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Effects of Covid19 Disease on Male Fertility

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Abstract

Object: In this study, it was aimed to look at the effect of COVID-19 on male fertility by comparing the results of spermiogram samples given before and 6 months after COVID-19 disease in men with a history of infertility.

Material and Methods: The method of this study is retrospective. In this study, the parameters were compared in the spermiogram in which the samples given before and 6 months after COVID-19 disease of patients who are 41 male patients between the ages of 21-41, who did not have chronic disease, no continuous medication, and did not receive infertility treatment, who applied to the Urology and Urology-Infertility polyclinics of Istanbul Training and Research Hospital between 01.03.2020-31.03.2022.

Results: When the parameters were compared in the spermiogram that samples taken before the COVID-19 disease and 6 months after the COVID-19 disease, it was seen that the total sperm count was significantly lower, while the motility ratio, forward motility ratio, in situ motility ratio and immotile ratio did not differ significantly.

Conclusion: Compared to the samples taken before COVID-19 disease, a decrease in the total sperm count was observed in the samples taken 6 months later.

Keywords: Covid-19, male, spermiogram, sperm, fertility

1. Introduction

COVID-19 disease first appeared in December 2019 in the city of Wuhan in China. At the end of December 2019, it affected the whole world in many areas and was declared a Global Pandemic by the World Health Organization in a short time. In Turkey, cases started to be seen in March of

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2020. Severe acute respiratory syndrome - coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19, was detected in feces, gastrointestinal tract, saliva and urine samples. However, there is not a lot of information about SARS-CoV-2 in sperm (1,2). There are studies on the effects of SARS-COV2 virus on male reproductive health on sperm parameters and testicular tissue. SARS CoV-2 uses Angiotensin Converting Enzyme-2 (ACE-2) as a receptor to enter human cells. ACE2, Angiotensin 1-7 and Macrophage Activation System (MAS) receptors were found in the lung, as well as in the testicles, especially in Leydig and Sertoli cells. The first hypothesis is that the virus may enter the testis and cause changes in testicular functionality. A second hypothesis is that binding of the virus to the ACE-2 receptor may cause excess ACE-2 and lead to a typical inflammatory response (3,4). Another study supporting this study showed significant seminiferous tubular damage, decreased Leydig cells, and mild lymphocytic inflammation in testicles from patients who died from COVID-19 disease. Inflammatory cells can interfere with the function of Leydig and Sertoli cells. Although it has been shown that the ACE-2 receptor, which has a high affinity for SARS-CoV-2 virus, is mostly expressed in the lungs, it is known that the ACE-2 receptor is also widely expressed, especially in spermatogonia, Leydig and Sertoli cells (5). Spermatogonium (plural Spermatogonia), the immature sperm cell, enters spermatogenesis to form mature spermatozoa in the seminiferous tubules of the testis. Spermatogenesis takes place in the seminiferous tubule of the testis, and the epithelium that forms the seminiferous tubule contains 2 types of cells. While germ cells are responsible for sperm production, a group of cells called Sertoli cells form the support tissue around the germ cells. Another type of cell found in the testicles is the Leydig cells that produce testosterone. The seminiferous tubule contains sperm precursor cells at all stages of spermatogenesis (6).

Since it is known that COVID-19 disease causes damage to the seminiferous tubules, this study aimed to reveal effects of COVID-19 disease on male fertility by comparing parameters such as number, motility and morphology in the semen analysis (Spermiogram sample) given samples before and 6 months after the COVID-19 disease.

2. Materials and Methods

The method of the study is retrospective. The study included 41 infertile men aged 21-41 years, with a history of COVID-19 disease, who applied to the Urology and Urology-Infertility polyclinics of Istanbul Training and Research Hospital between March 1, 2020 and March 31, 2022. The spermiogram samples given by 41 patients with COVID-19 disease included before and 6 months after Covid-19 disease were compared through the parameter values included. (IEAH Ethics Committee Approval Decision No: 229).

