

Original Article

## Safe Medication with Remdesivir for COVID-19 in Patients with Infertility

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### HIGHLIGHTS

- Remdesivir as the COVID-19 medication can have side effects on semen parameters in patients with confirmed infertility.
- Remdesivir has a statistically insignificant effect on semen parameters (sperm count, sperm motility, and sperm morphology).
- Although COVID-19 has negative consequences on semen parameters, Remdesivir can be considered a safe medication.

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### ABSTRACT

#### Introduction

SARS-CoV-2, also known as COVID-19, emerged in China in December 2019. SARS-CoV-2 viruses use angiotensin-converting enzyme 2 (ACE2) as a receptor to enter cells. Studies have indicated that SARS-CoV-2 has destructive impacts on spermatogenesis and semen parameters, including sperm count, sperm motility, and sperm morphology. In addition, there is a concern regarding the negative consequences of treatment of COVID-19 with Remdesivir on infertility status. We aimed to investigate the effects of Remdesivir and also COVID-19 on semen parameters in patients with confirmed infertility.

#### Methods

The present study included 90 patients aged between 23 to 51 years referring to our hospital between March 2021 and July 2022. All of the patients were diagnosed with primary or secondary infertility, which was confirmed by semen analysis, and also diagnosed with active COVID-19 by reverse transcription polymerase chain reaction (RT-PCR) tests. All patients underwent semen analysis four months after the recovery from COVID-19. Patients who had severe manifestations of COVID-19 received intravenous Remdesivir.

#### Results

The mean age of the study participants was 35.72±6.29 years. Twenty-one patients received Remdesivir for the treatment of COVID-19. The semen parameters, including sperm count, sperm motility, and sperm morphology, were analyzed before and after the development of COVID-19. Our analyses revealed a significant decrease in sperm count, sperm motility, and sperm morphology after the development of COVID-19 compared to the semen analysis results in the pre-disease period (P-value=0.000). We also showed that Remdesivir has a statistically insignificant effect on semen parameters with the P-value of 0.511, 0.408, and 0.940 for sperm count, sperm motility, and sperm morphology, respectively.

#### Conclusions

Although COVID-19 has negative consequences on semen parameters, Remdesivir can be considered a safe medication for the course of the disease.

**Keywords:** Infertility; SARS-CoV-2; COVID-19; Semen Analysis

## Introduction

Severe respiratory infections caused by coronaviruses were identified in 2002 for the first time following the severe acute respiratory syndrome (SARS) epidemic (1). Coronaviruses contain single-stranded RNA and belong to the Coronaviridae family. A new strain of coronaviruses causing SARS emerged in Wuhan, China, at the end of December 2019 called SARS-CoV-2 (2). The SARS-CoV-2 was named COVID-19 in March 2020 by World Health Organization (WHO) (3). COVID-19 has similarities to influenza flu in terms of affected organs, signs, and symptoms, varying from asymptomatic courses to pneumonia (4, 5). It has been reported that SARS-CoV-2 viruses use angiotensin-converting enzyme 2 (ACE2) as a receptor for entering cells (6). ACE2 is expressed dramatically in the lungs, making the lungs the mainly affected targets. Also, it has significantly high expression in other organs, including the kidney and small intestine. The damage to the kidney and also the cardiovascular system has a paramount role in the prognosis of this disease (7, 8). Previous studies have shown that Sertoli cells, Leydig cells, and Spermatogonia express high levels of ACE2 in their membranes (9). In addition, testosterone levels decrease in the patients affected by COVID-19 (10). Remdesivir (GS-5734) is an inhibitor of RNA polymerase, which is a promising therapeutic candidate for the treatment of COVID-19 (11). There have been concerns regarding the negative consequences of medication with Remdesivir on the infertility status of patients diagnosed with COVID-19. It has been reported that Remdesivir resulted in downward trends in sperm count and also sperm motility (12-14). To date, there are scarce available data regarding the potential impact of COVID-19 on spermatogenesis and also semen analysis disturbance. Also, there have not been trials evaluating the impact of treatment of COVID-19 with Remdesivir on semen parameters in patients with infertility. In the present study, we aimed to investigate the different aspects of semen analysis before and after developing COVID-19 and also evaluate the efficacy of intravenous Remdesivir therapy on the course of spermatogenesis in infertile patients for the first time.

