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IMPACT OF COVID-19 ON MALE REPRODUCTIVE HEALTH

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ABSTRACT

The COVID-19 virus, SARS-CoV-2, first appeared in December 2019 in Wuhan, China, and spread quickly across the world, resulting in a global pandemic of COVID-19. Among the possible effects of the virus are the ability to invade and/or harm the male reproductive system. This paper looks at how SARS-CoV-2 can injure the male reproductive system primarily through an inflammatory process that results in a cytokine storm. There is an ongoing debate about whether SARS-CoV-2 can infect human testes and create semen. The list of negative effects of the SARS-CoV-2 virus on male reproduction includes many additional areas needing sound evaluations and additional evidence-based research. Longitudinal studies of the reproductive abilities of male patients who have recovered from symptoms of the COVID-19 virus will provide insight into the complete spectrum of potential consequences associated with COVID-19 in men.

KEYWORDS: COVID-19, Male Infertility, Angiotensin Converting Enzyme 2 (ACE2).

INTRODUCTION

The human coronaviruses have been identified as a threat to human health only since 2002, when the outbreak of Severe Acute Respiratory Syndrome (SARS) showed the capacity of human coronaviruses for severe respiratory disease. The SARS virus was identified as a new coronavirus, named SARS-CoV. Just over one generation later, the health of the planet is under attack again, this time by the new coronavirus, SARS-CoV-2, which causes COVID-19. The

new coronavirus appears much easier to transmit, with many cases around the world, yet it has a much lower mortality rate than that recorded with SARS (2.1% vs. 9.6%) [1]. Interestingly, for the new virus, SARS-CoV-2, there have been significant findings that the rate of disease for this virus has been many times higher for males than for females, contrary to the pattern that was recorded with the initial outbreak with SARS. Furthermore, findings have shown that the virus has the capacity to remain much longer than anticipated in the human population. The model proposed by Kisseler et al. suggests that this virus re-emerges after periods of time when the disease appears eradicated [2].

Based upon clinical evidence available yet, it is clear that COVID and SARS share many similarities/characteristics especially in regard to their disease characteristics (i.e., one of the most significant similarities between both viruses is how they produce respiratory symptoms). Additionally, however, it has been shown that COVID has also affected other body systems by affecting specifically the cardiovascular system and gastrointestinal system [3,4]. Therefore, based upon what is currently known about COVID and the similarities between COVID and SARS, there is an important research question open to explore for further understanding of this relationship – does COVID have an effect on the male reproductive system? The male reproductive system is generally understood to be quite susceptible to injury. There is a considerable amount of data that shows that viral injuries have been adverse to the male reproductive system. Numerous viral injuries, including the Zika virus, Hepatitis B virus, Hepatitis C virus, HIV, HPV, herpes viruses, and Ebola virus, demonstrate damage to the male reproductive system, thus creating disorders of the male reproductive system. Therefore, understanding how these viruses infect male reproductive systems and cause damage represents an important issue that should be evaluated [5].

Viruses infect the male reproductive tract during an acute viral infection through the blood. The increase in temperature due to the high fever associated with most viral illnesses decreases the permeability of the blood-testis barrier and allows for access to this area [6]. Experimentally, it has been demonstrated that even small increases in temperature around the scrotum can affect the blood-testis barrier and permit the entrance of foreign substances to the testis. In the context of COVID-19, it is possible that one of the mechanisms of action is through angiotensin-converting enzyme 2 (ACE2), a cellular receptor for SARS-CoV-2. Testicular tissues, including spermatogonia, Sertoli cells, and Leydig cells, have high levels of Ace2 expression. It is hypothesized that binding of the virus to ACE2 may increase ACE2 expression and activate pro-inflammatory responses, disrupting the normal function of Sertoli and Leydig cells. These potential mechanisms provide evidence that COVID-19 has the potential to negatively impact

male reproduction and, therefore, should be investigated further [7].

Histopathological examination of testicular tissue has demonstrated inflammation of testicular tissue predominantly within the seminiferous tubules. Further, the presence of IgG in immunohistochemically stained testicular sections indicates that the IgG is associated with the seminiferous epithelium, interstitial tissue, degenerating germ cells, and Sertoli cells, which are known to have high levels of ACE2 expression. Interestingly, in situ hybridization studies failed to identify viral nucleic acid in the testicular tissue samples. The destruction of the testis is believed to result from an immune-related inflammatory response rather than a direct effect of viral invasion [8].

