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Effects of SARS-CoV-2 and vaccination on male fertility – a review

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ABSTRACT
The emergence of the second severe acute respiratory syndrome coronavirus (SARS-CoV-2) has resulted in a global pandemic declared by the World Health Organization in 2020. Numerous studies have demonstrated that males are more susceptible to SARS-CoV-2 infection, and recent evidence suggests that the presence of the angiotensin-converting enzyme 2 (ACE2) receptor in male gonads may render them particularly vulnerable to the virus. Consequently, it has become imperative to ascertain the potential impact of SARS-CoV-2 infection and the vaccines on male fertility. This article provides a comprehensive analysis of the literature concerning the incidence of morphological and histological changes in the testes, hormonal changes, and semen parameters resulting from SARS-CoV-2 infection, as well as the impact of vaccinations on sperm.
Keywords: COVID-19; male infertility; vaccination; SARS-CoV-2.

INTRODUCTION

Coronaviruses (CoVs) are a group of single-stranded RNA viruses that belong to the Coronaviridae family [1, 2]. They are capable of infecting animals and humans, causing a range of symptoms from flu-like manifestations, such as dry cough, sore throat, headache, fever, and fatigue, to more severe clinical syndromes like severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) that are characterized by high mortality rates [1, 2, 3].

A novel CoV, known as SARS-CoV-2, which shares nearly 80% genetic similarity with SARS-CoV-1, emerged in December 2019, with a significantly higher rate of transmission and infection than other CoVs [1, 4, 5]. Therefore, in March 2020, the World Health Organization (WHO) declared a global pandemic and named the new disease: coronavirus disease 2019 (COVID-19). By mid-September 2020, over 29 million cases and 900,000 deaths had been reported worldwide [2, 6]. In addition to the typical flu-like symptoms associated with the Coronaviridae family, COVID-19 infections have also been linked with gastrointestinal symptoms that could lead to shock or respiratory failure [7, 8]. Approximately 80% of infected individuals exhibit mild symptoms, while around 15% require hospitalization due to the severe course of the disease, and 5% need critical care, including mechanical ventilation. Mortality is estimated to be up to 3% of infections and is linked with age over 60 years [7].

Given the growing concern over reproductive health, both in terms of physical and psychological complications, this review aims to explore the impact of SARS-CoV-2 infection on male fertility, by analyzing the available literature [9].

MECHANISM OF INVASION

Coronaviruses are a group of single-stranded RNA viruses that consist of structural proteins, including matrix protein, envelope protein, nucleocapsid protein, and spike glycoprotein (S protein). Through this surface glycoprotein, the virus attaches to host receptors, gaining access to the cell [1, 10, 11,12]. One of these host receptors is the angiotensin-converting enzyme 2 (ACE2) receptor, expressed in the gastrointestinal, circulatory, renal, pulmonary, and male reproductive systems. Within these cells, the virus undergoes replication, generating mature forms ready to infect target cells [1, 13, 14, 15]. This process is initiated by the transmembrane protease serine 2 (TMPRSS2), which cleaves the S protein into 2 subunits, thus enabling viral infection [16]. Recent studies have additionally identified other potential receptors that might facilitate the virus' entry into host cells, including the receptor for basigin (BSG) and its cysteine protease, cathepsin L (CSTL) [9, 16].

THE PRESENCE OF ACE2 AND TMPRSS2 RECEPTORS IN THE MALE REPRODUCTIVE SYSTEM

Angiotensin-converting enzyme 2 serves as a regulator within the renin-angiotensin system [17]. Since its discovery in 2000, it has been linked to diabetes and hypertension [18], alongside cardiac function [19]. Studies have shown that ACE2 expression declines significantly with age across both genders [20, 21, 22]. The most pronounced and diminished expressions are evident in individuals aged around 30 and 60 years, respectively [23], and this pattern is observed within the human testis: in Sertoli and Leydig cells [24], spermatogonia [6], peritubular cells [25] and also in the epididymis [26, 27] and ejaculated sperm [28, 29]. Given Leydig cells' steroid hormone secretion, ACE2's modulation has been suggested to influence spermatogenesis [30]. Studies have indicated lower expression in infertile men with severely impaired spermatogenesis [31].

Conversely, TMPRSS2 exhibits substantial expression in the luminal cells of the prostate gland, with release into seminal

fluid. RNA-seq profiling studies have revealed ACE2 expression in the seminal vesicle at both the RNA and protein levels [16, 32], whereas TMPRSS2 expression has been detected in spermatids and spermatogonia [6].