In the study age, disease, medication, previous operation, occupation, infertility status (primary/secondary) of the patients participating were noted. The results of the spermiogram samples given before and 6 months after the COVID-19 disease were examined. The patients who gave samples abstained from sexual intercourse for 2-7 days (7) and didn't use soap, saliva, water, cream, etc. while giving samples. The samples were prepared according to the Gradient method. This method is based on the principle of placing the semen on a special suspension (containing colloidal silica particles) that creates a gradient (layer) and centrifuging it, thus

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moving the sperm to the bottom of the tube with the force of collapse. Sperm with the best motility and uniform morphology move to the bottom, and thus the most motile sperm are collected at the bottom of the tube. Studies have shown that free oxygen radicals that can be released are reduced by the removal of immature (immature) cells and leukocytes from the environment with this method. As a result of the preparation, immotile (immobile) or abnormal morphology sperms and leukocytes in the semen fluid are separated and only motile (motile) and normal morphology sperms are obtained (8,9). Semen samples got placed in conical tubes. The volume of the sperm sample was then measured. 1 drop of sperm from the injector was dropped into the Makler camera and the remaining sperm was put back into the patient's semen container. The conical tube of the patient, whose sperm was detected on the Makler camera, was opened. In our study, 0.5 ml 80% gradient sperm were placed first with a pipette, then 0.5 ml sperm with a syringe and rotated in a Heraeus Megafuge 1.0 centrifuge device at 1200 rpm for 10 minutes. The conical tube of the patient, whose sperm was not detected in the makler camera, was opened and all sperm were placed with an injector for gradient. It was rotated in the Heraeus Megafuge 1.0 centrifuge device at 2000 rpm for 5 minutes. Afterwards, 0.5 ml of the treated samples coming out of the centrifuge device were withdrawn and the supernatant in the pipette was left in the patient's semen container, and the remaining 0.5 ml sample pellet was given with a pipette for homogeneous mixing. 1 drop of sperm from the remaining sample was dropped into the Makler camera and examined for number, motility and morphology under the Olympus Bx50 microscope. In case of no sperm count, very few or no motile sperm in the Makler camera, in addition to these procedures, the sperm were examined by dropping 1 drop on the slide.

Patients whose examinations could not be reached, who had a chronic disease, who underwent IVF treatment, who were outside the age range of 21-41, and secondary infertile male patients were not included in the study.

3. Statistical Analysis

In the descriptive statistics of the data used in this study are mean, standard deviation, median lowest, highest, frequency and ratio values. Distribution of variables measured with the Kolmogorov-Smirnov test. Wilcox on test was used in the analysis of dependent quantitative data. A P value less than 0.05 was considered statistically significant. SPSS 28.0 program was used in the analysis.

Table-1

		Min-Max.	Median	Avg..±ss/n-%	
Age		21 - 42	32.0	32.8 ± 5.3	
Disease	No			40	100.0%
Medication	No			41	100.0%
Smoker	No			27	65.9%
	Yes			14	34.1%
Job	Textile Worker			3	7.3%
	Nurse			1	2.4%
	Chef			1	2.4%

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Construction Worker	1	2.4%
Business Manager	1	2.4%
Delivery Boy	1	2.4%
Chemist	1	2.4%
Market Attendant	1	2.4%
Sales Assistant	1	2.4%
Athlete	1	2.4%
Taxi Driver	1	2.4%
Textile Operator	1	2.4%
Cleaner	1	2.4%
Unknown	26	63.4%

4. Results

Table-**2**

	Min-Max.	Median	Avg..±ss/n-%
Total Sperm Count (mln)			
Pre- Covid	17 - 350	66.0	107.5 ± 89.3
Post- Covid	2 - 290	48.0	71.3 ± 69.0
Pre-Covid/Post-Covid Change	-17 - 215	20.0	36.2 ± 50.3
Post Wash Sperm Count(mln)			
Pre- Covid	3 - 101	22.0	27.6 ± 22.6
Post- Covid	1 - 99	20.0	28.0 ± 23.8
Motility (%)			
Pre- Covid	3 - 50	40.0	36.8 ± 13.9
Post- Covid	2 - 50	40.0	37.9 ± 13.8
Progressive Motility (%)			
Pre- Covid	1 - 30	20.0	18.3 ± 8.4
Post- Covid	2 - 38	22.5	21.1 ± 9.7
Non Progressive Motility (%)			
Pre- Covid	2 - 30	20.0	19.6 ± 5.8
Post- Covid	6 - 30	18.0	17.8 ± 5.9
Immotile (%)			
Pre- Covid	50 - 90	60.0	61.5 ± 12.0
Post- Covid	50 - 90	60.0	61.5 ± 13.1

