

Could SARS-CoV-2 affect male fertility?

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Abstract

We performed this systematic review to evaluate the possibility of an impact of SARS-CoV-2 infection on male fertility. SARS-CoV-2 enters the cells with the help of ACE2; therefore, testicular expression of ACE2 was analysed from transcriptome sequencing studies and our unpublished data. Literature suggested that SARS-CoV-1 (2002-2004 SARS) had a significant adverse impact on testicular architecture, suggesting a high possibility of the impact of SARS-CoV-2 as well. Out of two studies on semen samples from COVID-19 affected patients, one reported the presence of SARS-CoV-2 in the semen samples while the other denied it, raising conflict about its presence in the semen samples and the possibility of sexual transmission. Our transcriptome sequencing studies on rat testicular germ cells showed ACE expression in rat testicular germ cells. We also found ACE2 expression in transcriptome sequencing data for human spermatozoa, corroborating its presence in the testicular germ cells. Transcriptome sequencing data from literature search revealed ACE2 expression in the germ, Sertoli and Leydig cells. The presence of ACE2 on almost all testicular cells and the report of a significant impact of previous SARS coronavirus on testes suggest that SARS-CoV-2 is highly likely to affect testicular tissue, semen parameters and male fertility.

KEYWORDS

COVID-19, male fertility, SARS Coronaviruses, SARS-CoV-2

1 | INTRODUCTION

Wuhan city, the capital of Hubei province in China, became the epicentre of an outbreak of pneumonia in December 2019. Soon, the virus causing it was isolated, finding that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was responsible for it. The WHO later designated it as the coronavirus disease 2019 (COVID-19) in February 2020 (WHO Director-General's Remarks at the Media Briefing on, 2019-NCoV on 11 February 2020). The outbreak is supposed to have occurred as a result of zoonosis from the live animal market, but human to human transmission became evident soon. COVID-19 is rapidly spreading worldwide, leaving people in acute respiratory distress, and causing significant morbidity and mortality. COVID-19 has been announced a pandemic by the WHO, and it has already claimed 278,892 lives with about 4.0 million active

infections as of 11 May 2020 (WHO COVID-19 Dashboard, 2020). By the time you would read this article, the figures would have changed to more threatening numbers, that is how fast this virus is affecting and killing people. The most important aspect of this disease is the extraordinary length of morbidity, with a median of 22 days (Yang et al., 2020) and a high degree of the immune response, which may affect organs other than the primary infected organs.

While no study till date has analysed the influence of SARS-CoV-2 on testis or semen parameters, data from previous coronavirus outbreak provide critical information regarding its possible impact of male fertility. A lone study on testicular samples showed a significant impact of SARS coronavirus on the reproductive system (Xu et al., 2006). In this study, the authors inspected the pathological variations in the testis of six patients who deceased of SARS and compared it with controls. They found that SARS caused orchitis and

testes showed widespread damage of germ cells with very few or no spermatozoa in the seminiferous tubules. The seminiferous tubules had thickened basement membrane and showed significant leukocyte infiltration and macrophage staining, suggesting the impact of immune response on the testis. However, SARS genome sequences were not spotted in the affected testis, further suggesting that the impact on testis was due to immune response. This study clearly suggested that SARS coronaviruses cause orchitis and may lead to infertility (Xu et al., 2006).

In a recent study on 34 Chinese patients who had recovered from COVID-19, 6 (19%) patients reported scrotal discomfort at the time of active disease, though a comprehensive genitourinary examination was not performed (Pan et al., 2020). Since it affects people of all ages, including pre-pubertal children, its impact on fertility remains a major concern. Since collection of data from the infected individuals would take time, lessons learnt from other viruses can provide a great deal of information about the possible impact of SARS-CoV-2 on male fertility.

2 | LITERATURE SCAN

The relevant studies were searched from the electronic databases such as Google Scholar, PubMed, EMBASE, Scopus and COVID-19-specific databases such as LitCovid and WHO website till the 11th of May 2020. The keywords 'viruses and male infertility', 'viruses and testis', 'viruses and germ cells', 'SARS coronaviruses and testis' were used to retrieve studies evaluating the impact of viruses on male fertility. Similarly, keywords such as 'ACE2 expression', 'angiotensin-converting enzyme' and 'ACE2 transcript' were used to search transcriptome/gene expression studies for evaluating the expression of ACE2 in testis, germ cells, Sertoli cells and Leydig cells. The search was limited to human, mouse and rat studies published in English language only. Additional articles were identified through references cited in the retrieved articles.

There were a total 128 hits, of which 12 articles were relevant to our investigation of ACE2 expression, eight articles were on testis/germ cells, two were on Sertoli cells, two were on Leydig cells, and the remaining were on viruses and male fertility. We had recently performed transcriptome sequencing studies on testicular germ cells and mature human spermatozoa, which were searched for the presence of ACE2 transcripts.

2.1 | SARS coronaviruses in testis and semen

Two coronaviruses, namely SARS-CoV and MERS-CoV, are widely known infectious agents of respiratory diseases in humans (De Wit, Van Doremalen, Falzarano, & Munster, 2016). SARS coronavirus is known to damage multiple organs including human testes (Xu et al., 2006). SARS-infected patients display leukocyte infiltration, impaired spermatogenesis and testicular damage with wide-spread germ cell destruction with a few or completely absent spermatozoa

in the seminiferous tubules (Xu et al., 2006). SARS can cause orchitis in humans (Xu et al., 2006). In a study of COVID-19, 38 participants provided semen specimens, of which 23 participants (60.5%) had achieved clinical recovery and 15 participants (39.5%) were at the acute stage of infection. The results of semen testing found that six patients (15.8%) had results positive for SARS-CoV-2, including four of 15 patients (26.7%) who were at the acute stage of infection and two of 23 patients (8.7%) who were recovering, which is particularly noteworthy (Li, Jin, Bao, Zhao, & Zhang, 2020). Nevertheless, in another similar study from China, the virus was not detected in the semen samples of 34 COVID-19 patients after a median of 31 days. In this study, 6 out of 34 (19%) patients reported scrotal discomfort, which was taken to be suggestive of viral orchitis, but a comprehensive genitourinary examination was not performed (Pan et al., 2020).

2.2 | ACE2 in testicular cells

ACE2 is the first known human homologue of angiotensin-converting enzyme (ACE). While ACE expression is mostly ubiquitous, ACE2 transcripts are found only in heart, kidney and testis (Donoghue et al., 2000). Later on, it was shown that the catalytic activity of ACE2 was confined to the membrane preparations of whole testes and Leydig cells from adult rats. The immunohistochemical localisation showed the presence of ACE2 in the Leydig cells of rat testis. However, in human testis, it was localised to both, the Sertoli and Leydig cells (Douglas et al., 2004). They also showed that the expression of ACE2 in the testis is developmentally regulated as its expression increased progressively between day 7 and 19 postpartum, which was coincident with the maturation of progenitor cells into steroidogenic Leydig cells (Douglas et al., 2004). