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REVIEW ARTICLE

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Current status of the COVID-19 and male reproduction: A review of the literature

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Abstract

Background: Coronavirus disease 2019 (COVID-19), which causes serious respiratory illnesses such as pneumonia and lung failure, was first reported in mid-December 2019 in China and has spread around the world. In addition to causing serious respiratory illnesses such as pneumonia and lung failure, there have been conflicting reports about the presence of SARS-CoV-2 in the semen of patients who were previously diagnosed with COVID-19 and possible implications for the male reproductive tract.

Objective: The goal for the present study was to review the current status of the literature concerning COVID-19 and male reproduction.

Material and methods: An electronic literature search was done by using PubMed and Google Scholar databases. Relevant papers, concerning SARS-COV-2 and COVID-19 and male reproduction, published between January 2020 and December 2020 were selected, analyzed and eventually included in the present literature review.

Results: SARS-CoV-2 may infect any cell type expressing angiotensin-converting enzyme 2 (*ACE2*), including reproductive cells. Besides the presence of the SARS-CoV-2 receptor, the expression of host proteases, such as transmembrane serine protease 2 (*TMPRSS2*), is needed to cleave the viral S protein, allowing permanent fusion of the viral and host cell membranes. Here, we aimed to review the current status of the literature concerning COVID-19 and male reproduction. The lack of co-expression of *ACE2* and *TMPRSS2* in the testis suggests that sperm cells may not be at increased risk of viral entry and spread. However, the presence of orchitis in COVID-19-confirmed patients and compromised sex-related hormonal balance among these patients intrigues reproductive medicine.

Discussion: SARS-CoV-2 may use alternate receptors to enter certain cell types, or the expression of *ACE2* and *TMPRSS2* may not be detected in healthy individuals.

Conclusion: COVID-19 challenges all medical areas, including reproductive medicine. It is not yet clear what effects, if any, the COVID-19 pandemic will have on male reproduction. Further research is needed to understand the long-term impact of SARS-CoV-2 on male reproductive function.

KEYWORDS
COVID-19, male reproduction, SARS-CoV-2, testicles, viral

1 | INTRODUCTION

In December 2019, an increase in serious pneumonia cases with no known cause was observed in Wuhan, China. Soon after, the number of cases rose dramatically, spreading throughout the world on all continents. The causative agent of the disease was identified as a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease caused by this agent was formally named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO).

SARS-CoV-2 belongs to the β-coronavirus cluster. Coronaviruses primarily cause enzootic infections in birds and mammals but, in the last few decades, have shown to infect humans as well. The outbreak of severe acute respiratory syndrome (SARS) in 2003 and Middle-East respiratory syndrome (MERS) demonstrated the lethality of these viruses when they cross the species barrier and infect humans.[1] Current evidence indicates that SARS-CoV-2 was derived from bats.[2-5] Following SARS and MERS, COVID-19 is the third known zoonotic disease caused by coronaviruses.[6]

Coronaviruses are enveloped, non-segmented positive-sense RNA viruses belonging to the family Coronaviridae, which contain very large genomes for RNA viruses, with some viruses having the largest identified RNA genomes. Other common features within coronaviruses are (i) a highly conserved genomic organization, with a large replicase gene preceding structural and accessory genes; (ii) expression of many nonstructural genes by ribosomal frameshifting; (iii) several unique or unusual enzymatic activities encoded within the large replicase-transcriptase polyprotein; and (iv) expression of downstream genes by synthesis of 3′ nested subgenomic mRNAs.[7]

The coronaviral genome encodes four major structural proteins: the spike (S) protein, nucleocapsid (N) protein, membrane (M) protein, and envelope (E) protein, all of which are required to produce a structurally complete viral particle.[8,9] Individually, each protein primarily plays a role in the structure of the virus particle, but they are also involved in other aspects of the replication cycle.[1] The initial attachment of SARS-CoV-2 to the host cell is initiated by interactions between the S protein and its receptor.[7] Host proteases, such as transmembrane serine protease 2 (*TMPRSS2*), are needed to cleave the viral S protein, allowing permanent fusion of the viral and host cell membranes.[10,11] The accomplishment of these events drives the release of the viral RNA genome in the host cell and the subsequent start of the viral replication cycle.