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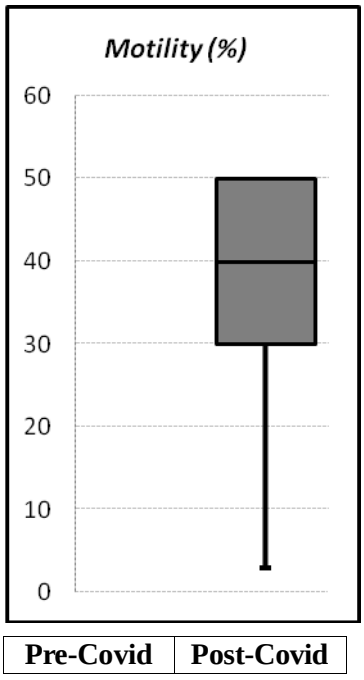
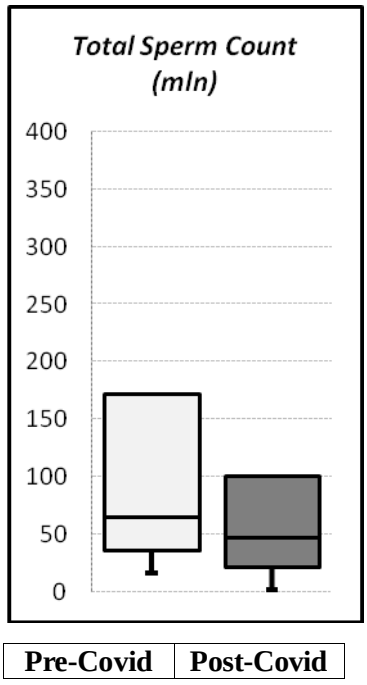
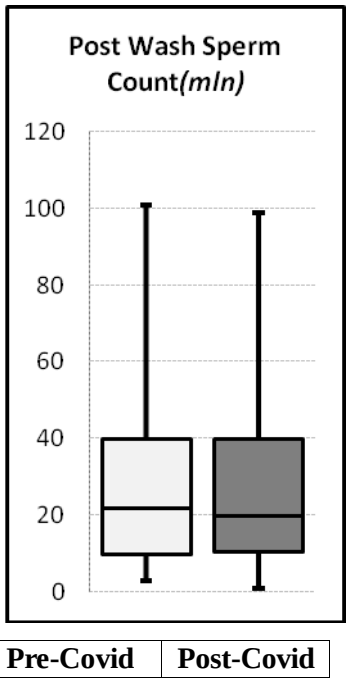
Table-3

	Pre-Covid		Post-Covid		P
	Avg.±ss	Median	Avg.±ss	Median	
Total Sperm Count (mln)	107.5 ± 89.3	66.0	71.3 ± 69.0	48.0	**0.000** [w]
Post Wash Sperm Count(mln)	27.6 ± 22.6	22.0	28.0 ± 23.8	20.0	0.518 [w]
Motility (%)	36.8 ± 13.9	40.0	37.9 ± 13.8	40.0	0.524 [w]
Progressive Motility (%)	18.3 ± 8.4	20.0	21.1 ± 9.7	22.5	0.053 [w]
Non Progressive Motility (%)	19.6 ± 5.8	20.0	17.8 ± 5.9	18.0	0.073 [w]
Immotile (%)	61.5 ± 12.0	60.0	61.5 ± 13.1	60.0	1.000 [w]

[w] Wilcox on test







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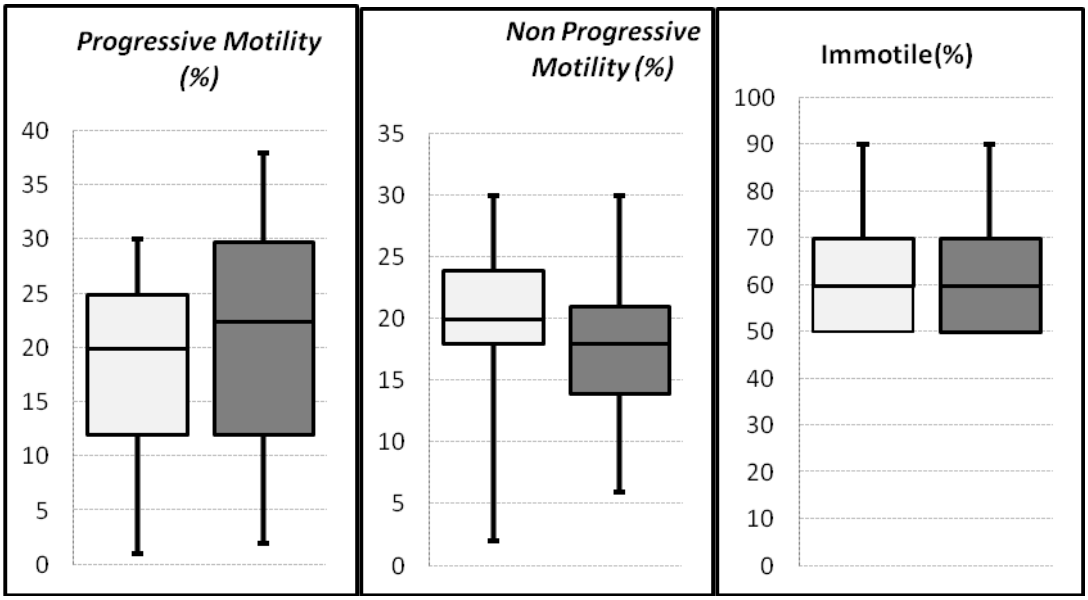

