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Orgınal Article

The Effect of the SARS-CoV-19 Virus on Sperm Parameters of Patients with Male Infertility

Erkek İnfertilitesi Olan Hastalarda SARS-CoV-2 Virüsünün Sperm Parametreleri Üzerine Etkisi

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Highlights

- Investigate the effects of COVID-19 disease in spermiogram parameters in male infertilitiy.
- SARS-CoV-2 virus can affect male fertility by resulting in deterioration of sperm volume, pH and morphology

Abstract

Background: Although Coronavirus Disease 2019 mainly affects the pulmonary system, the related studies on male reproductive health are limited. We aimed to investigate the effect of COVID-19 disease in spermiogram parameters of patients with male infertility.

Material and Methods: 39 outpatients with male infertility diagnosed with COVID-19 disease between 1st March 2020 and 31st March 2022 in our andrology policlinic were analysed, retropspectively. We evaluated the demographic data of the patients and the spermiogram analyzes before and after the COVID-19 disease.**Results:** The mean age of the patients were 33,44±7,52 years and body mass index (BMI) was 27,05±3,38 kg/m^2. The mean time between PCR test and second semen analysis was 3,95±3,59 months. There were statistically significant reduction in semen volüme ($p<0,03$) and significant deterioration in sperm morphology ($p<0,014$), but no detect alteration on sperm motility.

Conclusion: We observed adversly effects of SARS-CoV-2 virus on spermiogram parameters in patients with male infertility. Deterioration of spermiogram after COVID-19 disease may results with male infertility.

Keywords: Semen, COVID-19, Male infertiliy, SARS-CoV-2, Spermatogenesis

ÖZ

Amaç: Koronavirus hastalığı 2019 (COVID-19) esas olarak pulmoner sistemi etkilemesine rağmen, erkek üreme sağlığı üzerine çalışmalar sınırlıdır. Bizim kliniğimize erkek infertilitesi ile başvuran hastalarda COVID-19 hastalığının (virusunun) sperm parametrelerine etkisini araştırmayı amaçladık.

Gereç ve Yöntem: Bizim androloji kliniğimize 1 Mart 2020 ve 31 Mart 2022 tarihleri arasında başvuran ve daha öncesinde COVID-19 hastalığı tanısı almış 39 erkek infertilite hastası retrospektif olarak analiz edildi. Hastaların demografik verileri, COVID-19 hastalığı öncesi ve sonrası spermiogramları değerlendirildi. Bu verileri kaydettik ve istatistiksel olarak karşılaştırdık.**Bulgular:** Hastaların ortalama yaşı 33,44±7,52 yıl ve vücut kitle indeksi (BMI) 27,05±3,38 kg/m^2 olarak saptandı. PCR testi ile ikinci semen analizi arasındaki ortalama süre 3,95±3,59 ay olarak ölçüldü. Semen morfolojinde($p< 0,014$) önemli bozulma ve semen volümünde ($p<0,03$) önemli azalma istatiksel olarak gözlememize rağmen sperm motilitesi açısından anlamlı farklılık saptanmadı.

Sonuç: Erkek infertilite hastalarında spermiogram parametreleri üzerine SARS-CoV-2 virüsünün olumsuz etkisi olduğunu gözlemledik. COVID-19 hastalığından sonra spermiogramdaki bozulma erkek infertilitesi ile sonuçlanabilir.

Anahtar Kelimeler: Semen, COVID-19, Erkek infertilitesi, SARS-CoV-2, Spermatogenez

Introductıon

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and also known as corona virus disease 2019 (COVID-19) is a single strained RNA viruses belong to the coronaviridae family (1) Since it was first seen in Wuhan, China to the July of 2022, ıt has been reported resulting more than 6.5 million deaths and 623 million cases in the World (2). Recently, with increasing knowledge, COVID-19 has been defined as a systemic disease that most commonly affects the lungs, but can also affect more than one organ (3,4). SARS-CoV-2 uses the angiotensin-converting enzyme II receptor (ACE2) to enter the host cell similar to SARS-CoV. Angiotensin converting enzyme 2 (ACE2) is not just an enzyme, but a functional receptor highly expressed in heart, kidney, and lung cells. However, studies have shown that ACE2 receptors are abundantly expressed in spermatogonia, Leydig and Sertoli cells in testis (5,6). Another study showed that COVID-19 disease affect men 2.5 times more than women, and may cause changes in testoterone levels (7). Therefore, the human testis is a potential target for SARS-CoV-2 infection. The virus can directly damage the organs, as well as it may cause organ failure with systemic effects. In many studies on male infertility, it has been reported that COVID-19 disease may have unfavorable influence on semen parameters (8–12). Although the long-term effects of SARS-CoV-2 on male reproductive health are not known, it is inevitable that it will be an important health problem for humanity (13). There are limited studies on the effects of COVID-19 disease in spermiogram parameters in the literature. Therefore, we aimed to investigate effects of COVID-19 disease on spermiogram parameters in patients who applied our clinic with male infertility.