While ACE2 and TMPRSS2 are both expressed within the testis, their co-expression still necessitates further validation [33].

The concurrent presence of TMPRSS2 and ACE2 within the male gonad suggests its potential susceptibility to SARS-CoV-2 infection [6, 16]. Men might be more susceptible to developing the disease, as evidenced in the UK (where 60% of more than 20,000 infected patients were male) [34] and China (where 58.9% of over 1000 infected patients were male) [35]. These findings, combined with the fact that a significant proportion of affected individuals are of reproductive age, suggest a potential risk to their reproductive capacity [35, 36].

THE IMPACT OF SARS-COV-2 ON THE OCCURRENCE OF MORPHOLOGICAL AND HISTOLOGICAL CHANGES IN THE TESTES

The blood–testis barrier provides limited protection against viral invasion and infection, as many viruses including human immunodeficiency virus (HIV), mumps virus, and SARS-CoV can infect the testes [37, 38]. In the context of SARS-CoV infection, Xu et al. observed inflammatory infiltrates, reduced numbers of germ cells, and accumulation of immunoglobulin G (IgG) in interstitial tissue and seminiferous epithelium [39].

Data on morphological changes mainly come from autopsy studies involving tissues obtained from deceased COVID-19 patients. In Brazil, Duarte-Neto et al. reported fibrinous thrombi as the only observed changes in the testes (5 male patients,, age range 33–83 years, median illness duration: 10 days) [40]. In China, patients with SARS-CoV-2 (12 patients, age range 42–87 years, mean disease duration: 42 days), testes showed mild (2 patients), moderate (5 patients) and multiple (4 patients) tubular damage and changes, including swelling and vacuolization of Sertoli cells, reduction in the number of Leydig cells, interstitial edema and inflammatory infiltration. Angiotensin-converting enzyme 2 receptor expression was robust in Leydig cells and diffuse in Sertoli cells [41]. Other autopsy findings comprised basement membrane hypertrophy, decreased gametogenic cell numbers in seminal epithelium, testicular fragmentation, exfoliation of spermatocytes into tubular lumen, swelling and vacuolization of Sertoli cells, and multifocal microemboli (6 testicular samples from deceased patients, age range 22–83 years, positive on nasopharyngeal cavity swab) [42], as well as shedding of degenerated gametogenic cells into the lumen of seminal tubules (5 deceased patients, mean age 68 years) [43]. Autopsies by Achua et al. (6 patients, age range 20–87, mean time from a positive test result to death: 11 days) revealed macrophage and lymphocytic infiltrates in 4 patients, with 3 demonstrating disrupted spermatogenesis [44], which have been described along with varying degrees of tissue damage by Chinese researchers [45, 46]. Transmission electron microscopy (TEM) detected SARS-CoV-2 in testicular tissue from 2 patients, corroborating findings of the virus detected through TEM, immunohistochemistry, or RT-PCR. However, the virus was only detected in some patients [41, 44, 45, 47, 48].

Studies on testicular apoptosis in COVID-19 patients by Achua et al. [44] and Moghimi et al. [46] highlighted a significant increase in apoptotic cells and caspase 3 and ACE2 expression, indicating a potential link between impaired spermatogenesis and increased ACE2 levels. Thus, a higher level of ACE2 in SARS-CoV-2-infected individuals may be associated with a greater risk of impaired spermatogenesis [44, 46]. In addition, oxidative stress and inflammatory cytokines [43, 49], which contribute to the development of immune inflammation in the testes [43] or disruption of the blood–testis barrier [50], might disrupt spermatogenesis.

SARS-CoV-2's impact to extend to other male reproductive organs/glands, including the prostate. Ambiguous data regarding virus presence also apply to the prostate. While some researchers have described the presence of the virus in tissue [51], others have found no virus in expressed prostate secretions [52, 53, 54]. Haghpanah et al. suggested that the virus could probably damage the prostate and worsen benign prostatic hyperplasia (BHP) through the activation of proinflammatory pathways or ACE2 signaling [55]. The lack of effect of infection on prostate inflammation was described by Pecoraro et al., but the study was conducted on a small group [56]. Despite the expression of ACE2 and TMPRSS2, COVID-19's impact on the prostate is not universally acknowledged. The Human Protein Atlas database indicates that this discrepancy is likely due to low ACE2 expression [57].

