

The influence of SARS-CoV-2 on semen parameters of infected infertile male in comparison with those that noninfected

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Abstract

Background: Coronavirus disease (COVID-19) is an infectious disease caused by SARS COV-2 that has spread globally, the virus can cause different pathological alterations in many organs, such as the lung, kidney, and testis. The study aimed to determine the effect of COVID-19 on the seminal fluid parameters of infected infertile males compared with those who are noninfected.

Methods: The study was performed in Al-Hussein Teaching Hospital during the period from September to November, 2021 and it involved 318 patients. The patients' info included age, address, and vaccination. The sperm count, activity, and morphology were detected using Computer-assisted semen analysis CASA (Microptic-Spain) according to the WHO manual.

Results: There were high significant differences between the infertile males who were infected with COVID-19 and those who were vaccinated ($X^2 = 12.509$, $p = 0.001$). A high significant relation ($p < 0.001$) was recorded between types of infection severity and volume of semen ($p < 0.001$) and nonprogress life sperm (C) ($p < 0.001$). While significant differences were shown in the moderate progression sperm (B) ($p = 0.012$), and morphology ($p = 0.02$), respectively. High significant differences were reported between the types of infection severity (count of the sperm, presence of pus, B, C and D), ($p < 0.001$), while a significant difference was shown between severity types in relation to A and morphology of the sperms ($p = 0.021$ and 0.015), respectively.

Conclusion: The severity of COVID-19 has a significant impact on infertility and sperm parameters, particularly progression and sperm morphology, despite the fact that these parameters are unrelated to vaccination.

KEYWORDS

COVID-19, inflammation, male fertility, semen, testis

1 | INTRODUCTION

COVID-19 infection usually starts with flu-like symptoms¹ and can be asymptomatic or may have a mild-to-severe course.² The infection is characterized by an increased inflammatory burden. Various inflammatory markers are reported to be related to COVID-19 disease.³ On the other hand, inflammation has a deleterious effect on semen.⁴ Thus, the effects of COVID-19 infection on semen quality are a subject worthy of investigation.

Coronavirus disease (COVID-19) is an infectious disease caused by SARS-CoV-2 that has spread globally since its discovery in December 2019 in Wuhan, China.⁵ COVID-19 infections range from asymptomatic infections to life-threatening ones that need intensive care and special medicine. The SARS-CoV-2 is a new type of coronavirus that causes disease in humans. The coronavirus causes severe acute respiratory syndrome (SARS-CoV, commonly known as SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV), both of which experienced outbreaks in 2003 and 2013.⁶

COVID-19 affects men in a manner that differs from that of women. But, the causes of this are unclear.⁷ COVID-19's various health issues offer an inherent danger to the reproductive system.⁸ It is critical to determine how the COVID-19 pandemic impacts male infertility.

The coronavirus can enter the testes because the virus's inflammatory reaction penetrates the blood–testes barrier. Furthermore, testicular immunological privilege and the presence of regulatory T cells in this area may facilitate viral persistence. The presence of an active virus in human sperm samples is far less certain. SARS-CoV-2 penetrates the host cells via attaching to angiotensin-converting enzyme II (ACE2) receptors on the membrane.⁹ As a result, organs with high ACE2 receptor concentrations are sensitive to SARS-CoV-2 infection.¹⁰ Previous study has demonstrated that ACE2 receptors are expressed in reproductive organs and have a role in sperm function and conception.^{7,10} ACE2 receptor expression was enhanced in testicular cells, such as Spermatogonia, Sertoli and Leydig cells, and prostate cells. In addition, there is a report of testicular pathological alterations in patients' testes, including germ cell destruction, thickening of the basement membrane of the seminiferous tubules, leucocyte infiltration, and a decrease in the quantity of spermatozoa in the tubules.¹⁰

Several research studies on the sperm characteristics of COVID-19 patients have been undertaken. These studies' findings showed that COVID-19 infection may have a deleterious influence on sperm parameters; however, it is unclear whether these effects are the consequence of COVID-19's systemic infection and cytokine storms or a direct effect of the viral infection on male reproductive systems. In addition to fever and inflammation, systemic involvement of the body may cause the hypothalamic–pituitary–gonadal (HPG) axis to deregulate hormone production, impacting sperm development. Furthermore, there is a connection between inflammation and oxidative stress, implying that one might induce the other.^{11–14}

