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Investigation of the relationship between COVID-19 disease and semen parameters in idiopathic male infertility patients

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Abstract. – OBJECTIVE: Recent studies have shown that there may be a deterioration in sperm parameters in patients who had recovered from COVID-19 disease. We aimed to investigate the relationship between COVID-19 disease and semen parameters in idiopathic male infertility patients.

PATIENTS AND METHODS: The study was conducted among male patients who applied with infertility between June 2021 and February 2022 following the approval of the Ethics Committee. Idiopathic infertility patients who could give semen analysis were included in the study. Detailed medical history of all patients was obtained. The presence of detectable causes of infertility was defined as exclusion criteria. The patients who had COVID-19 disease history (Reverse Transcriptase-PCR or Computed Tomography findings) in the last year were divided into two groups COVID-19 (+) and COVID-19 (-). The semen samples obtained from patients after a 3 day sexual abstinence in accordance with the WHO 2021 criteria were recorded.

RESULTS: A total of 42 male idiopathic infertility patients who met the criteria were included in the study. It was analyzed that both groups were similar in terms of sociodemographic characteristics, comorbidities, and habits ($p>0.05$). It was determined that 40.4% (n=17) had COVID-19 disease. The mean duration time after COVID-19 was 9.6 (4-17) months. Mean sperm concentration was found to be statistically significantly lower than the COVID-19 (-) group (41.59±17.4 *vs.* 58.8±21.9; $p=0.021$). Semen volume (3.05±0.7 *vs.* 3.32±0.6 mL; $p>0.05$), progressive sperm motility (34.05±20.96 vs. 43.00±16.94; $p=0.12$) and normal sperm morphology (3.47±1.42 *vs.* 3.08±1.41; $p=0.41$) were similar in both groups. The mean sperm concentration of the patients who recovered in the last 6 months (25.37±9.07 vs. 56.03±29.67 million/ml; $p=0.013$) compared to patients with >6 months after recovery (n=9) was found to be significantly lower.

CONCLUSIONS: The COVID-19 disease can cause a significant decrease in sperm concentration in idiopathic infertility patients, especially in the first 6 months, and the rates of oligospermia and asthenospermia are higher.

Key Words:
COVID-19, Idiopathic male infertility, Semen parameters.

Introduction

The coronavirus disease (COVID-19), which was first detected in the Wuhan province of China in December 2019, spread rapidly all over the world and was defined as severe acute respiratory syndrome (SARS-CoV-2)[1]. The COVID-19 virus has been found to infect human cells by binding to Angiotensin Converting Enzyme (ACE-2) receptors *via* spike glycoprotein[1].

Renin-Angiotensin-Aldosterone system (RAAS) is a staggered hormonal system that regulates arterial pressure and fluid balance for homeostatic control in the body. ACE-2 receptors play an important role in the cycle of the RAAS[2]. The SARS-CoV-2 virus attaches to the cell *via* the ACE-2 receptor and the Transmembrane serine protease 2 (TMPRSS-2) enzyme and initiates infection[3]. In the male genital tract, RAAS is known to be present in the testicle, epididymis and prostate gland. It has a regulatory role in regulating steroidogenesis, sperm contractility, spermatogenesis, and testosterone production in the testicles and epididymis[4,5].

A meta-analysis showed that patients who had COVID-19 disease and recovered may have worsened sperm parameters compared to those who did not have the disease. This meta-analysis showed that semen volume, sperm concentration, total sperm count, and the progressive motility rates were lower than healthy volunteers after COVID-19 infection[6].

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In this study, we aimed to investigate the effect of COVID-19 disease on semen parameters in idiopathic infertility patients.

Patients and Methods

This study was conducted among male patients who applied with infertility between June 2021 and February 2022, following the approval of the Ethics Committee. Idiopathic infertility patients who could give semen analysis were included in the study. Detailed medical history of all patients was obtained. Age, sociodemographic characteristics, additional diseases, habits, previous operation histories of the patients were recorded. Urogenital examination and anamnesis were performed and the presence of primary/secondary infertility, previous scrotal or inguinal surgeries, previous medical or surgical treatments due to infertility or sexual dysfunction were recorded. Testicular size, localization, clinical varicocele presence/degree, presence of hydrocele or spermatocele, ductus deferens and epididymis examination findings were recorded as genital examination findings.

Men who were sexually active and wanted to have children but could not achieve fertility despite regular sexual intercourse without protection for at least 1 year were included in the study. Patients who could not/did not want to give samples for semen analysis, those with a history of hormonal/antioxidant supportive drugs use that may affect spermatogenesis, those with clinical varicocele, those with azoospermia, chromosomal abnormalities (such as karyotype or Y chromosome microdeletion syndromes), those with hyper/hypogonadotropic hypogonadism, those with a history of pelvic radiotherapy, those with a history of testicular surgery (undescended testicle, hydrocele, testicular torsion, testicular tumor), presence of detectable causes of infertility and receiving steroid therapy for the treatment of COVID-19 were also excluded from the study, considering that they may affect spermatogenesis.

Semen samples obtained from patients by masturbation after a 3-day sexual abstinence period were manually examined under a microscope according to World Health Organization (WHO) 2021 criteria within 30 minutes after liquefaction at room temperature[7]. Semen analyses were evaluated by a single biologist in a single center to prevent individual differences that may occur during the evaluation.

It was questioned and recorded whether the patients had symptomatic or asymptomatic COVID-19 disease (Reverse Transcriptase-PCR or Computed Tomography findings) within the last year. Patients were divided into two groups as COVID-19 (+) and COVID-19 (-). The results of semen samples given by both groups after 3 days of sexual abstinence were recorded and included in the statistical analysis.

Statistical Analysis

The Statistical Package of Social Sciences for Windows Version 20 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. We divided patients into two groups based on the recovery from the COVID-19 infection. Categorical variables were presented as numbers and percentages and compared using the Chi-squared test. Continuous variables were presented as mean and standard deviations and compared using the independent sample *t*-test. Dependent variables were examined by paired samples *t*-test. Statistical significance was considered when the two-tailed value of $p<0.05$.

Results

Forty-two male idiopathic infertility patients who met the criteria were included in the study. The mean age of the patients was 31.9±5.4 years. It was analyzed that COVID-19 (+) and COVID-19 (-) groups were similar in terms of sociodemographic characteristics, comorbidities, and habits ($p>0.05$). The mean semen volume in all patients was 3.23±1.1 mL, mean sperm concentration was 51.83±36.04 million/mL, and the percentage of progressive motility was 39.4±17.2%. It was calculated that the mean normal sperm morphology was 3.2±1.2% (Table I).

The patients with COVID-19 (+) were the 40.4% (n=17) of all patients. It was seen that 58.8% (n=10) of those who had COVID-19 disease had experienced asymptomatic infection, 41.1% (n=7) were symptomatic, and 14.2% (n=1) of those who were symptomatic had a history of hospitalization. In the patient group recovered after COVID-19 infection, the average time until outpatient admission and semen analysis performed was 9.6 (4-17) months.

In terms of mean semen volume, there were similar results between both groups (3.05±0.7 mL *vs.* 3.32±0.6 mL) ($p>0.05$). Mean sperm con-

Table I. Patients characteristics of the idiopathic male infertility.

Patient characteristics	No. (42)
Mean ± sd age, years	31.9 ± 5.4
No. COVID-19 (+) (%)	17 (40.4)
Asymptomatic	10 (58.8)
Symptomatic	7 (41)
Requiring hospitalization	1 (5.8)
No. COVID-19 (-) (%)	25 (59.6)
Body Mass Index (BMI) (kg/m^2)	26.8 ± 3.2
Duration of infertility (months)	23.4 ± 8.1
Mean ± sd semen volume (mL)	3.23 ± 1.1
Mean ± sd sperm concentration (million/mL)	51.83 ± 36.04
Mean ± sd progressive motility (%)	39.4 ± 17.2
Mean ± sd total motility (%)	45.8 ± 24.4
Mean ± sd normal sperm morphology (%)	3.2±1.2

centration in the COVID-19 (+) group was found to be statistically significantly lower than in the COVID-19 (-) group (41.59±17.4 *vs*. 58.8±21.9; p=0.021). Although the mean of the COVID-19 (+) group was lower in terms of the percentage of progressive sperm motility, there was no statistically significant difference between the two groups (34.05±20.96 *vs*. 43.00±16.94; p=0.12). In terms of the percentage of normal sperm morphology calculated according to Kruger there was no significant difference between the two groups (3.47±1.42 *vs*. 3.08±1.41; p=0.41) (Table II).