PATHOPHYSIOLOGY OF COVID-19

Coronaviruses are members of the family Coronaviridae, which consist of single-stranded positive-sense RNA (approximately 32 kb in size), and the structure of the virion contains four main proteins: spike protein (S), membrane protein (M), envelope protein (E), and nucleocapsid protein (N). The spike protein emerges from the surface of the virion to provide a means of attaching to host cell receptors; SARS-CoV and SARS-CoV-2 have been shown to use angiotensin-converting enzyme 2 (ACE2) as their primary receptor for binding. However, there are alternative receptors that serve as secondary binding targets for SARS-CoV. These include the C-type lectin CD209L and DC-SIGN. Therefore, while ACE2 is the principle receptor for SARS-CoV, it appears to be the major receptor used by its sibling, SARS-CoV-2 [9]. During the viral replicative cycle, binding of the viral spike to the virus receptor on the host cell membrane is critical for initiating replication, and the efficacy of viral infection relies heavily on this step. The exact pathway for SARS-CoV-2 to disseminate beyond the respiratory system remains to be determined, but there is evidence to suggest the potential for infection of other organ systems based on isolation of infectious coronavirus from respiratory specimens, as well as other body fluids from people with COVID-19. Therefore, many of the organ system failures attributed to the fatality of COVID-19 could be due to extrapulmonary organ infection [10].

COVID-19 AND SPERMATOGENESIS

Spermatogenesis is divided into three successive phases. In the first phase, spermatogonia undergo mitosis to differentiate into the B-type, which eventually will become the tetraploid primary spermatocyte. In the second phase, the primary spermatocyte undergoes meiotic I division to create the diploid secondary spermatocyte, and then undergoes meiotic II division

to create the haploid spermatid. In the final phase, spermatids undergo spermiogenesis (nuclear elongation and condensation, and acrosome biogenesis) to become spermatozoa. During spermatogenesis, several different types of germ cells form specialized cell junctions with Sertoli cells for the purpose of assisting their migration from the basement membrane (BM) into the abluminal compartment of the testis. Another important feature of spermatogenesis is the presence of the blood–testis barrier (BTB), which is created by the cell–cell junctions between Sertoli cells, limiting the ability of mature sperm to enter the circulatory system [11]. SARS-CoV-2 virus infection may negatively affect the levels of genes related to spermatogenesis via downregulation. Expression of ACE2 (angiotensin converting enzyme type 2) is observed at higher levels in the testis of males having infertility issues, suggesting that reproductive disorders resulting from COVID-19-related events may require the activation of ACE2, or that males having reproductive issues may be more vulnerable to COVID-19 viral infection [12]. Further, SARS-CoV-2 (mRNA) virus has been detected in seminal fluid, and research demonstrates that COVID-19 is associated with a reduced number of Leydig cells in the testis [13]. Several studies have demonstrated the negative effect of COVID-19 infection on sperm quality and spermatogenesis throughout the course of the infection and in recovery. For example, in comparison to control (non-infected) subjects, both semen volumes and total sperm counts were found to be lower in COVID-19 patients [14]. Decreased viability, motility, and progressive motility of the sperm were noted among COVID-19 patients compared to controls [15]. The sperm DNA Fragmentation Index (DFI) was shown to be positively correlated with COVID-19 [16]. Reduced serum testosterone (T) levels and sperm function appear to be linked to dysregulated serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [17]. Nevertheless, several studies describe no measurable impact on testis or epididymis function while reporting abnormal sperm parameters. Scroppo et al. describe normal serum levels of T, gonadotropins, and serum inflammatory factors in young males with mild or moderate COVID-19 infections when compared to subjects with abnormal seminal values despite similar overall health [18]. According to Guo's research, 23 male patients who had a positive test for COVID-19 all showed no trace of virus RNA in their semen and had normal sperm counts and morphology. In addition, Holtmann's research suggests that mild COVID-19 does not hurt the function of the testicles and epididymis, but semen characteristics in patients with moderate cases do appear to be impaired. It appears that there is emerging evidence regarding the adverse effects of SARS-CoV-2 infection on the process of spermatogenesis, although there are a few publications that state no impact on the quality of sperm with most likely due to most of the males being asymptomatic or very mildly infected.

An imbalance between production and elimination of reactive oxygen species (ROS) causes oxidative stress (OS). OS is a significant contributor to male fertility problems, and levels of OS are elevated in men infected with the COVID-19 virus. Several testicular dysfunctions have been associated with OS, including both impaired sperm quality and reduced endocrine (hormonal) function. Damage occurring in sperm from oxidative stress is thought to be the primary cause of increases in sperm DNA fragmentation (DFI). There have been studies that have shown total antioxidant capacity (TAC; an indicator of the overall ability to neutralize harmful oxidation from ROS) correlating negatively with COVID-19-positive men (higher DFI) and that during a 14-day window after a confirmed diagnosis of COVID-19, DFI values were significantly higher than those found at 120 days after the diagnosis. In a case report, it was demonstrated that SARS-CoV-2 can invade and cause damage to male germ cells through spermatogenesis (sperm assembly) before the onset of clinical symptoms (i.e., before the onset of any recognizable illness). In this case, measurement of oxidative DNA damage to sperm showed extremely high levels in comparison to healthy, unexposed males given in **Figure 1.**