A homolog of the angiotensin-converting enzyme (*ACE*), designated *ACE2*, was identified as the receptor for SARS-CoV-1[12] and SARS-CoV-2.[5] Previous evidence demonstrated that SARS-CoV-2 had a ten times higher affinity to *ACE2* than SARS-CoV-1, which was consistent with its higher efficiency of infection.[13] SARS-CoV-2 binding to *ACE2* leads to downregulation of these receptors.[14-16] As a result, the activity of *ACE2* is markedly attenuated.[17]

Although *ACE2* is ubiquitous, organs that express a high level of *ACE2* are potential targets of SARS-CoV-2 infection. Therefore, the distribution and abundance of *ACE2* in organs may be closely related to the clinical symptoms of COVID-19. *ACE2* is broadly distributed in the lungs, liver, intestine, and brain. This molecule is also enriched in the heart, kidneys, and testes.[18]

Extensive literature reveals that the lungs of SARS patients are commonly the most affected organs, with severe degeneration of the epithelium.[19-21] Nevertheless, other organs are also known to be damaged by the virus.[22-26]

As for human reproduction, concerns of potential vertical transmission have been raised.[27] Human embryos present all of the machinery needed for SARS-CoV-2 binding, internalization, and replication, suggesting that "in theory" viral infection may compromise embryonic and fetal development.

In males, *ACE2* and *TMPRSS2* are expressed in the testicular tissue, and the presence of SARS-CoV-2 in semen has been suggested.[28] However, information concerning the susceptibility of the male reproductive system to SARS-CoV-2 infection, sexual transmission, and possible effects on embryonic development remains inconsistent. Therefore, for the present study, a literature review was performed to determine whether male reproductive cells are vulnerable to SARS-CoV-2 infection and whether the infection may lead to decreased reproductive potential or transmission, resulting in deleterious effects on embryonic development and pregnancy outcomes.

2 | OTHER VIRAL INFECTIONS IN THE MALE REPRODUCTIVE SYSTEM

Infectious and inflammatory conditions in the reproductive system may cause male infertility. Viral infections may impair male fertility by directly affecting spermatozoa, inducing sperm death, reducing sperm count, and decreasing motility by inducing inflammatory cytokines. Infections may also indirectly affect sperm production and the function of genital organs.[29]

Several viruses may infect the testicles. Zika virus (ZIKV) can induce inflammation in the testis and epididymis, leading to testicular dysfunction and male infertility, as demonstrated in a mouse model.[30] In fact, ZIKV was detected in the semen of symptomatic men[31] and was shown to be sexually transmitted.[32] Mumps virus (MuV) has a high tropism for the testicles, and orchitis is a common complication.[33] Human immunodeficiency virus (HIV) infection also induces severe orchitis and results in male infertility.[34] HIV is detectable in semen shortly after infection and at all subsequent stages of the disease.[35]

Hepatitis B virus (HBV) and hepatitis C virus (HCV) can invade the human male germ line. Transcription of HBV genes was shown to occur in human sperm cells and is regulated by host genes.[36] Moreover, HCV infection has mutagenic effects on the chromosomes in sperm cells and may lead to extensive hereditary effects owing to genetic alterations and chromosomal aberrations.[37] Human papillomavirus (HPV) was also found in most parts of the male reproductive system, including the testis, epididymis, ductus deferens, and semen.[38-40] Finally, both cytomegalovirus (CMV)[41] and herpes simplex virus (HSV)[42] were detected in human spermatozoa. While CMV was found to have no impact on male reproductive health,

HSV detection in the ejaculate was directly correlated with reduced sperm motility and normal morphology.[43]