Pre-Covid	Post-Covid

Pre-Covid	Post-Covid

Pre-Covid	Post-Covid

The average age of the patients is 32.8, the rate of smokers is 34.1%, and the job of 63.4% is unknown (Table 1). "Total Sperm Count (mln)" after Covid showed a significant ($p < 0.05$) decrease compared to pre-Covid. "Post Wash Sperm Count (mln)" did not differ significantly between pre-Covid and post-Covid groups. "Motility (%) rate" did not differ significantly between pre-Covid and post-Covid groups. The "Progressive Motility (%) rate" did not differ significantly between the pre-Covid and post-Covid groups. "Non Progressive Motility (%) rate" did not differ significantly between pre-Covid and post-Covid groups. "İmmotile (%) rate" did not differ significantly between pre-covid and post-covid groups. (Table-3)

5. Discussion

There are studies on the effects of COVID-19 disease on male reproductive health, sperm characteristics and testicular tissue. SARS CoV-2 virus uses 'Angiotensin Converting Enzyme-2' (ACE-2) as a depot to enter human cells. ACE2, Angiotensin 1-7 and Macrophage Activation System (MAS) recipients were found in the scans, as well as in testicles, especially in Leydig and Sertoli cells. The first hypothesis is that virus collection may lead to changes in testis parts. A second threat is that virus binding to the ACE-2 receptor can cause excess ACE-2, leading to a typical inflammatory response (3,4). Another study supporting this study showed significant seminiferous tubular damage, decreased Leydig cells, and mild lymphocytic inflammation in testes from patients who died from COVID-19 (5). In the seminiferous tubule, there are sperm precursor cells at all stages of spermatogenesis (6). Therefore, in our study, we aimed to reveal the effects of COVID-19 disease on male fertility by comparing the parameters of the spermiogram samples before and 6 months after the COVID-19 disease of the patients who gave semen analysis (Spermiogram sample) for the examination of sperm samples in terms of number, motility and morphology, since it is known that COVID-19 disease causes damage to the

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seminiferous tubules. In our study, Spermiogram samples given by 41 male patients between the ages of 21-41 who do not have any disease, do not regularly use drugs, and do not receive infertility treatment were examined before the COVID-19 disease and 6 months after the COVID-19 disease, and a significant decrease was observed in the total sperm count.

In the meta-analysis study done by Klepinowski et al. (2023), it was aimed whether SARS-CoV-2 affects sperm or not, and 24 studies in which spermiograms of male patients infected with SARS-CoV-2 were evaluated. Foundings were a decrease in sperm motility, no significant change is observed in sperm motility (10). In our study, similarly there was a decrease in the number of sperm checked after 6 months of COVID-19. There was no significant difference in sperm motility.

In the study done by Stigliani et al. (2023), spermiogram samples taken before and at least 3 months after the COVID-19 disease were compared, and there was no significant difference in the parameters such as total sperm count, sperm volume, sperm concentration, and progressively motile sperm count (11). In our study, contrary to this study, Covid 19 There was a decrease in the number of sperm checked after 6 months of exposure.

In the study done by Mohammed et al. (2023) compared the spermiograms of mild to moderate COVID-19 patients during and after infection, and found that 33% had abnormal semen analysis during the infection period, and this rate decreased to 11% during the recovery period. When compared with the post-infection spermiogram, positive results were obtained in the total sperm count, sperm volume, sperm concentration, and progressively motile sperm count, and in this study, it is seen that the deterioration in spermatogenesis due to COVID-19 disease is reversible (12). In our study, no change was detected in the morphology of spermatogenesis.

In the study done by Balci et al. (2023), when spermiograms taken before and 6 months after COVID-19 disease were compared, there was no significant change in sperm volume and number of progressively motile sperm, and it was observed that there was a decrease in sperm concentration, and an increase in the rate of abnormalities such as oligospermia and asthenospermia (13). In our study, only a decrease in sperm count was found.

In the study done by Paoli et al. (2023), when spermiogram samples taken before and 3 months after COVID-19 disease were compared, no significant difference was found in sperm volume and the number of progressively motile sperm (14). In our study, it was examined 6 months after suffering from COVID-19 disease and low sperm count was found

In the study done by Al-Alami et al. (2022), spermiogram samples of groups infected and not infected with COVID-19 virus were compared, and no significant difference was observed in terms of sperm volume, sperm concentration, progressive motility, and normal morphology. The study shows that COVID-19 virus does not affect semen fluid parameters (15). In our study, only sperm samples were examined before and 6 months after the disease with COVID-19 disease.

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In the study done by Dipankar et al. (2022), spermiogram samples taken during COVID-19 disease and 74 days later were compared and it was seen that COVID-19 negatively affected semen parameters, including sperm DNA fragmentation index. In our study, sperm samples were examined before and 6 months after COVID-19 disease (16). Contrary to this study, in our study it was seen that sperm parameters remained not affected.

In the study done by Kumar et al. (2022), the spermiogram samples given by male patients before the COVID-19 pandemic are compared with those given during the COVID-19 pandemic, the overall spermiogram results, except for morphology, are seen more positively during the COVID-19 pandemic period (17). In our study, sperm samples were examined before and 6 months after COVID-19 disease.

In the study done by Ertaş et al. (2022), two groups were formed, patients with COVID-19 and the healthy group, and spermiogram samples, testicular size and density, serum total testosterone, FSH, LH, anti-mullerian hormone and Inhibin-B tests were analyzed. When spermiogram samples are compared, sperm count per 1 cc and total motility rate were higher in the healthy group. In the study, it was seen that COVID-19 disrupts sperm parameters, and this study, the collection of data shows that the cause of this deterioration may be cellular changes in the testis, therefore this raises doubts that the effects of COVID-19 on male fertility may be permanent (18). In our study, only the sperm samples of the groups with COVID-19 disease were examined before and 6 months after the disease. Contrary to this study, it was seen that sperm parameters were not affected in our study.

In the study done by Aksak et al. (2022), spermiogram samples of male patients who had COVID-19 and recovered, and male patients who have never had COVID-19 were compared, the sperm concentration of the group that had never had COVID-19 was found to be higher, and there was no significant difference between the groups in terms of sperm motility and morphology (19). In our study, the sperm samples of the groups that had COVID-19 disease were examined before and 6 months after the disease.

In the meta-analysis study done by Wang et al. (2022), the effect of Covid-19 on male fertility was investigated, and as a result of the compared spermiogram samples taken 90 days after the disease, the total sperm count, sperm concentration, and total sperm motility found decreased, however, the sperm volume, motile and immobile in situ were remained same. It was seen that there is no significant change in sperm count and morphology (20). In our study, the sperm samples of the groups that had COVID-19 disease were examined before and 6 months after the disease. Contrary to this study, a decrease was found in the number of sperm examined 6 months after they had COVID-19 disease. There was no difference in total sperm motility.

In the study done by Enikeev et al. (2022), it was aimed to examine the testicular function of the SARS-CoV-2 virus, the extent of its effect on spermatogenesis and the damage to the testicular tissue, the healthy group and the group with COVID-19 were compared. It was seen that sperm motility decreases and the number of immobile sperm increases in COVID-19 patients compared to the healthy group. When the spermiogram samples taken from the covid-19 group 3 months

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after discharge are compared with the spermiogram samples taken during the COVID-19 period, it is seen that all parameters returned to normal (21). In our study, the pre-disease and 6 months post-disease sperm samples of the groups that had COVID-19 disease were examined. Contrary to this study, a decrease was found in the sperm count 6 months after the Covid 19 disease. There was no difference in total sperm motility.