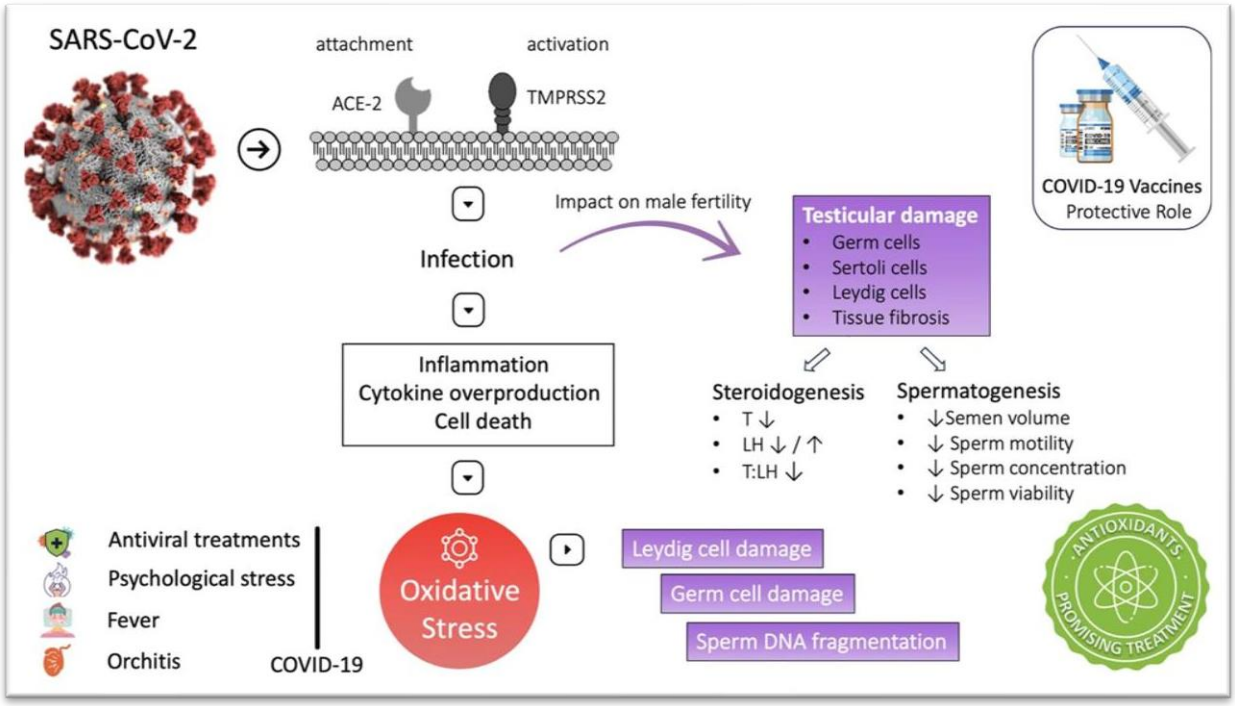

Figure 1. COVID-19 and male infertility: mechanisms and impact on fertility [19].

Testicular inflammation resulting from COVID-19 has likely had an adverse impact on spermatogenesis due to accompanying OS. It is unusual for COVID-19 to present with testicular pain, but it suggests an association with orchitis [20]. Testicular congestion,

thickening of the testicular basilemma, and interstitial edema were observed in the testes of men after having contracted COVID-19, all of which are positive for interstitial orchitis. The number of Sertoli and Leydig cells was also decreased in the testes of infected males [21]. There was a high level of vascular cell adhesion molecule (VCAM) expression in semen obtained from the vascular blood supply of the testes and within the cell types of fibroblasts, spermatogonia, Sertoli, and Leydig cells, which positively identified the SARS-CoV-2 virus antigen. Additionally, seminal plasma collected from infected males contained significantly elevated levels of pro-inflammatory cytokines, such as TNF-α, IFN-γ, IL-8, IL-10, IL-1β, and IL-6 [22]. These increased levels of pro-inflammatory cytokines result in the downregulation of junctional proteins at the BTB, including connexin-43, claudin-11, and occludin. Additionally, an increase was noted in gene expression for apoptosis pathways with increased BAX, caspase-3, caspase-8, and caspase-9 gene expression levels in testicular specimens and/or sperm from infected men [23]. A significant amount of germ cell loss, and also a large increase in apoptotic cells expressing CD3+ (mature T-lymphocyte), CD68+ (macrophage phenotype), and Caspase-3+ were observed in the testes of deceased males.

For males affected by COVID-19, there was a lot of evidence showing that the long-term effects of the virus are serious and have led to compromised reproductive function. Specifically, at 37 days post-infection, the total sperm count of COVID-19 males remained lower than that of age-matched uninfected controls. Moreover, Guo et al. found that males recovered from COVID-19 had lower sperm count, lower sperm concentration, and lower sperm motility compared to healthy controls 29 days after infection and that sperm morphology improved dramatically at 56 days post-infection [24]. On the other hand, data from another report showed that total motility and sperm concentration in males recovered from COVID-19 remained poor 80 days post-infection [25]. Furthermore, there is evidence that male sperm quality does not return to pre-infection levels until 6 months after infection [26]. Thus, it remains unclear whether sperm quality deteriorates via mechanisms that only occur in the testes or whether mechanisms of sperm control develop elsewhere in the body [27].

EFFECT OF SARS-CoV-2 ON THE EPIDIDYMIS

The epididymis serves as an important transport structure for sperm, connecting the vas deferens to the efferent ducts via three anatomically diverse regions: caput, corpus, and cauda. Along its lumen, there are four segments of greatly increased specialization where protein and ion secretions occur to establish the proper micro-environment for sperm to mature. The tests generate sperm while sperm mature in the epididymis and obtain their full ability to be motile

and capable of fertilization. The epididymis also serves as a storage and transport medium for sperm until they are released from the body at ejaculation [28]. Evidence exists of decreases in expression of angiotensin-converting enzyme 2 (ACE2) in epididymal tissue; however, additional cofactors and receptors, such as NPL, NRP1, and CD147 (Fig. 1), are very abundant in the epididymis and could potentially cause damage from SARS-CoV-2. The spike protein of SARS-CoV-2 can bind to sperm from within the epididymis [29]. In an examination of COVID-19-related deaths, histological examinations indicated large numbers of sperm and immature spermatids packed into the cauda of the epididymis [30]. In an example of a descendant case of COVID-19 and orchiepididymitis, Gagliardi and colleagues noted inhomogeneous testicular enlargement and epididymitis as well as hydrocele formation in the child with orchiepididymitis [31]. Similarly, Marca et al. identified slight testicular enlargement and mild accentuation of vascularity within the epididymis as indicators of epididymitis as a result of COVID-19. Hydroceles associated with epididymitis due to COVID-19 can manifest as reactional hydroceles with diverse echogenicities (microcysts or nonuniform echoes), evidenced by caput (enlargement of the epididymis to > 12 mm) and thickening of the scrotum [32]. A large cohort of 142 COVID-19 patients (Chen et al.) revealed 32 with acute epididymitis, orchitis, or orchiepididymitis. A direct correlation exists between acute scrotal infections and age; 53.3% of patients older than 80 years of age were infected. Severe infections are at an increased risk of developing orchiepididymitis compared to mild infections [33]. Histopathologic analysis of the epididymis following COVID-19 demonstrated remarkable differences from control subjects, including hyperemia and edema in the interstitium, as well as an effusion of red blood cells from the interstitium into the epididymis. A small number of infiltrating T-lymphocytes could also be seen infiltrating the blood supply to the testicle. All of these findings indicate that infection with SARS-CoV-2 has a negative impact on the epididymis, thus inhibiting sperm maturation. Therefore, special attention should be given to the possibility of epididymitis in young males who want to become fathers.

EFFECT OF SARS-CoV-2 ON THE PROSTATE

The prostate gland is an accessory reproductive organ in men. The epithelium and stroma make up the prostate gland. The cells that form the epithelium (prostate cells) produce prostatic fluid, and it comprises roughly 1/5th - 1/3rd of all ejaculate volume from the testes. The fluid is made up of numerous components that play a role in regulating the ejaculatory process, as well as facilitating sperm motility, liquefying semen, and activating the clotting mechanism [34]. With respect to ACE2 and TMPRSS2 expression in the prostate, single-cell RNA sequencing

indicated that 0.32 % of total prostate epithelial cells expressed ACE2 and 18.65% expressed TMPRSS2, with 0.61% expressing both ACE2 & TMPRSS2 [35]. Regarding pathological properties of the prostate post-SARS-CoV-2 infection, Zhang et al. were the first to show that males with confirmed SARS-CoV-2 had no detectable SARS-CoV-2 in their EPS, even though CRP (C-Reactive Protein), erythrocyte sedimentation & IL-6 were all found to be elevated in blood samples from these infected males [36]. Thus, it can be assumed that while all patients had mild, moderate, or severe forms of pneumonia, all had completely cleared the virus by 80 days post-infection as determined by RT-PCR. No inflammation of the prostate was seen in the hospitalised patients, and the mean serum level of prostate-specific antigen was within normal limits (1.13 ng/mL) [37].

EFFECT OF COVID-19 ON MALE GAMETES

A fever can affect the process of sperm production in men, resulting in infertility. As a result of an infection like COVID-19, men may experience infertility for up to 72-90 days due to a reduction in the number and quality of their sperm. Men infected with viruses such as hepatitis and HIV must follow the same safety protocols when using sperm from these men to prevent exposure of non-infected partners and to prevent contamination of reproductive tissues [38].

LITERATURE REVIEW

The findings in 2020 also indicated that it is highly unlikely that SARS-CoV-2 can enter the testicular cells of the host, as they do not utilize ACE2 receptors to gain access into the cells. This finding is based on the level of expression of ACE2 and TMPRSS2 proteins in the testicular cells. In order for SARS-CoV-2 to enter the cells, both ACE2 and TMPRSS2 proteins must be expressed in the same cell lines, and therefore, based on the data, there are only 4 out of 6490 testicular cell lines that express both genes, which would indicate a very low probability for SARS-CoV-2 entry. It should be noted that the cells that expressed both genes may be spermatogonia. However, it was also established that spets have very little expression of ACE2 protein, indicating that there is little translation of ACE2 protein in these cell types. Lastly, since spermatogenic dysfunction and decreased sperm count were observed in COVID-19 patients, and the testis and epididymis have an immune response, it is necessary to apply increased focus on men's health related to reproduction [39].