Similar to other viruses that can enter the testis and cause orchitis and, in some cases, result in male infertility,[44] the virus that causes SARS may lead to orchitis, testis damage, and defects in spermatogenesis.[45] However, after performing in situ hybridization, using both sense and antisense RNA probes to determine if the SARS virus infected the testis directly, researchers did not observe positive staining in any of the SARS testis sections. In this study, specific positive signals were obtained in lung sections of individuals with SARS, which were stained as a positive control.[45]

Temperature could be one reason for testis damage in SARS-positive patients. Germ cells must develop at a temperature lower than 37°C. Persistent high fever may negatively affect spermatogenesis and increase oxidative stress.[46] It has been suggested that heat-induced testicular cell degeneration may be mediated by apoptosis.[47] Although high fever is known to play an important role in viral orchitis, temperature might not be the only mechanism through which SARS affects testicular function. Xu et al[45] reported that the testes of non-SARS-infected patients with lasting high fever presented mild fibrosis and congestion, but there was no obvious germ cell loss or leukocyte infiltration.

The association with testicular damage in SARS and other types of viral orchitis could be attributed to endocrine dysfunction. The viruses per se might influence pituitary function. In HIV-infected patients, hypogonadism was shown to be common secondary to hypothalamic-pituitary-gonadal axis dysfunction and associated with low LH and FSH levels and not with primary testicular failure.[48] Indeed, HIV has been found in pituitary cells and might account for damage to the hypothalamus and pituitary gland.[49]

Hypogonadism has also been documented in HCV-infected men. Although the etiology has not been established, systemic inflammation associated with suppression of the hypothalamic-pituitary-gonadal axis cannot be eliminated.[50] Hemorrhagic fever virus (HFV)[51] and HSV[52] are also known to affect the pituitary-gonadal axis. Changes in several pituitary cell types have been observed in samples obtained from autopsies of SARS patients,[53] providing evidence of endocrine dysfunction in these patients, which may be correlated with defects in spermatogenesis.

3 | THE SARS-COV-2 RECEPTOR AND ITS EXPRESSION IN THE MALE REPRODUCTIVE TRACT

ACE2, the functional host receptor for SARS-CoV-2, is part of the renin-angiotensin-aldosterone system (RAAS), the main network responsible for the regulation of systemic arterial pressure and electrolyte homeostasis.[54] Angiotensinogen, produced by the liver, is converted by renin in angiotensin I (Ang I). Subsequently, *ACE* catalyzes the conversion of Ang I to angiotensin II (Ang II), inducing increased blood pressure, promoting vasoconstriction and inflammation.[55] *ACE2*, in turn, cleaves Ang II to angiotensin (1–7), which exerts vasodilating, anti-inflammatory, and anti-fibrotic effects.[56] In addition, *ACE2* cleaves Ang I into angiotensin (1–9), which is converted into angiotensin (1–7) by ACE. Therefore, *ACE2* plays a crucial role in the RAAS system because the RAAS activation depends on the tissue *ACE*/*ACE2* balance.[57]

It has been proposed that high *ACE2* levels might lead to an increased susceptibility to SARS-CoV-2 infection.[58] *ACE2* is widely distributed in various human tissues; however, *ACE2*-expressing organs do not equally participate in COVID-19 pathophysiology, implying that other mechanisms are involved in orchestrating cellular infection resulting in tissue damage.[54] In fact, although *ACE2* receptor is the best-known host factor for SARS-CoV-2 entry, the involvement of another essential element, the *TMPRSS2* protease, has been recognized.

Receptor recognition and membrane fusion occur through SARS-CoV-2 spike (S) protein. Virus entry requires S protein priming by cellular serine protease *TMPRSS2*, which involves S protein cleavage at S1/S2 and S2 subunits,[59] followed by viral release of the S1 subunit for post-fusion confirmation. Subsequently, the S1 subunit binds to *ACE2*, whereas membrane fusion takes place via the S2 subunit. This mechanism is crucial for viral infection[10,59–63] (Figure 1).