IMPACT OF SARS-COV-2 ON MALE SEX HORMONES

Severe SARS-CoV-2 infections have been linked to reduced total testosterone levels alongside elevated luteinizing hormone (LH), follicle-stimulating hormone (FSH), and lactate dehydrogenase in a combined total of 421 patients during both the active phase of the disease [58, 59, 60] and recovery [61]. These patients were compared to control groups consisting of intensive care unit patients without COVID-19 treatment [59] or men undergoing fertility evaluations [58]. A meta-analysis by Corona et al. revealed a similar decline in testosterone, without corresponding changes in LH and FSH levels, across over 2000 patients from 11 studies (the average age of the population was 44 and the average observation period was 24 days) [62]. Furthermore, evidence suggests that in men with severe disease, testosterone levels were lower than in those with milder cases. Testosterone levels were associated with the regulation of lymphocyte activity and T-cell activation, suggesting their potential as a predictor of disease severity [63, 64, 65].

A 7-month follow-up of recovered COVID-19 male patients (121 men, age range 49–65) showed an increase in testosterone levels (in 87.6% of patients) and reduced LH compared to the results obtained during hospitalization [66]. Disruption of the testosterone to LH ratio, indicative of impaired steroidogenesis and testicular function, can lead to hypogonadism in

SARS-CoV-2 patients [42, 67, 68], as confirmed by researchers who observed the development of this disease in some patients post-infection [61, 66, 67], with over 50% of patients exhibiting persistent hypogonadism for 7 months [66]. Nonetheless, the transient or permanent nature of hypogonadism is yet to be established [67], although its acute phase occurrence can be attributed to the activation of oxidant-sensitive inflammatory pathways and the mechanism of secondary immune responses [69].

Reduced testosterone levels in individuals infected with SARS-CoV-2 may also be caused by damage to Leydig cells [70], inhibition of its secretion by pro-inflammatory cytokines and modulation of the hypothalamic-pituitary-gonadal axis [71]. Thus, it seems that it is the interruption of gonadotropin regulation [70], by crossing the blood–brain barrier in the transcellular pathway [72], that may contribute to the occurrence of changes in the nucleus accumbens [70], which may be associated with a deterioration of semen parameters and result in male infertility [73].

THE PRESENCE OF SARS-COV-2 IN SEMEN AND ITS IMPACT ON SPERM PARAMETERS

Male infertility can result from issues within: (i) the ejaculatory, (ii) testicular, or (iii) hormonal components of the male reproductive system. Approximately 50% of diagnosed male infertility cases stem from semen parameter disorders (morphology, count, and motility of sperm), specifically relating to spermatogenesis issues [74, 75].

Elevated body temperature, a prominent symptom of SARS-CoV-2 infection, can have a harmful effect on the quality of semen and the entire male reproductive system [76]. Scientific reports indicate that COVID-19 induces these changes through 3 fever-related mechanisms: (i) temperature-induced disturbances in Leydig and Sertoli cells, (ii) induced damage to gametogenic cell lines, and (iii) disruption of accessory gland secretion processes [74, 75, 76].

Several studies, with limited patient cohorts, report SARS-CoV-2 presence in semen. Such cases involve patients in acute infection or recovery phases [77, 78, 79, 80]. However, retesting yielded negative results when swabs were taken from the nose and throat [79] and potential material contamination during collection was associated with virus presence in semen [78]. In other instances, virus presence in semen might result from changes in the blood–testis barrier and a possible secondary viral excretion into semen [62]. Yet, most studies did not detect SARS-CoV-2 in semen samples [49, 58, 81, 82, 83, 84, 85, 86], even if the virus was detected in sputum, stool, or urine [84, 87, 88, 89, 90].

Semen studies of SARS-CoV-2-infected patients often indicate reductions in sperm concentration [46, 49, 53, 58, 60, 81, 84, 86, 91, 92] and sperm motility [49, 53, 58, 73, 84, 91, 93, 94], with all 3 parameters (sperm concentration, sperm motility and total sperm count) declining in 7 publications [49, 53, 58, 59, 84, 93, 94]. Other studies indicate decreases in 1 parameter (sperm motility) [73, 79] or 2 parameters (sperm concentration and total sperm count) [81, 92] while others remained unchanged [73, 79, 81, 92]. Unaltered values across all 3 parameters were documented in a single paper [85]. All of the parameter changes described above are shown in Table 1.