In this cohort study, we discovered that SARS-CoV-2 may be found in the sperm of patients with COVID-19, and that SARS-CoV-2 can still be present in the sperm of recovered patients. SARS-CoV-2 might be transferred to the male reproductive tract due to weak blood–testes/deferens/epididymis barriers, particularly in the context of systemic local inflammation. Even though the virus cannot replicate in the male reproductive system, it may survive due to the special immunity of the testes.¹⁵

If SARS-CoV-2 may be transferred sexually, sexual transmission might be an essential aspect of transmission prevention, especially because SARS-CoV-2 has been discovered in recovered patients' sperm. Some patients may benefit from abstinence or condom usage as a prophylactic method. As a result, avoiding contact with the patient's saliva and blood may be insufficient, because SARS-CoV-2 survival in a recovered patient's sperm increases the probability of infection in others.

The goal of this study was to identify the effects of SARS-CoV-2 infection on male fertility in Iraqi men.

2 | METHODS

2.1 | Study design

The study was performed in Al-Hussein Teaching Hospital/Unit of Infertility in Al-Nasiriyah city, Iraq, during the period from September to November 2021. Infertility is defined as a failure to conceive after 12 months. The patients' info included age, address, COVID-19 vaccination, and COVID-19 infection. The results of the PCR examination were obtained from patients, and these were confirmed by the patient data in the laboratories for testing corona disease. As for the vaccination status, it was obtained from the official vaccination cards for patients, in addition to the information center for the vaccination against COVID-19 disease. The patient number was 318 males with different causes of infertility. Seminal fluid parameters, including volume, count, progression, morphology, and pus cells as an indicator for infections were determined. The exclusion criteria consist of a grouping of males and females having factors related to infertility.

2.2 | Ethical consideration

The research was approved by Thi-Qar Health Directorate according to their instruction. Verbal agreement from the patients and or their next of kin after a full exploration of the study aims by communication via social media (Whatsapp application, Viber and Telegram).

2.3 | Semen analysis

The seminal fluid was analyzed based on WHO criteria (WHO, 2010), the semen samples were collected after 3–5 days of sexual

abstinence in a sterile container, and the volume was determined by a gradual tube and the presence of leukocytes was detected microscopically. The sperm count, activity, and morphology were detected using Computer-assisted semen analysis CASA (Microptic-Spain) according to the WHO manual.¹⁶

2.4 | Statistics

The results were computed as mean \pm standard Deviation. In all tests, only $p \leq 0.05$ was measured as significant. Differences among groups were analyzed by one-way analysis of variance (ANOVA) and Chi-square test. The correlation coefficient was performed by the Pearson correlation coefficient test (r). All these tests were analyzed by the Statistical Package for Social Sciences (SPSS) program version 24.

3 | RESULTS

Table 1 showed high significant differences between the infertile males who were infected with COVID-19 and those that were vaccinated ($X^2 = 12.509$, $p = 0.001$).

The relationship between the infections with COVID-19 and semen parameters is revealed in Table 2. A high significant relation ($p < 0.001$) was recorded between types of infection severity and volume of semen ($p < 0.001$) and nonprogress life sperm (C) ($p < 0.001$), while significant differences were shown in the moderate progression sperm (B) ($p = 0.012$), and morphology ($p = 0.02$), respectively. Insignificant differences between COVID-19 severity and other seminal fluid parameters ($P > 0.05$) were noticed also.

Table 3 and Table 4 showed the comparison between the types of COVID 19 severity in their effects on semen parameters. A high significant difference was reported between the types of infection severity and volume (count of the sperm, presence of pus, B, C and D), ($p < 0.001$), while a significant difference was shown between severity types in relation to A and morphology of the sperms ($p = 0.021$ and 0.015), respectively. The results showed a significant correlation between each of the following (COVID-19 with C and age), (age with C and morphology), (vaccination and morphology), (volume and C),

(count with A, B, D and pus), (A with B and D), (B with D and pus), (D with pus), ($p < 0.05$). Figure 1