While eight patients who had COVID-19 (+) had recovered from the disease within the last 6 months, the mean sperm concentration of these patients (25.37±9.07 *vs*. 56.03±29.67 million/mL; p=0.013) was significantly lower than in patients who had >6 months after recovery (n=9). In addition, there was no significant difference between the sperm concentration averages of the COVID-19 (-) group and (56.03±29.67 *vs*. 58.8±21.9; p>0.05) the patient group who had a >6 months on the COVID-19 disease.

When the semen analysis results of both groups were compared, it was found that the rate of oligospermia was significantly higher in the COVID-19 (+) group (29% *vs*. 4.5%; p=0.03). Although the rate of asthenospermia was higher in the COVID-19 (+) group (45.4% *vs*. 17.2%; p=0.06), there was no statistically significant difference. In terms of teratospermia rate (40% *vs*. 17%; p=0.11), there was no significant difference between both groups (Table II).

Discussion

Infertility is generally defined as not being able to get pregnant after 1 year of unprotected sex. Infertility is a condition seen in approximately 10% of couples. Idiopathic infertility is seen in

Table II. Comparison of the COVID 19 (+) and COVID (-) groups according to semen analysis.

	Covid (+) Group (n = 17)	Covid (-) Group (n = 25)	p
Mean ± sd age, years	31.1 ± 5.9	33.5 ± 4.2	> 0.05
Body Mass Index (BMI) (kg/m^2)	26.1 ± 2.5	28.1 ± 3.2	> 0.05
Smoker, n (%)	6 (35.2%)	9 (33.3%)	> 0.05
Duration time between COVID-19 and semen analysis, months	8.9 ± 2.5	9.8 ± 4.2	> 0.05
Duration of infertility, months	20.4 ± 9.8	22 ± 10.4	> 0.05
Semen volume, mL	3.05 ± 0.7	3.32 ± 0.6	> 0.05
Sperm concentration, mil/mL	41.59 ± 17.4	58.8 ± 21.9	0.021
Progressive motility, (%)	34.05 ± 20.96	43.00 ± 16.94	0.012
Normal sperm morphology, (%)	3.47 ± 1.42	3.08 ± 1.41	0.41
Oligospermia rate n, (%)	5 (29)	1 (4.5)	0.03
Asthenospermia rate n, (%)	8 (45.4)	3 (17.2)	0.06
Teratospermia rate n, (%)	7 (40)	3 (17.2)	0.11

approximately 25% of the infertility patient population and no reason can be found to explain the abnormal semen analysis present in the patient[8]. Although idiopathic infertility is a disease whose etiology has not been elucidated, the existence of a multifactorial pathology including the presence of genetic, environmental and hormonal parameters and especially oxidative stress and DNA fragmentation are held responsible[9,10].

The COVID-19 virus has affected the whole world and caused a global pandemic. SARS CoV-2 has been described as a respiratory-transmitted RNA virus whose main pathology causes pneumonia *via* alveolar ACE-2 receptors[1]. It has been shown[1,4] to use viral spike protein (Protein S) and ACE-2 receptors for cell entry. Protein S is prepared by TRMPSS-2. ACE-2 and TMPRSS-2 are the two main host molecules identified for the infectivity of SARS-CoV-2, but other possible actors are being studied. Because ACE-2 is expressed in the testis and seminal vesicles, and TMPRSS-2 can be detected in the prostate gland, testicles, and epididymis, these are potential targets of SARS-CoV-2, suggesting that COVID-19 may have an impact on men's fertility[11].

In this study, we investigated the existence of the negative effect of COVID-19 disease on infertility. For this purpose, semen analysis of those who had COVID-19 disease in idiopathic infertility patients and those who had not had the disease were compared. To the best of our knowledge, this is the first study to investigate the history of COVID-19 in the infertile population. Although it is thought that the testicles will be protected from the direct effects of viruses by the blood-testicular barrier, about 30 viruses have been isolated from testicular tissue so far[12]. Apart from the direct effect of the virus on the testicular tissue, it is thought that it may also affect spermatogenesis by affecting fever, inflammation, and the hypothalamic-pituitary-gonadal axis. Since the spermatogenetic cycle lasts 74 days, it is thought that the effects of SARS CoV-2 virus may last for 74 days, and these effects will disappear in the long term[13]. In addition, 19% of COVID-19 (+) patients were shown to have scrotal problems and edema, inflammatory leaks and various degrees of spermatogenic cell reduction and injury in the testicles, suggesting the possibility of having orchitis in the autopsy reports[14-16]. The accepted evidence in the literature is that the virus cannot be isolated in semen. The current idea about the pathophysiology of this virus, which cannot be isolated in semen causing damage to the testicle, is that the inflammatory cytokines produced as a result of the immune response generated by the virus may disrupt the blood testicular barrier and cause disruption of spermatogenesis[17]. As in most infectious diseases, the inflammatory process caused by fever is thought to cause germ cell damage by leukocyte infiltration and to decrease testosterone levels by causing Leydig cell dysfunction[16].

Tiwari et al[6] reported that COVID-19 disease had a negative effect on semen volume (-0.2 mL), sperm concentration (-16.59 million/mL), total sperm count (-45.44 million), and progressive motility percentage (-1.73%) in the early period after disease. Guo et al[18] performed semen analysis twice in 41 patients after they had COVID-19 disease. The first semen analysis was performed, on average, 76 days after the onset of symptoms. It was stated that there was an average of 29 days between the second semen analysis and the first. They reported that there was a significant increase in sperm concentration (p=0.0066), total sperm count (p=0.0029), and total motile sperm count (p=0.0391) in the second semen analysis results compared to the mean of the first semen analysis[18]. In our study, we found lower sperm concentration in the group that had the disease (41.72±17.4 *vs*. 58.7±21.9 million/mL; p=0.021) in the semen analysis which performed an average of 9.6 (4-17) months after the COVID-19 disease. When considering the previous studies, there is no study examining sperm parameters before and after COVID-19 transmission.

In a study comparing the results of long-term semen analysis after COVID-19 disease, Hu et al[19] reported that while semen parameters worsened in the first 6 months after COVID-19, there were improvements in total sperm count after the 150th day[19]. In previous studies[18-20], they stated that the sperm count was significantly lower in those who had a longer recovery time (>90 days) than sperm parameters in the first 90 days after the disease. In our study, after recovery from the disease, the mean elapsed time was calculated as 9.6 (4-17) months. The mean sperm concentration of patients with in the first 6 months after recovery (n=8), (25.37±9.07 *vs*. 56.03±29.67 million/mL; p=0.013) was found to be significantly lower than the patients with >6 months after recovery (n=9). We also calculated the sperm concentration averages between the sperm concentration of the COVID-19 (-) group and the >6 months patient group (56.03±29.67 *vs*. 58.8±21.9; p>0.05) similarly.

In the studies[18-20] conducted with semen analysis after COVID-19 disease recovery, no information was given about the fertility of men. Our study differs from other studies in that it was conducted in the population presenting with infertility, which suggests that COVID-19 may have negative effects, especially in a multifactorial situation such as idiopathic infertility. We found that men with SARS-CoV-2 disease had lower sperm concentrations, but when differentiated according to the time elapsed after the disease, patients with more than 6 months were similar to COVID-19 (-) similar to the literature.

Limitations

The limitations of our study are that there is no semen analysis taken before and after the disease and it is evaluated by single semen analysis. Another is that the number of patients present in the infertility population cannot be analyzed in subgroups according to the severity of the disease - mild, moderate and serious groups - sperm parameters.

Conclusions

The results of limited and low-evidence studies in the literature and this study suggest that male fertility may be adversely affected by COVİD-19. It can be said that COVİD-19 infection can cause a significant decrease in sperm concentration in idiopathic infertility patients, especially in the first 6 months, and the rates of oligospermia and asthenospermia are higher. The short and long-term effects of SARS-CoV-2 virus in the infertility population, its responses to infertility treatment and its effects on the success of assisted reproductive techniques should be investigated in prospective studies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved as document number 79 by the Ethic Committee of Gaziosmanpasa Education and Research Hospital.

Informed Consent

Written informed consent form was provided from all patients.

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Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author, (MBCB), upon reasonable request.

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