Activation of caspases (caspase-3, caspase-8, caspase-9), interleukins (IL-1β, IL-6, IL-8, IL-10), an increase in reactive oxygen species (ROS) [87], the relationship between IgA/IgA-ASA (anti-sperm antibodies) deficiency and slower or incomplete recovery, a higher described sperm DNA fragmentation index (DFI) and the presence of sIgG-N in the blood [95] suggest the formation of molecular alterations [49] stemming from an immune response [95]. Researchers propose semen and sex hormone analysis, alongside measurement of DFI, as SARS-CoV-2 invasion can indirectly lead to testicular damage and impaired gonadal function, including failure of spermatogenesis, DNA fragmentation, abnormal sperm motility and male infertility [96] as a result of the disease stage, fever [59, 97] and immune response [95].

TABLE 1. List of changes in semen parameters described in the literature

Authors	Country	Number of patients	Status (active/ healed/ deceased)	Presence of the virus in semen	Sperm concentration	Total sperm number	Sperm motility	Control group
Best JC et al. 2021 [81]	USA	30	active	absence	↓	↓	N/D	men who volunteer for sperm cryopreservation or fertility control
Erbay G et al. 2021 [93]	Turkey	69	healed	N/D	↓	↓	↓	N/D
Guo TH et al. 2021 [94]	China	41	healed	N/D	↓	↓	↓	50 men of similar age who did not suffer from COVID-19
Guo L et al. 2021 [84]	Germany	18	active	absence	↓	↓	↓	N/D
Holtmann N et al. 2020 [85]	China	23	active	absence	normal	normal	normal	healthy volunteers with no reported andrological pathology

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Authors	Country	Number of patients	Status (active/ healed/ deceased)	Presence of the virus in semen	Sperm concentration	Total sperm number	Sperm motility	Control group
Ma L et al. 2021 [58]	China	12	healed	absence	↓	↓	↓	men who received sex hormone measurements as part of a fertility evaluation
Li H et al. 2020 [86]	China	6	deceased	absence	↓	N/D	N/D	patients with prostate cancer, without additional medical history
Ruan Y et al. 2021 [53]	China	74	healed	absence	↓	↓	↓	age-matched men
Temiz MZ et al. 2021 [98]	Turkey	55	healed	absence	normal	normal	normal	healthy men, without any clinical or laboratory COVID-19 results
Donders GGG et al. 2022 [91]	Belgium	120	healed	absence	↓	↓	↓	COVID-19-negative men
Gacci M et al. 2021 [79]	Italy	43	healed	positive	normal	↓	normal	N/D
Hajizadeh Maleki B and Tartibian B 2021 [49]	Germany	84	healed	N/D	↓	↓	↓	healthy controls
Hamarat MB et al. 2022 [92]	Turkey	41	healed	N/D	↓	↓	normal	N/D
Koç E and Keseroğlu BB 2021 [73]	Turkey	21	healed	N/D	normal	normal	↓	N/D

↓ – decrease; N/D – no data available

THE IMPACT OF SARS-COV-2 VACCINATION ON SPERM

Patients' hesitance towards receiving SARS-CoV-2 vaccines is partly due to concerns about potential negative effects on fertility, an aspect not thoroughly investigated during clinical trials. Therefore, it became crucial to establish alterations in semen parameters following mRNA vaccination [91]. An Israeli study by Gat et al. examined 37 patients to assess short-, medium-, and long-term changes in semen parameters after completing a full vaccination cycle. In the medium-term group (75–125 days after completing the vaccination cycle), there was a decrease in the total and motile sperm count compared to controls. However, subsequent examinations of the long-term group (over 145 days after completing the vaccination cycle) no longer showed these changes [82]. It seems that adverse effects of the vaccine, such as pain, fever redness or swelling at the site of vaccine administration [82], potentially stemming from a cytokine storm and systemic immune response, may manifest as decreased semen parameters due to testicular damage [82, 99]. A separate study involving 47 men found no significant differences in sperm parameters within 3 months post-vaccination [100]. This is in line with research from various groups, which did not identify harmful effects of the vaccine on semen quality [76, 83, 91, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110].

In conclusion, over the past 3 years, significant progress has been made in clarifying the relationship between SARS-CoV-2 infection and its impact on histomorphological changes in the testes, hormonal and semen parameters changes, as well as the impact of vaccinations on sperm. The available data allow us to draw some general conclusions:

1. There is a likelihood of testicular damage after SARS-CoV-2 infection, potentially arising from a secondary inflammatory response or the virus binding to ACE-2 receptors.
2. After infection, semen quality appears to be reduced, accompanied by disrupted semen profiles involving spermatozoa morphology and motility of spermatozoa, and sperm volume. This effect is likely linked to the infection's progression, encompassing the duration of infection and the severity of the disease.
3. Vaccine administration may lead to short variations in semen parameters; however, the majority of available data suggests that vaccines generally do not have adverse effects on semen quality.

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