Evidently, SARS-CoV-2 cell entry and pathologic effects mainly occur in cells of the respiratory tract, and further dissemination in the host, such as in the testis, may be related to local *ACE2* and *TMPRSS2* expression. Several tissues and cells have been described to possess an intrinsic RAAS that acts locally through different paracrine and autocrine mechanisms.[64] In the male reproductive system, components of this system have been observed in various organs and tissues, such as the testicles.[65,66] Members of the RAAS in the testes are regulated by steroids and gonadotropins.[67,68] Apparently, the local RAAS is isolated from the plasma RAAS by a testicular blood barrier that protects male fertility from substances such as *ACE* inhibitors.[69]

As for *ACE2*, single-cell RNA sequencing data on human testes showed predominant expression of *ACE2* in spermatogonia and Leydig and Sertoli cells[70]; however, at the protein level, *ACE2* has been found to be expressed only in Leydig cells.[71,72] Men with severely impaired spermatogenesis have lower levels of *ACE2* than fertile men, suggesting that this enzyme may modulate sperm formation.[73–75] *ACE2* has also been reported to play key roles in the regulation of testosterone production and in the local vascular regulatory system.[76]

TMPRSS2 is mainly expressed in the lung, salivary gland, thyroid, gastrointestinal tract, pancreas, kidney, and liver, according to RNA and protein expression data available at the Human Protein Atlas (HPA) database. Notably, it is also expressed in many male tissues, such as the ductus deferens, epididymis, seminal vesicle, and prostate. *TMPRSS2* is highly expressed in prostate epithelial cells[77] and is androgen-responsive. *TMPRSS2* was also found to be released into semen in prostasomes.[78] More recently, it was suggested that spermatogonia express high levels of *TMPRSS2*.[77]

When it comes to testis expression, available data are inconsistent. Ren et al,[79] revealed that not only *TMPRSS2* but also *ACE2* was highly expressed in genitourinary organs. The testis was also