Materials and Methods

The data of the study were recorded after the ethics committee approval was obtained from the local Non-Interventional Clinical Research Ethics Committee (Decision No: 2022/35, date: 23.02.2022). We designed a single-center, retrospective, cohort study between March 2020 and March 2022. After detailed history and physical examination of patients, sexually active male patients between the ages of 18-50 who diagnosed COVID-19 disease with nasopharyngeal or oropharyngeal swab test and have spermiogram analyses before the diagnosis of COVID-19 disease were included in the study. Second spermiogram tests were performed after COVID-19 disease recovered. Patients' age, body mass index (BMI), semen analysis, and the times between COVID-19 infection and second semen analysis were recorded. Patients younger than 18 years old, older than 50 years old, using medication affecting spermatogenesis, diagnosed with endocrinological disease affecting spermatogenesis, presence of genetic diseases, with gender disorders, history of varicocele or cryptorchidism operations, having only one sample and diagnosed azoospermia according to the spermiogram analyses were excluded from the study. After exclusison criteria, total 39 patients' data recorded and analysed.

Swab samples of all patients were studied by reverse transcription polymerase chain reaction (RT-PCR) method in the medical microbiology laboratory of our university.

Spermiogram analyses

All semen samples obtained by masturbation after at least 2-7 days of sexual abstinence were evaluated in the andrology laboratory of our faculty according to the World Health Organization (WHO) laboratory manual instructions. In the evaluation, first of all, after the semen sample reached the laboratory, it was placed on the shaker to ensure complete liquefaction at room temperature at a certain cycle. After full liquefaction, macroscopic and microscopic examinations were performed by experienced laboratory workers within 30-60 minutes. In macroscopic and microscopic examination, liquefaction, viscosity, color, volume, pH, sperm concentration (10^6/ml), motility (%), round cells and morphology (%) parameters were examined. For the evaluation of sperm concentration and motility, 8-10 µl semen sample was placed in the Makler counting chamber (Sefi Medical Instruments, Israel) and examined under a phase contrast microscope at 100x magnification. Then, diff-quick staining set (bes-quick) was used to evaluate sperm morphology. For evaluation, 200 cells at 1000 x magnification were examined under a phase contrast microscope (Plan Apo 100 x 1.45 Oil; Nikon, Japan). Spermatozoa were classified as having normal or abnormal morphological features according to WHO criteria (14).

Statistical Analyse

SPSS v23.0 statistical package programme was used for all statistical analyses (SPSS, Inc., Chicago, IL). Shapiro-Wilk test was used to evaluate the distrubition of variables. Descriptive statistic methods were evaluated with the mean±standart deviation and median±interquartile range. Student-t paired test was used to compare

the variables with normal distribution before and after the diagnosis of COVID-19 disease, and Wilcoxon signed-rank test was used for variables that did not show normal distribution. $p<0.05$ was considered as criterion for the statistical significance.

Results

Demographic characteristics were shown in Table 1. Mean age of the patients were 33,44±7,52 years and body mass index (BMI) was 27,05±3,38 kg/m^2. The mean time between PCR test and second semen analysis was 3,95±3,59 months. Semen parameters of the participants were summarized on table-2. We observed that sperm volume was decreased ($p<0,03$) and sperm morphology was impaired ($p<0,014$) after COVID-19 disease. Other main semen parameters such as pH and motility was not change after COVID-19 disease.