A 2020 research study included 50 patients. Twelve patients were excluded from the study because they were unable to give a semen specimen due to either erectile dysfunction, being comatose, or passing away before they could be recruited for the study. Thus, 38 patients were

included as semen specimen donors. Of the 38 semen specimen donors, 23 (60.5%) of the patients had clinically recovered from their COVID-19 illness, and 15 (39.5%) of the patients were in the early acute stage of their COVID-19 illness. Of the 38 patients who provided a semen specimen to be tested for SARS-CoV-2 (the virus that causes the illness COVID-19), the semen testing discovered that 6 (15.8%) of the patients tested positive for SARS-CoV-2. This included 4 (26.7%) of the 15 patients who were in the acute stage of their COVID-19 illness, and 2 (8.7%) of the 23 patients who had clinically recovered from their COVID-19 illness. This was particularly significant because there were no statistically significant differences between negative and positive semen tests with regard to the following patient demographic and clinical characteristics: age; previous history of urogenital disease; days from onset of COVID-19 illness; days from hospital admission; and days from clinical recovery [40].

According to a study from 2020, there is currently not enough evidence available to conclusively state how SARS-CoV-2 COVID-19 can potentially impact male reproduction or how SARS-CoV-2 can be transmitted through seminal fluid. Other studies related to COVID-19, however, have indicated that there may be a potential link between the virus and testicular damage, which could lead to future infertility due to natural viral damage or via the immune or inflammatory response, which can negatively impact adult fertility and reproductive outcomes for children. One example of a mechanism by which testosterone could protect against inflammation and aging of blood vessels, is that testosterone levels that are low in COVID-19 patients would be associated with higher levels of inflammatory markers such as interferon-γ and interleukin-2. Additionally, there are anti-inflammatory and immunoregulatory properties associated with testosterone because testosterone regulates the differentiation of T-lymphocytes [41].

In 2020, researchers conducted a cross-sectional study in which they enrolled 34 male subjects who had recently recovered from COVID-19. The average time between their diagnosis and when they provided the sample for testing was 31 days (29 - 36). Most of these men had mild to moderate symptoms of COVID-19 while being ill. Six (6) men experienced scrotal pain or discomfort during the time they were infected, which suggested that they had developed orchitis. None of the men were laboratory-positive for SARS-CoV-2 nucleic acid using RT-PCR (Reverse Transcriptase Polymerase Chain Reaction) testing [42].

In 2021, research has shown a theoretical possibility of testicular injury and subsequent infertility due to the COVID-19 virus infecting the body's reproductive organs via the ACE2 receptors. The age of the patient plays a role in the level of expression of ACE2 in the testicles.

The maximum amount is expressed by patients aged 30 years, more than in their 20's. Conversely, the lowest amount is shown in the 60-year-olds. Young males (aged under 30) would be more susceptible to testicular damage from COVID-19 than older males. One study examined the testicles of six SARS-CoV-infected patients from autopsy specimens taken in 2002, which showed evidence of orchitis. The histopathological examination of the testicles demonstrated the inflammatory infiltration, particularly in the seminiferous tubules. Through immunohistochemical staining, IgG antibodies were deposited primarily in the seminiferous epithelium, interstitium, degenerated germ cells, and Sertoli cells. Most of these same cell types are also highly expressed in the ACE2 receptors. Interestingly, in-situ hybridization assays failed to find any evidence of SARS-CoV genomic material in the testicular tissues, showing that the injury to the testicles likely occurred because of inflammation and the immune response, and not from the direct action of the virus [43].

The age of participants for a similar research done in 2021 was 23.26 years old (ranging from 19 to 43 years old). Of the 15 participants in the study, 2 were asymptomatic (13.66%). For the 13 symptomatic participants: 3 of them experienced symptoms for less than 3 days (20%), 5 for approximately 1 week (30%), 3 for approximately 1-2 weeks (20%), and 1 for approximately 2-3 weeks (6.66%). The most common symptom among participants was fever, with 8 (53.33%) reporting it as a symptom. All samples were collected within 2 weeks of the onset of symptoms, but no individual data were collected on each sample. No study participants had undergone vasectomies. SARS-CoV-2 RNA was detected in 1 sample of semen (6.66%) from one study participant [44].

This essay in 2021 suggests that after COVID-19 infection, it appears that there is a suppression of semen quality due to several potential mechanisms, including lowered testosterone levels and disruption of all aspects of the semen profile (i.e., sperm count, motility, morphology, and leukocyte infiltration). The degree of suppression appears to be influenced by the severity and duration of the disease. In addition, it has been suggested that damage to sperm DNA may be present in patients' semen and may pose risks to both affected patients' fertility and the health and welfare of their potential offspring [45].