4 | DISCUSSION

It has been established that inflammation involves recurrent hospital admission,¹⁷ and frailty in Covid-19 era.¹⁸ One of the most important hormones that affects inflammatory responses is testosterone with a sex-specific protective. SARS-CoV-2 patients have a reduced level of testosterone which may be linked to the highest levels of inflammatory cytokines, such as interleukin-2 and interferon- γ . Furthermore, the anti-inflammatory and immune-modulatory properties of testosterone may control the differentiation of T-lymphocytes. Nevertheless, conflicting with the potentially defensive nature of testosterone, others have recommended that COVID-19 infection may be facilitated by testosterone.^{17,18}

The possible effects of COVID-19-related inflammation on semen discussed by high leukocyte count, pro-inflammatory cytokines, such as IL-6 and TNF- α were higher than in healthy persons. An increase of WBCs in semen may lead to sperm anomalies due to the triggering of reactive oxygen species. Infected male changes in the ACE2 signaling pathway, oxidative stress, and inflammation may lead to DNA breakage of sperms and the rise of sperm DNA fragmentation index (DFI).¹⁹

In December 2019, a new CoV emerged, this virus has outperformed previous forms of CoVs in terms of infection rate. SARS-CoV-2 has been identified as a member of the -coronavirus subgroup, having a positive-sense single-strand RNA encased within a nucleocapsid contained within an envelope. Coronaviruses have the potential to evolve quickly, change tissue tropism, pass the species barrier, and adapt to epidemiological circumstances.^{20,21}

This virus can cause extra pulmonary illnesses and causes histopathological abnormalities in various organs, including the kidney, liver, and heart. SARS-CoV-2 was found in the sperm of male patients, and like other viruses, such as mumps, herpes simplex, and HIV, it has the potential to contaminate the constituents of the genital tract of male and impairment male fertility. Orchitis may lead to decrease male reproduction as a SARS complication, which may provision that SARS-CoV-2 can infect reproductive cells thru ACE2, which is present in testicular cells, seminiferous tubule cells, and

TABLE 1 The correlation between COVID-19 and vaccination in infertile males

COVID-19	Vaccine			X^2 (p value)
	1	2	Total	
No symptom	31 (31.6)	34 (15.5)	65 (20.4)	12.509 (0.001)
Mild	21 (21.4)	69 (31.4)	90 (28.3)	
Severe	11 (11.2)	20 (9.1)	31 (9.7)	
No infection	35 (35.7)	97 (44.1)	132 (41.5)	
Total	98 (30.7)	220 (69.3)	318 (100)	

TABLE 2 The relationship between COVID-19 infections and seminal fluid parameters

		Mean \pm SD	95% CI	ANOVA	P value
Volume	1	3.982 \pm 2.2	3.129–4.835	12.384	<0.001
	2	4.616 \pm 6.449	2.888–6.343		
	3	3.25 \pm 40.658	–334.053– –396.553		
	4	3.542 \pm 6.018	2.505–4.578		
Count	1	38 \pm 19.688	30.365–45.6343	1.696	0.169
	2	48.268 \pm 65.052	30.846–65.689		
	3	8.5 \pm 9.192	–74.09– –91.09		
	4	36.848 \pm 21.397	33.164–40.532		
A	1	10 \pm 18.509	2.822–17.177	1.232	0.299
	2	7.321 \pm 6.176	5.667–8.975		
	3	12.5 \pm 17.677	–146.327– –171.327		
	4	6.78 \pm 6.335	5.689–7.871		
B	1	40.893 \pm 12.696	35.97–45.816	3.760	0.012
	2	37.678 \pm 16.208	33.338–42.019		
	3	2.5 \pm 3.535	–29.265– –34.265		
	4	37.538 \pm 16.033	34.777–40.298		
C	1	5.893 \pm 3.862	4.395–7.39	8.909	<0.001
	2	5.625 \pm 4.052	4.54–6.71		
	3	27.5 \pm 38.89	–321.92– –376.92		
	4	5.795 \pm 5.984	4.765–6.826		
D	1	42.857 \pm 14.429	37.262–48.452	2.038	0.110
	2	44.196 \pm 18.58	39.22–49.172		
	3	75 \pm 35.355	–242.655– –392.655		
	4	45.454 \pm 18.29	42.305–48.604		
Morphology	1	43.75 \pm 12.219	39.012–48.488	3.346	0.02
	2	37.75 \pm 12.549	34.389–41.111		
	3	60 \pm 56.568	–448.248– –568.248		
	4	42.803 \pm 13.225	40.526–45.08		
Pus	1	8.642 \pm 6.02	6.308–10.977	0.726	0.537
	2	8.678 \pm 7.734	6.607–10.75		
	3	3 \pm 1.414	–9.706– –15.706		
	4	7.894 \pm 5.523	6.942–8.845		

testicular Leydig cells, demonstrating that SARS-CoV-2 is likely to invade the reproductive system.^{22–24}

