

## REVIEW ARTICLE

# Human semen quality as affected by SARS-CoV-2 infection: An up-to-date review

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**Abstract**

Revealing the effect of SARS-CoV-2 infection on semen quality is a dynamic priority for many healthcare providers in the field as well as subfertile patients. Therefore, the collective summary in this research approach is still highly needed, especially with the continuous increase in original publications. Here, we provide an up-to-date review and discussion to collectively reveal the effect of SARS-CoV-2 infection on human semen quality. To do this, we reviewed all articles and abstracts published in Scopus and PubMed using the keywords 'SARS-CoV-2' and 'COVID' versus 'sperm' and 'semen'. In summary, it can be revealed that, at both symptomatic and recovery stages of infection, no investigational evidence of SARS-CoV-2 shedding in human semen. Also, the mainstream of the up-to-date published work reveals a negative impact of SARS-CoV-2 infection on semen quality parameters, particularly sperm count and motility. However, long-term post-recovery comparative studies seem very important in this particular setting.

**KEYWORDS**

COVID-19, SARS-CoV-2, semen quality, sperm

## 1 | INTRODUCTION

The 2020 coronavirus outbreak, which is caused by SARS-CoV-2 (a virus belonging to the family Coronaviridae and cause COVID-19), is an unexpected global situation. It has become an extraordinary challenge for health systems in various countries, since, in one important lateral, various health policies as well as medical protocols and procedures had to mandatory be reviewed and renovated to flatten the mounting curve of infected people. This renovation or makeover includes the main protocols and procedures in andrology laboratories to avoid any possible negative effects on, for instance, assisted reproductive technologies outcomes. For example, various andrology laboratories in the assisted reproductive technologies units have requested negative coronavirus tests for males undergoing *in vitro* fertilization.

Therefore, revealing the effect of SARS-CoV-2 infection on semen quality and sperm parameters, which mimicked principally in sperm quality and quantity (Banihani, 2017), is of great importance at this time, particularly for healthcare providers (e.g. andrologists, urologists and embryologists), researchers in the field and patients with COVID-19. Accordingly, this work discusses and summarizes such effect considering, mainly, all original studies published in this research approach as per Scopus and PubMed databases.

To date, there are more than 50 published articles in Scopus and PubMed databases that are linking between SARS-CoV-2 infection and semen quality. To extract, review and collectively summarize these studies, we have searched these databases using the keywords 'SARS-CoV-2' and 'COVID' versus 'sperm' and 'semen'. In addition, relevant articles to support the discussion, and hence to frame the up-to-date summary in this context of research, were considered and cited.

**TABLE 1** Research studies conducted to test the presence of SARS-CoV-2 in human semen and the effects SARS-CoV-2 on sperm parameters

First date of publication (Location)	Study design (No. of participants)	Stage of SARS-CoV-2 testing	Testing Method	Presence of SARS-CoV-2 in semen
December 2020 (Italy)	Case study (n = 1)	Symptomatic period	RT-PCR*	Not detected
December 2020 (Turkey)	A cross-sectional, pilot study (n = 55)	After the end of medical treatment for confirmed cases	RT-PCR	Not detected
December 2020 (China)	Retrospective cohort study (n = 100)	During and after the pandemic wave	OSN-qRT-PCR**	Not detected
January 2021 (China)	Observational analytic-Cohort study. (n = 74)	Recovery stage	Pharyngeal swab RT-PCR test	Not detected
November 2020 (China)	Hospital-based observational study (n = 23)	Recovery stage	RT-qPCR	Not detected
May 2020 (Germany)	Pilot cohort study (n = 34)	Acute phase of infection. (n = 2)	RT-PCR	Not detected
		Recovered phase. (n = 18)	M D	RT-PCR RT-PCR
January 2021 (China)	Prospective cohort study (n = 23)	Acute phase Recovery phase	RT-PCR	Not detected
September, 2020 (China)	Observational analytic (In vitro study) (n = 12)	Deceased COVID-19 patients	RT-PCR	Not detected
February 2021 (USA)	Prospective Observational Study (n = 30)	Recovery phase	RT-PCR	Not detected
March 2021 (USA)	Prospective cohort study	Acute phase	RT-PCR	Not detected
		Recovery phase		
April 2021 (Turkey)	Cross sectional cohort study (n = 69)	Recovery phase	M D	RT-PCR RT-PCR
				- -
July 2021 (Turkey)	Prospective cohort study (n = 24)	Recovery Phase	RT-PCR	

↓Decrease; ↔No effect.

D, Moderate (patient required hospitalization); M, Mild.