Research conducted in 2021 looked at 30 patients suffering from acute market manifestations of the COVID-19 disease in order to explore the presence of the virus via sample analysis of semen and urine. All patients had samples drawn 1 day after confirming results of SARS-CoV-2 via the nasal pharyngeal swab. Using the RT-PCR method, the presence of SARS-CoV-2 was identified by analyzing four out of 30 patient semen samples and seven out of 30 patient urine samples. Following recovery from COVID-19, neither semen nor urine samples from patients

had any detectable presence of the virus. In addition to having detectable virus in vaginal secretion, these seminated individuals also exhibited significantly increased regular blood cells, neutrophil production, C-reactive protein, ferritin levels, alanine transaminase, lactate dehydrogenase, and prolactin levels ($p < 0.05$). The six people with SARS-CoV-2 present in their respective semen samples were identified as having been diagnosed at the acute stage of their illness, were also diagnosed with severe pneumonia associated with COVID-19, and had a higher level of viral load when compared to the other patients sampled during this study [46].

The research conducted in the year 2021 studied how temperature affects the sperm, the level of expression of angiotensin-converting enzyme 2 (ACE2) in the testes and how SARS-CoV-2 affects the male reproductive system. The virus SARS-CoV-2 enters the human body by binding to the ACE2 receptor found on the surface of the cell. The presence of high levels of ACE2 on the outer surface of spermatogonia and Sertoli cells, along with the immune response to a COVID-19 infection, has the potential to disrupt normal testicular spermatogenesis, which may result in decreased sperm production. COVID-19 has been shown to alter male reproductive function, and thus there should be intervention plans in place to support men with COVID-19 [47].

In a 2021 study that examined a group of individuals diagnosed with acute SARS-CoV-2-based disease (0 to 8 days after onset), there were 32 individuals sampled. The sample consisted of 27 individuals with light-moderate degrees of symptoms and 5 (asymptomatic) who did not report any COVID-19 symptomology. Ultimately, only 1 of the samples that were run for use on semen or seminal plasma tested positive for SARS-CoV-2. There were no positive samples detected in the spermatozoa pellets across the group of samples. However, there was a high likelihood that there were manual (touching) or droplet (coughing or sneezing contamination) forms of contamination found with the presence of some bacterial DNA in the SARS-CoV-2 positive samples [48].

An additional cohort study was conducted in 2021 involving 18 men diagnosed with either recent COVID-19 or in the recovery stage. The time from SARS-CoV-2 positive testing to semen sample collection had a median time of six days (1–28). One man was classified as being asymptomatic, while two were classified as having mild COVID-19, and 15 were classified as suffering from moderate COVID-19; No SARS-CoV-2 (viral RNA) was detected in any of the samples obtained, regardless of whether they were classified as having COVID-19 symptoms at the time of semen sample collection [49].

An analysis conducted in 2022 has shown that COVID-19 has caused a decrease in the amount of testosterone that is produced and caused temporary hypogonadism (hypogonadism). This

condition was thought to be caused by the testes being the primary target tissue for the SARS-CoV-2 virus because of their ACE2 receptor content and, thus, was thought to have a negative impact on male fertility. However, while there continues to be a difference of opinion concerning the mechanisms behind this reduction in testosterone, there is now evidence supporting that a decrease in testosterone is likely a consequence of either systemic or localised inflammation, causing an indirect effect on the testes rather than an infection of the testes themselves. Because of the rapid changes with COVID-19, it is important to continue to be aware of the potential for delays in care and/or various treatments that may ultimately lead to long-term impacts on male fertility [50].

According to research done in 2022, COVID-19 infection can have a negative impact on the HPG axis. Levels of testosterone were found to be representative of the pathologically impaired steroidogenesis of the testis and were related to disrupted LH and FSH levels in the testis of COVID-19-infected individuals. Impaired testosterone production can result in erectile dysfunction and altered spermatogenesis that can lead to subfertility. Higher levels of both LH and FSH may indicate testicular damage and other pathological conditions. A dysregulated HPG axis can contribute not only to hypothyroidism but also to neurodegenerative senescence, liver cirrhosis, and chronic kidney disease. The potential mechanisms by which SARS-CoV-2 affects spermatogenesis include: direct damage to testicular tissue or sperm; exacerbated immune response and oxidative stress, and apoptosis secondary to SARS-CoV-2 infection; and dysregulated levels of hormones. However, the effects of SARS-CoV-2 on HPG function and spermatogenesis may be long-term. Due to the high levels of prolactin, which do inhibit HPG axis signaling, evaluating prolactin levels in male COVID-19 patients may improve prognosis and management of this disease [51].

In 2023, this study investigates how the coronavirus (COVID-19) may affect testicular function, particularly whether some antioxidants may protect against damage to the testicles via oxidative stress (OS). Although it typically has not been demonstrated that the virus is present in sperm or testicular tissue, it has been shown that infected people develop poor quality of their semen (cellular) compared to uninfected individuals, as well as have altered hormones. Some of these hormonal changes most likely occur throughout the entire duration of spermatogenesis. Used as evidence of testicular pathology, histopathologic studies of deceased patients show that abnormalities (sperm development), reduced blood supply, and inflammation of the testes occur. Most of the patients exhibiting primary acute hypogonadism have experienced at least one severe instance of infection. The high levels of OS and the

increase in sperm DNA fragmentation provide evidence to support the conclusion that changes in fertility may have resulted from a redox (oxidative and/or reductive) imbalance [52].