The goal of the study was to evaluate the SARS-CoV-2 infection severity effects and vaccination on the fertility of males. The results are well-matched with some earlier studies that have established an increased risk of abnormalities in sperm parameters in the individuals with vigorous SARS-CoV-2 infection and those who recovered.^{25,26}

The findings showed that COVID-19 infection had an adverse effect on some seminal fluid parameters such as sperm volume, progression, and morphology, which are consistent with previous studies,^{14,27,28} in which these factors were significantly affected by COVID-19 infection in comparison with those of noninfected infertile males. This could be caused by a virus invading male genital

tissues, differences in genetic susceptibility, the presence of other diseases, or the severity of the immune response to the virus. Several studies did not detect the SARS-CoV-2 in the semen of infected patients, but these results may not reflect the reality due to the small size of patients who participated in these studies.

The study indicated that the intensity of the viral infection affected the overall quantity, effectiveness, and morphology of sperms in infected males compared with men who were not infected with the virus, which is consistent with the earlier research.^{26,27,29} Although a number of studies were unable to detect virus RNA in the sperm and tissues of the reproductive system of patients and the deceased, the cause for this consequence could be the immune reaction against the virus, and this effect may be proportionate to the strength of the immune and inflammatory reactions, which rise

TABLE 3 Correlation between COVID-19, vaccination and semen parameters

	COVID-19	Age	Vaccine	Volume	Count	A	B	C	D	Morph	Pus
Age	r	-0.209-									
	p value	<0.001									
Vaccine	r	0.119	0.074								
	p value	0.035	0.187								
Volume	r	-0.021-	0.039								
	p value	0.708	0.896	0.485							
Count	r	-0.024-	0.045	0.005							
	p value	0.673	0.419	0.055	0.928						
A	r	-0.027-	0.071	0.059	0.305						
	p value	0.627	0.113	0.205	<0.001						
B	r	-0.099-	0.049	-0.009-	0.221	0.313					
	p value	0.077	0.383	0.867	<0.001	<0.001					
C	r	-0.138-	0.187	-0.143-	0.278	-0.020-	0.011				
	p value	0.013	0.001	0.011	<0.001	0.722	0.844				
D	r	0.082	0.004	-0.055-	0.031	-0.319-	-0.625-	-0.066-			
	p value	0.146	0.937	0.324	0.583	<0.001	<0.001	0.242			
Morph	r	0.049	0.172	-0.334-	0.013	0.095	0.136	0.010	0.248		
	p value	0.386	0.002	<0.001	0.488	0.090	0.015	0.857	<0.001		
Pus	r	0.04	-0.061-	0.024	-0.036-	0.041	-0.133-	0.013	-0.112-	-0.124-	
	p value	0.479	0.275	0.664	0.522	0.468	0.018	0.813	0.046	0.028	

TABLE 4 Normality analysis of semen variables in this study

Variable	Mean ± SD
Sperm volume (cc)	1.6 ± 0.87
Sperm concentration (10 ⁶ /ml)	18.5 ± 2.55
Total sperm count (10 ⁶)	30.5 ± 6.75
Sperm progressive motility (A+B)	30.4 ± 10.32
Sperm normal morphology (%)	8.75 ± 3.33
Sperm viability (%)	35.7 ± 4.65
Non-sperm cells (WBC)	2.95 ± 1.33

in severe cases, especially when there is a cytokine storm, which can cause tissue and cell damage.^{30,31}

The study found a high correlation between COVID-19 and some variables of sperm efficacy and age, as well as a correlation between the fertilization factor and the morphology of the sperm, in addition, an important correlation was observed between the existence of pus-filled cells and the ratio of abnormal shaped sperm, and these conclusions support the findings of prior studies on the impact of virus infection and the effect of the immune response on the numbers and proportions of normal sperm.^{25,27,28}