## Methods

The ethics committee of the local clinical research of our institution approved performing the present study on the Tehran University of Medical Sciences Ethical Committee (IR.TUMS.MEDICINE.REC.1401.583). Patients referring to our hospital between March 2021 and July 2022 who had primary or secondary infertility, which was confirmed by semen analysis and also diagnosed with active COVID-19, were included in the study. The COVID-19 diagnosis was based on the positive results of reverse transcription polymerase chain reaction (RT-PCR) tests. RT-PCR tests were performed

using nasopharyngeal and also oropharyngeal swabs. All patients underwent semen analysis four months after the recovery from COVID-19. All laboratory semen analyzes were conducted in one center and by the same technician following WHO criteria. The age, weight, and smoking status of the patients were questioned. The morphology, count, and motility of the sperms were evaluated and compared before and after the development of COVID-19. The sperm count is defined as the number of sperm in one milliliter of semen. Normal sperm count is 20 million/ml in semen samples. Normal sperm morphology is a condition when four percent or more of the sperm are normal-shaped. Normal sperm motility is when at least 40% of sperm have progressive movement (15). Patients who had severe manifestations of COVID-19 received intravenous Remdesivir based on the decision of an infectious disease specialist. There was no applied treatment to the patients regarding COVID-19, and also sperm quality improvement by the main urologist physician during the period between the two semen analyses.

## Statistical analysis

All statistical analyses of the present study were performed using the Statistical Package for the Social Sciences (SPSS) statistical software, version 26 (IBM SPSS Inc., Chicago, IL). The degree of statistical significance was considered as a P-value below 0.05. Mean, standard deviation and data range were used to evaluate the baseline data of the study patients. The paired sample t-test was used for comparing the semen analyses before and after the development of COVID-19. Evaluation of the impact of treatment with Remdesivir on the results of semen analysis compared to patients who did not receive Remdesivir was performed using a one-way analysis of variance (ANOVA) test.

## Results

The study population included 90 men with confirmed infertility before the course of COVID-19. Age, weight,

**Table 1.** Baseline characteristics of the included participants

Characteristics	
Age (years)	35.72 ± 6.29 (23-51)
Weight (kg)	74.60 ± 6.23 (58-95)
Smokers, n (%)	35 (38.9)
Non-smokers n (%)	55 (61.1)
Remdesivir received, n (%)	21 (23.3)
Remdesivir did not receive, n (%)	69 (76.7)
Primary infertility, n (%)	51 (56.7)
Secondary infertility, n (%)	39 (43.3)

The results are shown as mean ± standard deviation + range, or number with a percent.

**Table 2.** Comparison of semen parameters before and after the development of COVID-19

Semen Parameters	Sperm Count	Sperm Motility	Sperm Morphology
<b>All patients</b>			
Before COVID-19	11.28 ± 6.59	16.07 ± 11.10	2.50 ± 1.59
After COVID-19	8.17 ± 5.78	10.34 ± 8.31	1.31 ± 1.53
P-value	0.000	0.000	0.000
<b>Patients received Remdesivir (n = 21)</b>			
Before COVID-19	12.04 ± 6.20	17.47 ± 10.56	2.57 ± 1.63
After COVID-19	8.90 ± 6.75	11.66 ± 9.17	1.33 ± 1.31
P-value	0.000	0.000	0.000
<b>Patients did not receive Remdesivir (n = 69)</b>			
Before COVID-19	11.05 ± 6.73	15.65 ± 11.30	2.47 ± 1.59
After COVID-19	7.95 ± 5.48	9.94 ± 8.06	1.30 ± 1.60
P value	0.000	0.000	0.000
<b>Remdesivir effect</b>			
P-value	0.511	0.408	0.940

The results are shown as mean ± Standard deviation.

smoking status, type of infertility, treatment status with Remdesivir, and semen analyses before and after the development of COVID-19, including sperm count, sperm motility, and sperm morphology, were registered for each participant. The baseline characteristics of the study participants are presented in Table 1. There was a significant decrease in sperm count, sperm motility, and sperm morphology after the development of COVID-19 when comparing all of the participants regarding the semen analysis results before COVID-19 (P-value=0.000) (Table 2). There was also a significant decrease in sperm count, sperm motility, and sperm morphology when considering the patients who received Remdesivir and patients with no Remdesivir treatment, separately, after the course of COVID-19 compared to pre-COVID-19 semen analysis results (P-value=0.000) (Table 2). There was a statistically insignificant difference when considering the efficacy of the treatment with Remdesivir on the post-COVID-19 semen analysis result with the P-value of 0.511, 0.408, and 0.940 for sperm count, sperm motility, and sperm morphology, respectively.