The Covid-19 pandemic has placed an unquantifiable burden on global health systems as of 2025, which may have various effects on men's reproductive health, mostly from being infected by SARS-CoV-2. SARS-CoV-2 infects testicular cells and uses receptors to mediate systemic inflammation (causing hormonal imbalances). Therefore, it is likely that these two mechanisms will ultimately interfere with spermatogenesis. Finding ways to address the negative effects of SARS-CoV-2 infections on fertility in men through a global standard for monitoring and intervention will be vital to limiting the negative effects of COVID-19 on men's fertility [53].

This essay in 2025 states the effects of SARS-CoV-2 (the virus that causes COVID-19) on male reproductive health. Therefore, they recruited 781 male patients who had been diagnosed as infertile, but whose infertility was not related to COVID-19, so that they could look at their semen and blood samples pre- and post-infection with COVID-19. Our results showed that SARS-CoV-2 RNA was not detected in the semen. The overall sperm counts, concentration of sperm, vitality and motility, as well as percentage of sperm with appropriate morphology, demonstrated a significant decline in the first month post-COVID-19 compared to pre-COVID-19 levels. However, by month 3, the previously observed decreases in sperm parameters were reversed. In addition, by month 3, seminal plasma samples were noted to exhibit relatively lower levels of pro-inflammatory cytokines and greater differences in amino acid, nucleic acid, and carbohydrate metabolism compared to month 1. However, reproductive hormone levels did not change between months 1 and 3. Sperm vitality, progressive motility and total motility were all negatively correlated to body temperature when body temperature was ≥38°C. Therefore, they conclude that sperm quality initially declines post COVID-19; however, it returns to normal after approximately 3 months, with the initial decline being associated with fever and inflammation. These findings will help guide infertile male patients who require assisted reproductive technology [54].

The study explores how COVID-19 affects the male reproductive system through its physiologic and mechanical aspects in 2025, looking at potential outcomes of the changes. There are two significant ways that SARS-CoV-2 has been shown to impact reproductive health: hyperthermia (fever) and oxidative stress. To begin with, in the hyperthermia pathway as described above, there is strong evidence that sperm aneuploidy is substantially increased as a result of hyperthermia, which will result in negative outcomes related to sperm production

and breakage in sperm DNA. The second mode of the coronavirus's effect on infertility is oxidative stress. Oxidative stress causes increased production of reactive oxygen species (ROS) that lead to damaging membranes of sperm cells due to lipid peroxidation. Hyperthermia-induced oxidative stress can cause disruptions in the redox-active metal homeostasis, which can further contribute to cellular damage. Understanding these pathogenic processes can facilitate the development of targeted therapeutic interventions and prevention strategies for male reproductive dysfunction from COVID [55].

An investigation conducted in 2026 has shown that the COVID-19 Pandemic has had a terrible effect on Male Fertility. COVID-19 has a tendency to attach to the Angiotensin Converting Enzyme (ACE-2) Receptor, and the ACE-2 receptor is readily available in Spermatogonia, Testicular Stroma, and Sertoli cells inside the Testes. Severe Acute Respiratory Syndrome (SARS) has been found at significantly higher levels in the semen of Men With COVID-19, potentially causing decreased volume of semen, low Motility of Sperm, defective Sperm, low concentrations of Sperm and lower sperm counts and causing longer-term issues. SARS-CoV-2 infection can cause HPG Axis function to be disrupted, causing HPG Axis Dysfunction. Exposure to HPG Axis Dysfunction, along with fever as a common complication, may contribute independently to the Male Reproductive system. The patient with ARDS and impaired gas exchange results in systemic Hypoxia that ultimately leads to histopathological change to testicular tissue. In the last two years, there has been an increased burden on male infertility in Africa, compared to other world regions between 2019 and 2021. COVID-19 has resulted in the largest rate of increase of the Male Infertility burden in Africa, for many reasons. One of which is that Africa’s Healthcare systems are underdeveloped when compared to other regions of the world, thus making it more difficult to control the spread of COVID-19 (over time), and also their Public Health policies have been seriously inadequate, among other reasons [56].

EVIDENCE

There is considerable debate about whether or not SARS-CoV-2 was present in the semen of men who had symptoms consistent with COVID-19. The majority of studies suggest there is support for the BTB (blood-testis barrier) being impacted by an inflammatory reaction caused by the virus, the overproduction of proinflammatory cytokines, and oxidative stress from the disease, and those aspects of the disease [45].

Statistical comparisons among groups were made using Mann-Whitney, Kruskal-Wallis, one-way ANOVA, and t-tests, where appropriate. All statistical testing was two-tailed, and

significance was determined at $P < 0.05$ [40].