Table 1. Demografic characteristics of the patients

	Count	Mean	Sd
Age	39	34	7
BMI	39	27.12	3.56
Covid-19 Time(mounth)	39	3.95	3.59

BMI: Body Mass Index Sd: Standard Deviation

Table 2. Semen parameters characteristics of patients according to the spermiograme analyse

	Pre- COVID-19	**Post- COVID-19**	**P**
Semen volume, *mL (mean±Sd)*	4.09±1.91	3.63±1.63	0.030
Semen pH, *mean±Sd.*	7.58±0.37	7.36±0.63	0.049
Total sperm count, *million±Sd*	151.70±148.30	135.53±160.21	0.081
Total sperm motility, *(mean±Sd) %*	33.46±14.74	34.95±15.76	0.488
Progressive sperm motility (a+b), *(mean±Sd) %*	32.26±14.60	32.05±15.86	0.424
Non-progressive sperm motility (c+d), *(mean±Sd) %*	63.74±14.60	65.05±15.76	0.276
Morphologically normal forms, *(mean±Sd) %*	2.97±2.88	2.21±2.37	0.014

Sd: Standard Deviation

Discussion

Today, after the pandemic period, there is a little information about the impact of the SARS-CoV-2 virus on semen. There are limited studies on male infertility after COVID-19 disease. In this study, we observed that SARS-CoV-2 virus can affect male fertility by resulting in deterioration of sperm volume, pH and morphology. When the effects of the SARS-CoV-2 virus on semen parameters in men are examined, it is estimated that the direct effect of the infection and the social restrictions caused by the pandemic process have possible negative psychophysiological effects on male reproductive health (15) It has been shown that many viruses such as mumps virus, herpes simplex virus (HSV), human immunodeficiency virus (HIV), human papilloma virus (HPV), hepatitis B virus, hepatitis C virus and SARS CoV-2 virus adversely affect the male reproductive system and sperm quality (16–18). In studies examining the pathophysiology of viruses on testicles, It has been reported that the direct tissue damage of the virus, the inflammation and temperature increase that develop as a result of the immune response against the virus may damage the testicular tissue (19). We consider that virus may effect testicles by direct tissue damage or inflammation that may result with decreased semen volume and impaired sperm morphology in our study, as well. We could not detect virus directly on semen, because of the design of the study, but our results can support this theory indireclty.

It has been showed that the ACE2 receptor is a functional receptor for coronaviruses to enter the virus into the host and it is also commonly found in spermatogonia, sertoli and Leydig cells (20). Studies on infertile men found high levels of ACE2 receptors and it was stated that this could cause infertility through its activation (21). It has been shown that SARS-CoV-2 virus can be found in the semen of patients with COVID-19, as well as in

the male reproductive system through systemic and local inflammation (22). There is TMPRSS2, which can increase viral transmission through the ACE2 receptor in sperm cells. SARS-CoV-2 abolishes phosphoinocyte 3-kinase and protein kinase B by targeting spike protein at ACE2 receptor, reducing sperm viability by causing sperm apoptosis. In addition, it is thought that the decrease in sperm motility and count may be related to this pathway (23–25). Decreased sperm volume and deteriorated sperm morphology in our study also may be related with these pathways.

Although SARS-CoV-2 RNA was not detected in the semen of patients with acute stage and recovered COVID-19, it caused deterioration in sperm concentration, total sperm count, and total motility in moderately ill patients. It has been found to be associated with a disorder in semen parameters in those with severe disease (26). In another study using data collected from 41 men, a significant decrease was observed in sperm concentration, total sperm count and morphology of patients after COVID-19 infection (27). Erbay G. et al., in their study, divided the patients diagnosed with COVID-19 into mild and moderate severity, and examined the spermiogram tests performed before the disease and at the 3rd month after the disease. It was determined that progressive motile sperm, total motility and vitality were decreased in patients with mild disease. In those with moderate disease, deterioration was observed in all sperm parameters. They observed that there was no difference between the groups with and without fever in the disease (28). Although we could not separate the patients by the severity of the COVID-19 disease, we observed similar results in terms of sperm volume and morphology, but the sperm motility was not affected by the COVID-19 disease in our study.

This study also has some limitations. First, we could not compare the infertile men with healthy men. Deterioration on semen after SARS-CoV-2 virus infection may be different in healthy men. Second, we could not detect SARS-CoV-2 virus mRNA on spermiogram analyses. Detection of SARS-CoV-2 on semen analyse coud be more valuable in terms of the effect on fertility. Despite all this, we think that the results of our study contribute to the studies on the effects of SARS-CoV-2 virus on male infertility.

Conclusıons

Since the COVID-19 disease entered our daily practice with the pandemic, its effects on male reproductive health are not yet well-known. There is a limited number of studies on this subject, and both the literature and the study we conducted show that this disease adversely affects male reproductive health in the short term. Although our study showed negative effects in the short term, long-term follow-up and results of the effects of the disease on male reproductive health are needed.

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