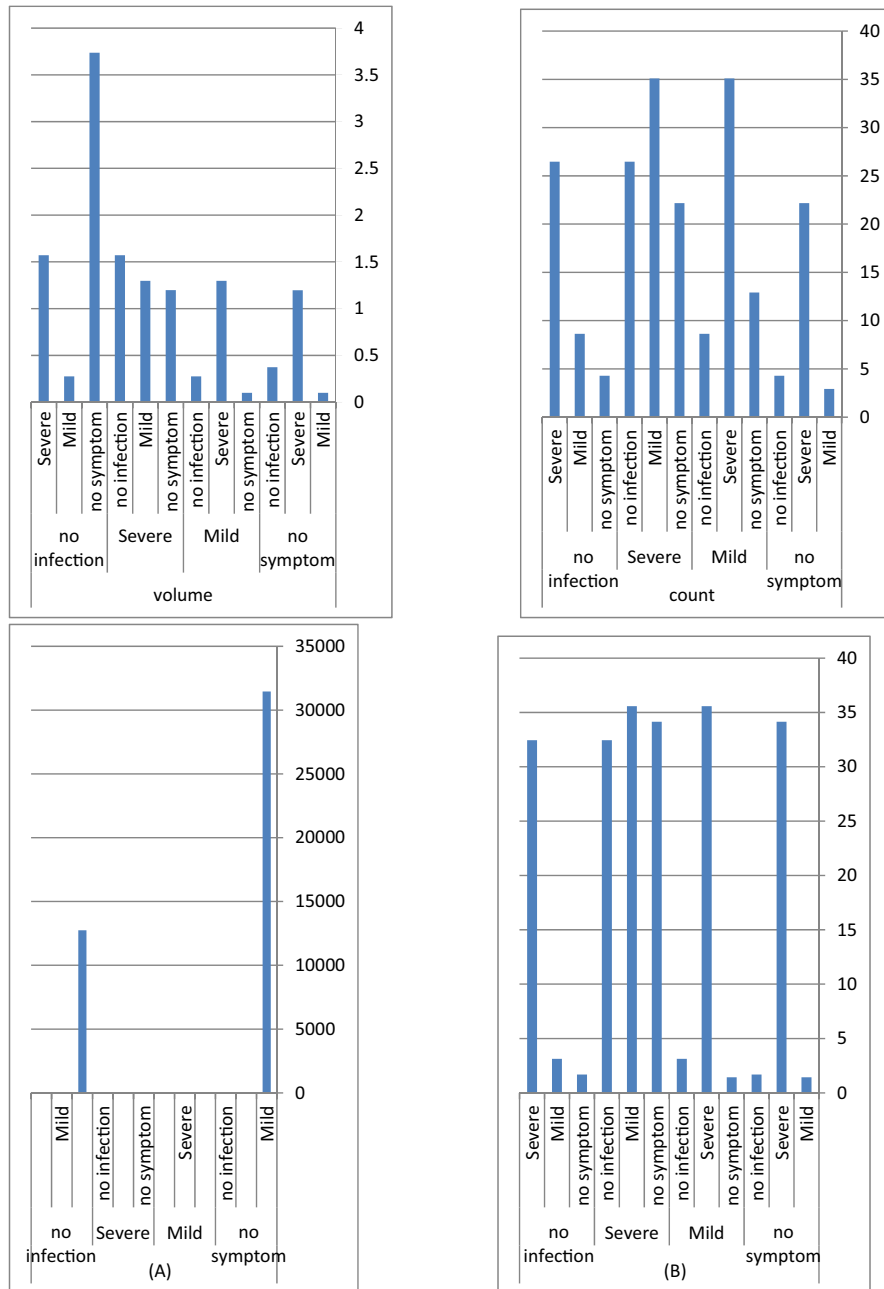
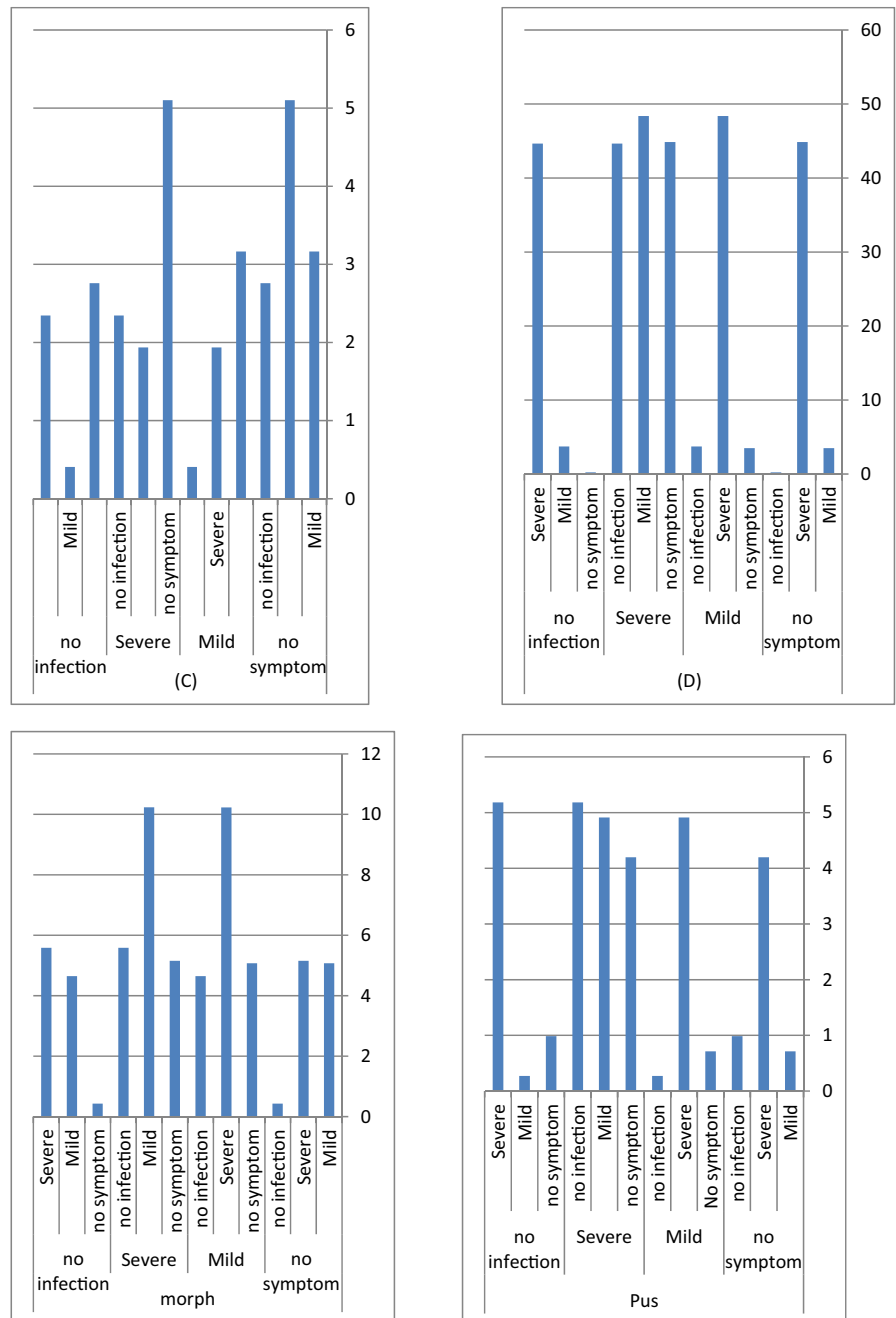


FIGURE 1 (continues)

FIGURE 1 The effects of COVID 19 severity on semen parameters under the study



The data demonstrated that pus cells were significantly associated with the severity of COVID-19 infections, which might be attributed to differences in the strength of the inflammation and immune response to the virus, as well as subsequent secondary infections. The findings of this study are similar to those of another that revealed Leukocytospermia was connected with male accessory gland infection and increased in men with severe instances of COVID-19 who were admitted to the critical care unit compared with nonhospitalized patients.^{14,29}

The most important finding is the vaccination process, which has no effects on seminal quality, which can help in raising health awareness of the need to use antiviral vaccines and reduce the state of anxiety arising among people about the use of vaccines. Also, infection with the Corona virus is an important risk factor

in the development of infertility cases that must be taken into account.

5 | CONCLUSION

The severity of COVID-19 has a significant impact on infertility and sperm parameters, particularly progression and sperm morphology, despite the fact that these parameters are unrelated to vaccination.

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CONFLICT OF INTERESTS

None.

DATA AVAILABILITY STATEMENT

All data included in article.

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