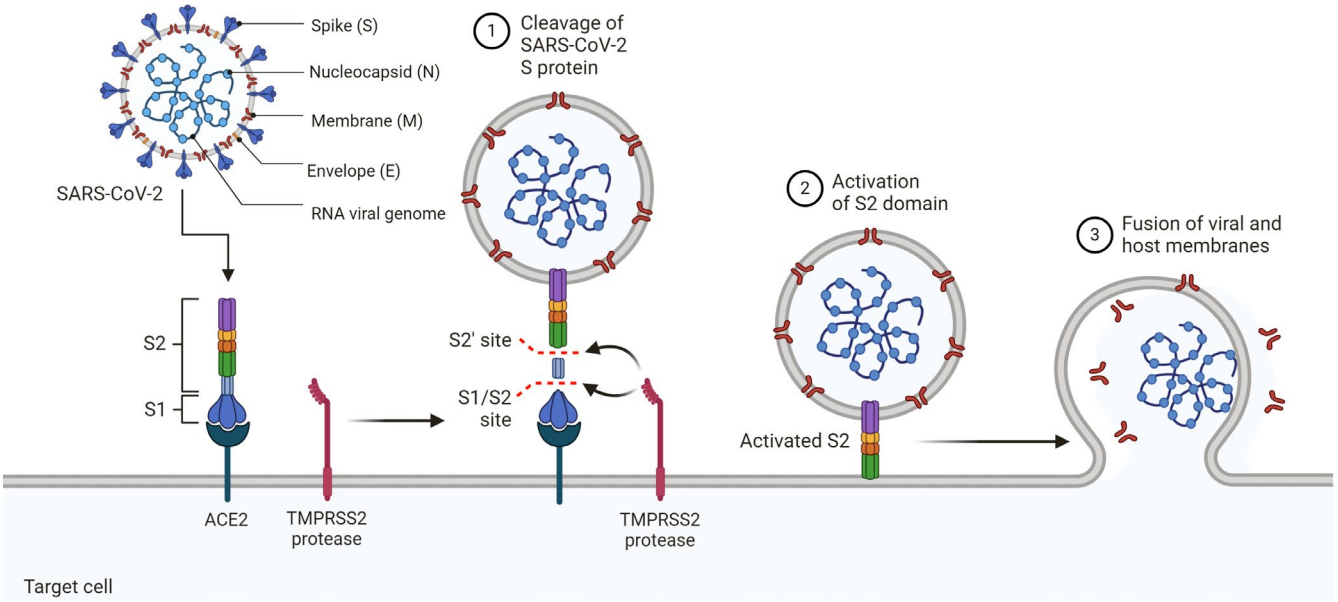

FIGURE 1 Mechanism of SARS-CoV-2 Viral Entry. The spike (S) protein of SARS-CoV-2 facilitates viral entry into target cells. Entry depends on binding of the surface unit, S1, of the S protein to the cellular receptor, the *ACE2*, which facilitates viral attachment to the surface of target cells. Entry requires S protein priming by cellular proteases, which involves S protein cleavage at the S1/S2 and the S2 sites and allows fusion of viral and cellular membranes, a process driven by the S2 subunit

identified as a high-risk organ because of the high expression level of *TMPRSS2* and *ACE2*. On the other side, Stanley et al[80] suggested that sperm cells may not be at increased risk of *ACE2*- and *TMPRSS2*-mediated viral entry and spread, given the lack of co-expression in any testicular cell type.

However, clinical data identified SARS-CoV-2 infection of several organs, where *ACE2* expression could not be detected in healthy individuals. These findings suggested that *ACE2* expression levels may vary substantially between individuals or during an infection[81] or that SARS-CoV-2 can use alternate receptors to enter certain cell types (ie, the cell surface protein basigin (*BSG*, also known as *CD147*)[82] and *CD26*.[83]

Several proteins have been recently identified to interact with SARS-CoV-2, including lectin receptors and multiple innate immune receptors,[84] heparan sulfate,[85] neuropilins, asialoglycoprotein receptor 1, and Kremen protein 1.[86] However, most of them lack virology-related evidence to support their roles as SARS-CoV-2 entry factors.

It was suggested that the human tyrosine-protein kinase receptor (*AXL*), a member of the *TAM* receptor family, which is abundantly expressed in Sertoli and Leydig cells,[87] not only interacts with the SARS-CoV-2 S glycoprotein but also facilities SARS-CoV-2 entry into human pulmonary epithelial cells in an *ACE2*-independent manner.[88]

Likewise, besides *TMPRSS2*, many proteases have been found to activate coronaviruses. Furin,[89] the endosomal cysteine proteases cathepsin L (*CatB/L*),[62] trypsin,[90] thermolysin,[91] elastase,[92] and factor Xa[93] have been shown to cleave SARS-CoV-1-S. The amino acid homology between SARS-CoV-2-S protein and SARS-CoV-1-S protein is nearly 76%[10]; however, apparently, *TMPRSS2* is an essential host cell factor for SARS-CoV-2.[89]

4 | THE EFFECT OF THE SARS-COV-2 INFECTION ON THE MALE REPRODUCTIVE TRACT

The blood-testicular or blood-epididymis barrier, often described as Sertoli cell-Sertoli cell tight junctions or tight junctions between the epithelium, is much more complex than just the tight junctions. These barriers consist of three components: anatomical, physiological, and immunological factors. Together, these components create a unique, anatomical, physiological, and immunological microenvironment, which is responsible for the proper development of germ cells into fully functional spermatozoa.[94] Nevertheless, several viruses, such as MuV,[95] ZIKV,[96] Ebola,[97] HBV, and HCV,[98] have been shown to disrupt the blood-testis barrier and infect human testes.

Some viruses, such as ZIKV, may persist in the seminal fluid for a very long time.[99] Likewise, the Ebola virus has been detected in the semen of men after they have recovered from the disease, demonstrating the long-term presence of the virus in semen.[100] These reports suggest that the blood-testicular barrier may not be an efficient barrier to viruses.