\*RT-PCR: real-time polymerase chain reaction; \*\* OSN-qRT-PCR: One-step single-tube nested quantitative real-time polymerase chain reaction; \*\*\* NA: not available.

## 2 | THE PRESENCE OF SARS-COV-2 IN HUMAN SEMEN

Angiotensin-converting enzyme 2 (ACE-2) has been recognized to be the cell entry receptor for SARS-CoV-2 (Doyle et al., 2021; Hoffmann et al., 2020; Wang et al., 2020). This receptor was not only found to be localized in the lungs, but also in the testes (Barker & Parkkila, 2020; Fu et al., 2020; Wang & Xu, 2020). Accordingly,

it was hypothesized that the testes, and hence the semen, are targets for SARS-CoV-2 (Cardona Maya et al., 2020). Consequently, in effect, it is suggested that the presence of SARS-CoV-2 in semen may negatively affect sperm parameters and hence male fertility. In addition, this may have implications for sexual spread and consequently, for example, congenital disease, embryonic infection and miscarriage (Rodriguez Bustos et al., 2021). Such rationale explains the designation of several research studies to probe the presence of SARS-CoV-2 in human semen.

Effect of SARS-CoV-2 infection on sperm parameters						Ref.
Sperm motility	Sperm count	Sperm Conc.	Sperm vitality	Sperm Morph-ology	Semen volume	
NA***	NA	NA	NA	NA	NA	(Paoli et al., 2020)
NA	NA	NA	NA	NA	NA	(Temiz et al., 2021)
NA	NA	NA	NA	NA	NA	(Huang et al., 2020)
↓	↓	↓				(Ruan et al., 2021)
		↓				(Li et al., 2020)
NA	NA	NA	NA	NA	NA	(Hoffmann et al., 2020)
↔		↔				
↓		↓				(Guo et al., 2021)
↔	↔			↔		
NA	NA	NA	NA	NA	NA	(Yang et al., 2020)
	↓					(Best et al., 2021)
NA	NA	NA	NA	NA	NA	(Burke et al., 2021)
↓			↓			(Erbay et al., 2021)
↓	↓	↓	↓		↓	
↓	↓	↔			↔	(Pazir et al., 2021)

The up-to-date research studies that are conducted to test the presence of SARS-COV-2 were presented in Table 1. Yet, there are at least 12 research studies in this specific set of research; all are recent ones (2020 and 2021) published after the beginning of the global COVID-19 outbreak. The studies were conducted in different countries (China, Italy, Turkey, Germany and United States), five of which were conducted in China, which is the origin of COVID-19 outbreak. In terms of design, the majority of these studies were observational analytic ones that investigated the presence of SARS-CoV-2,

primarily, utilizing the reverse transcription polymerase chain reaction (RT-PCR) technique. The testing phases of the disease were distributed between both diseased phase and recovery phase.

Together, as a result, to date, in all published studies and at both tested phases of infection, the presence of SARS-CoV-2 in human semen was not detected. However, more studies will provide more confirmation to this collective finding. Consequently, it can be revealed that there is no transmission for SARS-CoV-2 during assisted reproductive technologies (i.e. intrauterine insemination, *in*

*in vitro* fertilization and intracytoplasmic sperm injection) and sexual contact.

### 3 | EFFECT OF SARS-COV-2 INFECTION ON HUMAN SPERM PARAMETERS

As presented in Table 1, seven of the research studies have tested effect of SARS-CoV-2 infection on sperm parameters, three of which were conducted in China. In terms of design, the majority of these studies are observational analytic. In almost all of these studies, semen analysis was conducted in the recovery stage of infection and tested utilizing RT-PCR.

Further, as indicated in Table 1, six of the studies conducted on the effect of SARS-CoV-2 infection on sperm parameters have revealed negative effects on sperm parameters. Accordingly, to date, it can be concluded that the mainstream of research appears to reveal an effect of the SARS-CoV-2 infection on sperm parameters, peculiarly sperm count. However, in fact, further research studies are still highly acknowledged in this specific gap of information to provide a more robust and a collective conclusion, especially, given that SARS-CoV-2 was not detected in semen as discussed above.