### Discussion

In the present study, we evaluated the impact of treatment of COVID-19 with Remdesivir on semen parameters in infertile patients for the first time. We also compared the semen analyses of the participants with confirmed primary or secondary infertility before COVID-19 and four months after diagnosis with COVID-19. The analyzed semen parameters yielded the number of sperms per milliliters, the percentage of precursor sperms with normal motility in

the semen, and the percentage of normal-shaped sperms. All of the analyzed semen parameters decreased greatly after the development of COVID-19 compared to the pre-disease period. We also assessed the possible efficacy of treatment with Remdesivir on semen parameters, which showed that Remdesivir has no impact on sperm parameters. Remdesivir is an adenosine nucleoside prodrug, and it's analog of adenosine triphosphate, which is an active metabolite produced by hydrolysis. It inhibits RNA polymerase, which is vital for RNA virus replication, including SARS-CoV-2. The efficacy of Remdesivir has been confirmed for COVID-19, especially in adult patients (16, 17). On the other hand, the inability of a couple to achieve a pregnancy after one year of regular sexual intercourse without any protection is defined as infertility. Infertility is a major health issue, with about 48.5 million couples affected worldwide. Fifty percent of cases are related to the male factor (18, 19). According to the report by Agarwal et al., (20), the global male infertility prevalence ranges between 2.5% to 12%. Also, it has been reported in another study that there is a strong association between delayed parenthood and also high socioeconomic status with male infertility (21). There have been multiple causes and risk factors regarding male infertility, including environmental risk factors, socio-demographic risk factors, behavioral/lifestyle risk factors, and biological/physiological causes (22). However, smoking, alcohol consumption, medications, obesity, testicular infections, testicle exposure to excessive heat, exposure to toxins in the environment, hormonal disorders, and trauma to the testicles are among some

important causes of male infertility (23, 24). Wang et al. , (25) were the first team to report the detection of SARS-CoV-2 in other parts of the body besides the respiratory tract, including blood and feces. Furthermore, Li et al., (26) demonstrated that SARS-CoV-2 was detected in the semen samples of some of their study participants. In addition, in a cohort study by Holtmann et al. (27), the same result has achieved. Also, they reported that SARS-CoV-2 was present only in moderate and not in mild COVID-19 infection. In the study by Li and colleagues (28), there were some valuable results regarding the correlation between COVID-19 and male spermatogenesis course. On the one hand, they showed that there was increased apoptotic cell concentration in epididymis and testicles in testicular autopsies of cadavers of patients who died of COVID-19. On the other hand, they demonstrated that in patients who survived and recovered from the disease, there were increased levels of interleukin-6, evidence of leukospermia, and also oligozoospermia. It can be concluded that the current manifestations of the patients, including increased cytokine levels and increased apoptotic cells, occurs in the background of orchitis. Also, they revealed that 39.3% of their patients had oligospermia. However, the data regarding the correlation between COVID-19 and oligospermia is scarce. In another article published by Gacci et al., (29), the trial was to determine the presence of the RNA of SARS-CoV-2 in semen, urine, and saliva in 48 men who were sexually active and also recovered from COVID-19. They also evaluated the effects of the disease on semen parameters. They reported that the genome of SARS-CoV-2 was detected in biological fluids. In addition, they observed azoospermia and oligozoospermia in some of their study participants and concluded that there was a correlation between the severity of the disease and azoospermia. As mentioned, our study confirms the results of the previously published papers with similar topics, although we evaluated the same group of patients with infertility both in the pre-disease condition and also in the post-COVID-19 period. We observed that COVID-19 significantly affects the spermatogenesis course and lowers the measured parameters of the semen in infertile men. However, Remdesivir had no effect on sperm parameters, indicating that it can be used in patients with infertility as a safe therapeutic option.

### Conclusions

In conclusion, our findings primarily indicate that Remdesivir has no negative consequence on semen parameters and, overall, on infertility status and can be utilized safely in patients diagnosed with infertility. Furthermore, we showed that COVID-19 plays a significant role in the course of spermatogenesis. It leads semen analysis parameters to decrease significantly after the development of the disease compared to the pre-

disease period. We reported that SARS-CoV-2 affects sperm count, progressive sperm motility, and the number of sperms with normal morphology, although, Remdesivir had no significant effect.

### Authors' contributions

All authors contributed equally.

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### Conflict of interest

All authors declare that there is no conflict of interest.

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### Ethics statement

The study was approved by the Tehran University of Medical Sciences' Ethical Committee (IR.TUMS.MEDICINE.REC.1401.583).

### Data availability

Data will be provided on request.

### Abbreviations

ACE2	Angiotensin-converting enzyme 2
RT-PCR	Reverse transcription polymerase chain reaction
SARS	Severe acute respiratory syndrome



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