In the study done by Klepinowska et al. (2022), when spermiogram samples of two different groups exposed and not exposed to the COVID-19 virus were compared, it was seen that sperm concentration and total sperm count decreased significantly. However, it was seen that the spermiogram samples of the same group after exposure were not included in the study, and due to the limited information of the current research, it was seen as a result of the study that longer follow-up is required to see the delayed or progressive effect (22). In our study, the sperm samples of the groups that had COVID-19 disease were examined before and 6 months after the disease. As in our study, a decrease in the sperm count of the group with COVID-19 disease was detected.

In the meta-analysis study doen by Xie et al. (2022), 12 studies were included in the meta-analysis, and it was seen that sperm volume, sperm concentration, total sperm count and advanced motile sperm count are adversely affected by COVID-19 infection. However, no significant difference was found in the number of motile sperm in situ (23). In our study, the sperm samples of the groups that had COVID-19 disease were examined before and 6 months after the disease. Contrary to this study, a decrease was found in the number of sperm examined 6 months after they had COVID-19 disease. There was no difference in total sperm motility.

In the study done by Hamarat et al. (2022), spermiogram samples of male patients before and after SARS-CoV-2 infection were compared and a significant decrease was observed in the mean sperm concentration, total sperm count and the average percentage of samples with normal morphology (24). In our study, the pre-disease and 6 months post-disease sperm samples of the groups that had COVID-19 disease were examined. Contrary to this study, a decrease was found in the sperm count 6 months after the COVID-19 disease. There was no difference in total sperm motility.

In the study done by Hu et al. (2022), the spermiogram samples of the group who had COVID-19 and the spermiogram samples taken after the recovery of the same group and the spermiogram samples of the male patients in the control group were compared, and there was no significant difference in semen parameters between the recovered male patients and the controls. In addition, the changes in the recovery period and sperm count were investigated. It was observed that the total sperm count was significantly lower in the spermiogram samples taken less than 5 months after contracting COVID-19, compared to the controls, and spermiogram samples taken 5 months and later after COVID-19 were found to be better with the control group. There was no significant difference when compared. While the sperm quality of the patients who recovered from the disease showed an improvement after a period of approximately 6 months, it was seen that an increase was observed in the total sperm count after a period of

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approximately 5 months after COVID-19 (25). In our study, the pre-disease and 6 months post-disease sperm samples of the groups that had COVID-19 disease were examined. Contrary to this study, a decrease was found in the number of sperm examined 6 months after suffering from COVID-19 disease.

In the study done by Guo et al. (2021), the spermiogram samples of the control group who did not have COVID-19, and those who had COVID-19, taken an average of 29 days and 56 days after the infection. When spermiogram samples taken after an average of 29 days were compared, a significant decrease was observed in the total sperm count, sperm concentration, and percentage of motile and forward motile sperm in the patients who had COVID-19, but it was seen that sperm viability and morphology were not affected. When spermiogram samples taken an average of 56 days after contracting COVID-19 are compared with spermiogram samples taken an average of 29 days, it was seen that the total sperm count, sperm concentration and percentage of motile sperm had increased and the percentage of morphologically abnormal sperm had decreased. The findings in this study appear to indicate that COVID-19 has a negative but reversible effect on sperm quality (26). In our study, the pre-disease and 6-month post-disease sperm samples of the groups with COVID-19 disease were examined. A decrease was observed in the number of sperm examined 6 months after suffering from COVID-19 disease. There was no change in the percentage of motile sperm.

In the study done by Erbay et al. (2021), when spermiogram samples taken from male patients before and at least 3 months after COVID-19 were compared, it was found that the number of progressively motile and motile sperm decreased in the mild symptomatic group, and a significant decrease was observed in all sperm parameters, including sperm volume, in the moderately symptomatic group. In this study, although the effect of fever on semen parameters was examined, it was seen that sperm motility and viability decrease in COVID-19. It was seen that the presence of fever during the COVID-19 period does not contribute to this result (27). In our study, the pre-disease and 6-month post-disease sperm samples of the groups with COVID-19 disease were examined. A decrease was observed in the number of sperm examined 6 months after suffering from COVID-19 disease. There was no change in the percentage of motile sperm.

6. Conclusion and Recommendations

In our study, it was observed that the Covid19 virus adversely affected the total sperm count in men. Considering that fertility may be affected in men with Covid-19 infection, treatment planning and timing can be adjusted. However, there are not enough studies in the literature. Therefore, studies on the long-term effects of the Covid-19 virus on male fertility with larger groups are needed.

Resources

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