### 4 | POSSIBLE MECHANISMS OF ACTION OF SARS-COV-2 INFECTION ON SPERM FUNCTION AND SPERMATOGENESIS

#### 4.1 | Effect of SARS-COV-2 infection on gonadal hormones

In human males, spermatogenesis is under control by gonadal hormones, mainly luteinizing hormone, follicle-stimulating hormone and testosterone (Achard et al., 2009; Banihani, 2018; Bremner et al., 1981; Sharpe et al., 1992). Specifically, it was found that the number of Leydig cells in the testes is controlled by luteinizing hormone and follicle-stimulating hormone (Duckett et al., 1997; Teerds et al., 1989; Verhagen et al., 2014). These hormones promote the synthesis of testosterone in the testes (Baburski et al., 2019; Banihani, 2019a; Ewing et al., 1983). Testosterone is synthesized primarily in Leydig cells, and the amount of testosterone formed was found to be under control by luteinizing hormone via controlling expression of 17- $\beta$ -hydroxysteroid dehydrogenase (Banihani, 2019b; Zhou et al., 2014). It has been shown that patients with COVID-19 had lower levels of luteinizing hormone and testosterone compared with healthy individuals (Salonia et al., 2021). In addition, COVID-19 patients were found to have higher level of luteinizing and prolactin and lower level of total testosterone compared with control (Kadihasanoglu et al., 2021). Also, serious COVID-19 cases were found to induce further reduction in total testosterone level (Kadihasanoglu et al., 2021). In fact, clinically, increased serum levels of luteinizing hormone and decreased testosterone:luteinizing hormone ratio reveal testicular dysfunction, which consequently may impact spermatogenesis

(Holm et al., 2003). Accordingly, the observed negative effect of SARS-CoV-2 infection on sperm parameters may be because, albeit partially, of reduced production of testosterone. However, further confirmatory studies in this research setting seem to be very imperative.

#### 4.2 | Effect of SARS-COV-2 infection on testicular function

Mechanistically, it has been shown that the entry of SARS-CoV-2 into the cell depends on ACE-2 and transmembrane serine protease 2 (Hoffmann et al., 2020; Liu et al., 2020; Sakamoto et al., 2021). However, it has been shown that transmembrane serine protease 2 is expressed only in a subpopulation of germ cells during development, while ACE-2 is mostly transcribed in Sertoli cells (Wang et al., 2018). Also, it was suggested that ACE-2 and transmembrane serine protease 2 do not overlap and have a limited expression in testicular tissue (Anifandis et al., 2021; Pan et al., 2020). Accordingly, such evidence, however indirectly, supports the concept that the entrance of virus into testis tissue is unlikely to occur. Indeed, however this is a partial support, as collectively concluded from this review, SARS-CoV-2 was not detected in seminal fluid.

In general, fever of more than or equal to 39°C for more than or equal to three days can lead to severe impairment to semen quality and, in the worst-case scenario, to azoospermia (Jung et al., 2001). It has been recognized that a fever at even limited duration of time may significantly reduce sperm parameters (e.g. count, motility and/or vitality) and alter integrity of sperm DNA (Bendayan & Boitrelle, 2021; Durairajanayagam et al., 2015; Sergerie et al., 2007). As a consequence, it is worth mentioning that the arrival to the basal level of the altered sperm parameters may relatively take long time (at least 3 months) (Bendayan & Boitrelle, 2021; Lazarus & Zorngiotti, 1975). Therefore, given that fever is a symptom that can be seen in more than 80% of infected people with COVID-19, then fever-induced COVID-19, even in the absence of immune response and the virus in the semen, can alter semen quality and reduce sperm parameters. Such negative effect on semen quality could have more impact on subfertile men.

#### 4.3 | Effect of SARS-COV-2 infection on the testes

Even though, in general, the testes are most of time unaffected by host response to antigens compared with other bodily organs (Zhao et al., 2014), it is found that several expressed proteins were downregulated in testicular tissues from autopsy samples of COVID-19 patients (Nie et al., 2021), which suggests unusual physiological processes in the testis during the COVID-19 for those patients.

For example, insulin-like factor-3, which is the most expressed protein in testicular tissue, particularly in Leydig cells (Uhlen et al., 2015), was found to be markedly reduced in testicular tissue of

COVID-19 (Nie et al., 2021). This reduction was suggested to impair the function and/or the population of Leydig cells (Nie et al., 2021). Moreover, the E3 ubiquitin-protein ligase, which is a crucial enzyme for spermatogenesis (Melnick et al., 2019; Richburg et al., 2014), and the dynein regulatory complex subunit-7, which is an essential factor for motility of spermatozoa (Morohoshi et al., 2020; Wirschell et al., 2013), were found to be reduced in COVID-19 patients, indicating an impairment in spermatogenesis and sperm function as a result of SARS-CoV-2 infection (Nie et al., 2021).

In addition, autopsied testicular samples of COVID-19 were found to have several histological/physiological disorders such as erythrocytes exudation in the epididymides and the testes and thinning in seminiferous tubules (Li et al., 2020). Further, in COVID-19, seminiferous tubules had higher number of apoptotic cells compared with control (Li et al., 2020). Furthermore, testes from patients with COVID-19 were found to have reduced Leydig cells and injured seminiferous tubules (Yang et al., 2020). Furthermore, a study conducted on postmortem testicular specimen from eleven fatal cases of COVID-19 presented several testicular histological changes including orchitis, vascular changes, Sertoli and Leydig cells scarcity, basal membrane thickening and reduced spermatogenesis (Duarte-Neto et al., 2021). Therefore, such testicular injury is attributable to SARS-CoV-2-induced inflammatory changes in the parenchyma of testis as well as different degrees of vascular injury with secondary ischaemia (Duarte-Neto et al., 2021).

Moreover, Carneiro and coworkers have used colour Doppler ultrasound to diagnose testicular abnormalities in COVID-19 males with mild-to-moderate cases (Carneiro et al., 2021). Surprisingly, even though all diagnosed patients were asymptomatic regarding scrotal complaints, approximately 42% of men were found to have epididymitis, 54.5% with enlarged epididymal head, and 19.2% with bilateralism. In effect, this deleterious effect on the testes was suggested to be indirect and mediated by cytokines as theorized by Hallak and his coworkers (Hallak et al., 2021).

#### 4.4 | Effect of immune response induced SARS-CoV-2 infection on semen quality

It has been shown that immunohistochemistry of autopsied samples showed presence of IgG, which is the main antibody in the extracellular fluid of the body, within seminiferous tubules and increased concentrations of CD68+ (macrophages) and CD3+ (T lymphocytes) in interstitial cells of testicular tissue (Li et al., 2020). In addition, it showed higher seminal concentrations of immune factors such as tumour necrosis factor- $\alpha$ , interleukin-6 and monocyte chemoattractant protein-1 (Li et al., 2020).

In November (2020), Renu et al. hypothesized that SARS-CoV-2 infection augments the T helper type 2 cells, which disturbs the level of interleukin-4, Janus kinases-signal transducer and activator of transcription proteins (JAK-STAT) signalling, basic leucine zipper transcription factor/interferon regulatory factor 4 (Batf/Irf4), and broad complex-tramtrack-bric a brac and Cap'n'collar homology 2

(Bach2)/Batf pathway, and, consequently, the disturbed interleukin-4 reduces ACE-2 level with the inflammation, which further has a negative impact on male fertility in patients with COVID-19 (Renu et al., 2020), though, such mechanistic hypothesis requires approval by experimental work.

Furthermore, the multi-organ and tissue injury that can be seen in COVID-19, particularly in severe cases, may be attributable to several immunological mechanisms. One remarkable contributable mechanism is the cytokine storm (Tisoncik et al., 2012), also called cytokine-release syndrome (CRS), which is an enhanced inflammatory cytokine (e.g. IL-1, IL-6 and IL-10 (Qin et al., 2020)) release results from excessive proliferation of immune cells (Teixeira et al., 2021). Other recognized mechanisms in COVID-19 that seem to contribute to tissue damage and multi-organ dysfunction are the haemophagocytic lympho-histiocytosis (HLH), also called haemophagocytic syndrome, which is a substantial systemic inflammatory syndrome, and the T-cell dysregulation (Teixeira et al., 2021). Such immunologically induced multi-organ damage also includes testicular damage, which may negatively impact spermatogenesis, and hence the quality of semen produced.

## 5 | CONCLUSIONS AND FUTURE PERSPECTIVES

In conclusion, to date, at this stage of research, it can be revealed that no investigational evidence of SARS-CoV-2 shedding in human semen at both symptomatic and recovery stages of infection. However, further confirmatory studies, particularly the ones that include larger study population, are still desired.

On the other hand, however it is inconsistent, the mainstream of the up-to-date research revealed adverse effects of SARS-CoV-2 infection on sperm parameters, peculiarly on sperm concentration. But, at this phase of investigation, especially with the absence of SARS-CoV-2 in semen, further studies are still of great importance to release confident evidence towards this effect in this specific gap of knowledge. In addition, longer-term studies as well as comparative observational analytic studies (i.e. studies that investigate sperm parameters before and after the infection) seem to have impact in this particular setting to ensure the reversibility of sperm parameters in the infected patients.

Mechanistically, SARS-CoV-2 infection, initially and regardless of irreversibility, was found to induce testicular injury and reduce testicular function; in particular, this may be occurred, at least in part, by an alteration in gonadal hormones or as a consequence of immunological and inflammatory responses.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

#### DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated during the current study.

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