This study is a cross-sectional observational study, and the samples were tested for viral RNA using real-time reverse-transcription polymerase chain reaction (rRT-PCR) with 2 different genetic probes, and re-tested after 24 hours to confirm the results. SARS-CoV-2 Viral RNA was detected in 1 out of 15 patients [6.66%] in these samples. Thus, SARS-CoV-2 RNA can be detected in human semen even using a small sample size [44].

The study conducted (a cross-sectional study) found SARS-CoV-2 in four (13.3 %) semen samples and seven (23.3%) urine samples from the total sample size. Patients with SARS-CoV-2 in their semen had significantly ($p < .05$) higher blood cell counts (WBC), neutrophils, C-reactive protein (CRP), ferritin, alanine transaminase (ALT), lactate dehydrogenase (LDH) and procalcitonin compared to patients without semen contamination but no statistically significant difference between patients who were PCR positive and negative in urine ($p > .05$). Additionally, patients who exhibited severe pneumonia on chest CT scan are more likely to be PCR positive in both semen and urine samples than those who do not have pneumonia on chest CT ($p = .005$, $p = .001$). No SARS-CoV-2 was detected at an average of 23 ± 4 days after recovery in either urine or semen. This indicates that SARS-CoV-2 may be detectable in the urogenital secretions of individuals who are severely ill with elevated viral loads [46]. Semen samples (semen, seminal plasma, and spermatozoa pellet) from each COVID-19 patient were tested for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR) except for one patient (patient n°24) who had undergone a vasectomy and therefore had only one semen sample available to test, which contained only seminal plasma. The semen samples of patients n°14 and n°25, the seminal plasma of patient n°25, and the spermatozoa pellets of patient n°18 were determined to be uninterpretable due to the presence of inhibitors. No patient samples tested positive for the presence of SARS-CoV-2, except for those collected from one individual [48].

Scrotal discomfort suggesting viral orchitis was noted in 6 patients (19%) during the time of COVID-19 diagnosis; 31 days (interquartile range, 29-36 days) after their COVID-19 diagnosis, there was no detection of SARS-CoV-2 in semen. Single-cell transcriptome analysis shows little expression of ACE2 and TMPRSS2, with little overlap in their gene expression [42].

The time between being diagnosed and giving a specimen was anywhere from 1 to 28 days (and on average, took 6 days). Of the men who provided a semen sample, 15 had symptoms, whereas 3 did not have any symptoms and were recovering. None of the semen samples tested positive for SARS-CoV-2 [49].

In summary, the diverse data about the amount of SARS-CoV-2 found in semen suggest that there is still a need for more research on the presence of SARS-CoV-2 in semen **(Table 2)**.

Table 2. Semen SARS-CoV-2 detection results in studies assessing COVID-19.

Author	Study Design	Sample size, stage	Specime n	Time since Diagnosi s (days)	Clinical category	Results	
Li et al.	Cohort study	15 acute	Semen	6 to 16	NP	Positive	4
[40]		stage,				of 15 and	2
		23				of 23	
		recover					
		y stage					
Pan et al.	Cross-	34	Semen	8 to 75	Mild,	Negative	
[44]	sectional	recover			moderate		
	study	y stage			symptoms		
Machado	Cross-	15	Semen	2 to 8	2	Positive	1
et al. [46]	sectional	active			asymptomatic,	case	
	study	phase			13 mild		
					symptoms		
Saylam et al. [48]	Cross-sectional study	30 acute stage	Semen, urine	1	NP	Positive semen samples, urine samples	4 7
Delaroch e et al. [42]Burke et al. [49]	Prospective observationa l study	32 acute stage Cohort study 18 acute and recover y phase	Semen Semen	0 to 1 1 to 28	NP 1 asymptomatic, 2 mild, 15 Moderate	Positive case semen and seminal plasma, not spermatozo a pellet	1 in Negative

CONCLUSION

There is a strong chance that there have been alterations in the male reproductive system resulting from SARS-CoV-2 infection, but how long these problems last is unknown. With the high levels of expression for the ACE-2 receptor and the TMPRSS-2 membrane protease on testicular cells, likely that the reason men and their reproductive functioning are particularly vulnerable to COVID-19 is due to the amount of testicular tissue containing these two important proteins.

In addition to the lungs and airways, the testicles continue to be affected by COVID-19. From semen analyses performed on COVID-19-positive individuals, we have evidence of abnormalities in semen parameters. Furthermore, individuals who tested positive for COVID-19 also exhibited hypogonadism during the acute phase of the disease, which indicated an altered hormonal environment. Testicular tissue pathology reports from

autopsy studies of male individuals who died due to COVID-19 have also given us valuable insight into how COVID-19 affects the male reproductive system. Most studies indicate that orchitis, vascular changes, thickening of the basal membrane, and damage to both Leydig and Sertoli cells have been found along with reduced levels of spermatogenesis when associated with SARS-CoV-2. However, study results show that the presence of the virus in the ejaculate and/or testicular tissue is infrequent; we can conclude that other indirect mechanisms of damage are also present in addition to direct damage by the virus.

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