cells and affect many organs, including the organs of the male reproductive system [16]. This condition of the vascular system is another significant factor in the development of oxidative stress. The increased production of CP by leukocytes appears to be a direct consequence of inflammatory processes or vascular diseases leading to hypoxia or ischemia.

In all the above cases, antioxidants are effective in the treatment of patients with similar diseases of the male reproductive system complicated by the excretory-toxic norm of infertility [12, 13, 25]. However, it has been proven that taking antioxidant supplements does not cure the underlying disease that causes decreased fertility. For specialists, it should be considered important to identify and treat the cause of increased production of reactive oxygen species. In our case, of course, we consider the coronavirus infection COVID-19 to be the main root cause. But the results of studies on the restoration of normal spermatogenesis after coronavirus infection are alarming. The estimated recovery time is 3 months, but ongoing further research reveals that a number of men have suffered irreversible damage. Their frequency varies – from 9 to 28% of men who have had COVID-19. Therefore, in any case, the first step for all these men who have been ill with COVID-19, in order to preserve fertility, and especially for those who initially suffer from infertility, may be the appointment of antioxidant supplements. They can help maintain a balance between CP production and clearance and thus improve sperm quality. A number of studies prior to COVID-19 found a lower incidence of sperm aneuploidy in men with higher dietary intake of antioxidants than those with lower intake [26, 27]. The most well-known and popular components of the complex of antioxidant supplements are Vitamin E, Vitamin C, N-acetyl-L-cysteine, ZnSO4, Glutathione, Pentoxifylline, Carnitine, Catalase, Selenium, nicotinamide adenine dinucleotide phosphate, reactive oxygen species, Coenzyme Q10, superoxide dismutase. Taking such combined antioxidant supplements as part of therapy during COVID-19 treatment and subsequent rehabilitation may seem to be an adequate strategy for optimizing fertility in patients with SARS-CoV-2 virus infection.

Conclusion. Thus, men who have had COVID-19 and who have elevated levels of SARS-CoV-2 IgG in their blood serum are characterized by significant changes in fertility. Compared with similar indicators of individuals who did not have subjective and laboratory signs of COVID-19 infection (with normal levels of SARS-CoV-2 IgG in the blood serum), our patients showed a decrease in ejaculate volume and total sperm count, an increase in the percentage of pathological forms and the pH of the sperm fluid. Against the background of a worldwide downward trend in key spermogram indicators, these data indicate an aggravation of fertility disorders and an expected decrease in the birth rate in the selected region. In this regard, in our opinion, it is advisable to supplement the complex of medical treatment of COVID-19, both during the acute period of treatment and later during rehabilitation, with means to protect and improve spermatogenesis. In-depth randomized studies to determine the suspected causes and mechanisms of the observed changes in the reproductive system of men with coronavirus infection, to determine the timing of normalization of qualitative and quantitative parameters of sperm should still be considered in demand. And to assess the effectiveness of the treatment and rehabilitation, the main result of any study should be not only changes in spermogram parameters, but, of course, the indicator of pregnancy.

Conflict of interests. The authors confirm that there is no conflict of interest or financial support.

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