4.1 | Orchitis

Orchitis[101] and orchiepididymitis[102] were identified as complications of SARS-CoV-2. Immunohistochemistry demonstrated abundant IgG precipitation in the seminiferous epithelium of testes of individuals with SARS, indicating a possible immune response as the cause for the damage.[45]

Additionally, thrombotic complications of SARS-CoV-2 may affect the genitourinary system,[101] with priapism reported in a critically ill patient, with acute respiratory distress syndrome and coagulopathic complications.[103] The high expression of *ACE-2* is the human testis[71,104] with viral binding may also lead to tissue inflammation and the development of orchi-epididymitis with testicular pain.[105] In fact, testes from COVID-19 patients exhibited significant seminiferous tubular injury, reduced Leydig cells, and mild lymphocytic inflammation.[106]

4.2 | Presence of SARS-CoV-2 on seminal fluid

A recent report by Li et al[28] described the presence of SARS-CoV-2 in semen samples from six patients, four of whom were at the acute stage of SARS-CoV-2 infection and the remaining two were recovering from the disease. Scientific evidence of this report is low due to the small sample size and lack of subsequent follow-up. Moreover, the methodology used for the detection of the virus in the semen was unclear, and RT-PCR was used to detect SARS-CoV-2 in nasal and pharyngeal swabs; however, it was not clear whether the same assay was used to detect SARS-CoV-2 in semen samples. Finally, the possible contamination of semen samples by other body fluids must also be considered, especially if samples were collected by masturbation.

The SARS-CoV-2 particle size ranges from 70 to 90 nm,[107] raising the question of whether it is possible that such a large virus would bypass the blood-testis barrier. However, the MuV virus, a virus with larger dimensions than SARS-CoV-2, can disrupt the blood-testis barrier and infect human testes.[95]

As described previously, SARS-CoV-2 infection depends on the virus binding to its receptor *ACE2*[7] and fusion of the viral and host cell membranes by *TMPRSS2*.[108] The co-expression of both the *ACE2* and *TMPRSS2* genes was reported in spermatogonia and prostate endocrine cells,[70,77] suggesting a potential vulnerability to SARS-CoV-2.[77] Nonetheless, the presence of SARS-CoV-2-associated receptors does not guarantee infection.

In contrast to these findings, SARS-CoV-2 was not detected in the semen of a recovering patient with COVID-19.[109] In this study, a semen sample was collected one week after the last positive nasopharyngeal swab and fifteen days after the onset of the disease. Despite the limitations of the nature of the study, a single case report, the absence of viral RNA amplification on the semen sample raises the question as to whether the virus was ever present or if it was present at the peak of the infection, and SARS-CoV-2 clearance in seminal fluid coincided with clinical recovery. It can also be speculated that the virus may be detected in the semen of patients experiencing a more severe disease or in samples collected during the acute phase.

Song et al[110] examined semen samples from COVID-19-confirmed patients at both the acute and recovery phases of the disease, and Guo et al[111] examined samples of a cohort of patients with a recent infection or recovering from COVID-19. Comparable results with the abovementioned report were achieved, suggesting that SARS-CoV-2 is absent in the semen of men infected with COVID-19; the articles also indicate the unlikely possibility of sexual transmission through the semen at about one month after the first detection. Song et al[110] also tested testicular specimens from a deceased COVID-19 subject and did not detect the presence of viral RNA.

Investigating a larger group of patients, Pan et al[112] reported that SARS-CoV-2 was not detected in the semen of patients recovering from COVID-19. The samples were tested 29–36 days after COVID-19 diagnosis by qRT-PCR. The authors also investigated the gene expression levels of *ACE2* and *TMPRSS2* in different cells of the testes and found that the expression of both genes was low.[112]

Nora et al[113] also investigated the presence of SARS-CoV-2 in (i) 18 semen samples of patients in convalescence, obtained 8–54 days after the absence of COVID-19 symptoms, (ii) two samples from patients with an active COVID-19 infection, and (iii) 14 samples from negative controls. Consistent with the other studies previously mentioned,[109,110,112] in this trial, no RNA was detected by RT-PCR.

Taken together, these studies indicated that it is unlikely that recovering subjects may still have and transmit SARS-CoV-2 through seminal fluid. Questions remain as to whether SARS-CoV-2 infection involves the testis and the seminal fluid under other circumstances. It may be hypothesized that more severe forms of the disease reflect a higher blood viral load and a higher chance to reach other organs and body fluids, including the testes and semen.

Until sexual transmission of SARS-CoV-2 from infected men to their partners is ruled out, patients need to be counseled to protect themselves and to consider all possible options to protect their pregnancy if motherhood is desirable.

4.3 | Implication on seminal quality

The fact that SARS-CoV-2 shares the same receptor as SARS-CoV-1 and SARS-CoV-1 was determined to cause not only orchitis and testis damage but also defects in spermatogenesis,[45] suggests a possible implication of SARS-CoV-2 infection in the seminal quality. Testicular morphological changes in the testes of COVID-19 patients indicate that SARS-CoV-2 infection may impair male germinal cell development and eventually lead to germinal cell loss.[114] In facts, scrotal discomfort has been described in COVID-19-diagnosed patients[110]; moreover, moderate infection was associated with decreased sperm concentration[113,115] and motility.[113]

Autopsied testicular and epididymal specimens of COVID-19 patients showed the presence of interstitial edema, congestion, red blood cell exudation in testes, and epididymides. Thinning of seminiferous tubules was also observed.[115]

TUNEL assays revealed that the number of apoptotic cells in COVID-19 testes was significantly higher,[114,115] suggesting that SARS-CoV-2 damages the immune privilege and innate immune

homeostasis of the testis and triggers a secondary autoimmune response contributing to the primary pathogenesis of viral orchitis and consequent testicular damage.[114]

Oxidative stress by reactive oxygen species (ROS) is related to all the main changes observed in inflammatory and infectious diseases.[116] The spermatozoa are particularly susceptible to oxidative stress, leading to lipid peroxidation, resulting in disruption of membrane permeability and, thus, efflux of ATP, impairing flagellar movement.[116,117] The detrimental impact of oxidative stress on sperm parameters and fertility potential has been determined.[118] Sperm viability, motility, and fertilization potential are disrupted by oxidative stress in the reproductive tissues, evidenced by the presence of high levels of ROS in the semen of infertile men.[119] Therefore, it is suggested that the addition of sperm DNA fragmentation measurement to conventional diagnosing options such as semen analysis can play a crucial role in investigating the possibility of male fertility impairment caused by COVID-19.[120]

4.4 | Hormonal milieu

Male subjects seem to not only be more susceptible to COVID-19 than female subjects[121,122] but also their case fatality rate attributable to SARS-CoV-2 infection is also higher.[123] *ACE2* expression levels have been demonstrated to be higher in male than in female patients, at least in the lungs[124]; moreover, *ACE2* is largely expressed in the testes, which show almost the highest *ACE2* expression among various body tissues.[125]

Salonia et al[126] speculated that a different hormonal situation could play an important role in the pathophysiology of COVID-19. Even though *ACE2* is expressed in Leydig cells,[125] in a testosterone-independent manner, in these cells, the enzyme has been proposed to play a role in steroidogenesis.[127] When comparing sex-related hormones of a cohort of men of reproductive age infected with SARS-CoV-2 with those of age-matched healthy men, Ma et al[128] found a potential alteration of the androgenic hormonal milieu.

Evidence indicates that SARS-CoV-2 infection in male individuals per se causes acute-stage hypogonadism,[129] the depletion of androgenic action triggering serious or an even fatal course of the disease. Patients with COVID-19 without clinical testicular involvement have been found to present a reduced testosterone/LH ratio, indicating possible subclinical damage to male gonadal function.[128] Çayan et al[130] observed that the serum testosterone level at baseline has a significant increased risk for hospitalization in the intensive care unit and mortality in patients with COVID-19. COVID-19 might deteriorate the serum testosterone level in SARS-CoV-2-infected male patients.

4.5 | Transmission to the fetus

ACE2 is expressed in several human ovarian compartments, and it can be quantified in follicular fluid.[131] Nevertheless, RNA expression of *TMPRSS2* in human cumulus cells was shown to be low or absent.[80] In contrast, a high level of *ACE2* and *TMPRSS2*, found in the trophectoderm that gives rise to placenta, suggests that the developing placenta may be vulnerable to SARS-CoV-2 infection.[77] Tissues collected at the maternal-fetal interface during the first semester of pregnancy, including both embryo-derived cells (fetal placenta), maternal blood, and decidual cells, displayed a complex pattern in the expression of SARS-CoV-2-associated receptors and factors.[132] Finally, by quantifying the fraction of each cell type co-expressing different combinations of SARS-CoV-2 receptors with proteases, researchers suggested that the placenta is one of the most susceptible tissues to coronavirus infection.[77]

Although it is unlikely that COVID-19-recovered subjects transmitted SARS-CoV-2 through seminal fluid, it is imperative to monitor these patients' reproductive functions for any abnormalities that might impair future fertility. The possible presence of SARS-CoV-2 in seminal fluid must also be analyzed, with caution, in patients who have had different levels of viremia, are at different stages of the disease with different intervals between sample testing, and have recovered from systemic disease.

Evaluating the presence of SARS-CoV-2 in seminal samples is particularly important for patients planning parenthood. For those undergoing assisted reproduction treatments, semen washing may be a safe reproductive strategy to achieve pregnancy. As shown with other viruses present in seminal samples, semen washing removes spermatozoa, which are not vectors for the virus, from surrounding seminal fluid, and the virus-negative sperm fractions may be used in assisted reproduction.[133–135]

Stanley et al[80] examined the expression patterns of known viral host entry proteins to gain insights into the possible biological consequences of SARS-CoV-2 infection on reproduction. Transcripts of *TMPRSS2* were either absent or existed at very low levels in cumulus cells. The authors suggested that assisted reproductive treatments, in which oocytes are collected and fertilized in vitro, may potentially reduce or eliminate exposure of susceptible cell types to infection when compared with natural conception. Therefore, it is possible that in vitro fertilization (IVF) may represent a safer reproductive strategy than natural conception at this time. Additionally, the association of sperm washing with IVF may be an alternative to significantly reduce the risk of viral transition to the fetus.

5 | CONCLUSION

In conclusion, COVID-19 challenges all medical areas, including reproductive medicine. The occurrence of COVID-19 shows gender differences with men being more susceptible to SARS-CoV-2 infection and showing higher fatality rate than women. The male-related susceptibility in COVID-19 may be explained, in part, by the cell entry mechanisms of SARS-CoV-2. The *ACE2*, the cellular receptor for SARS-CoV-2, is largely expressed in the testes, which show almost the highest *ACE2* expression among various body tissues.[125]

Although the testes are immunologically privileged in case of viremia, some viruses can cross the blood-testis barrier, causing local inflammation, persist after an acute infection, and theoretically replicate within the male reproductive tract, which seems to be the case of SARS-CoV-2.

In fact, a testicular involvement in COVID-19 has been suggested. Previous studies demonstrated an association of SARS-CoV-2 and orchitis or orchiepididymitis.[101,102] SAR-CoV-2 may also disrupt male reproductive function through other mechanisms. It may activate oxidant-sensitive pathways via inflammatory responses, inducing oxidative stress. Compromised sex-related hormonal balance caused by acute-stage hypogonadism or possible damage to male gonadal function is also a matter of debate. Finally, possible implications of varying levels of viremia for sexual transmission and consequently for embryonic infection, pregnancy outcome, and congenital disease cannot be excluded.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

AUTHOR'S CONTRIBUTION

EBJ designed the study and wrote specific sections; AS and AIJ wrote specific sections of the paper; and DB designed the study, wrote specific sections, and critically analyzed and edited the final manuscript.

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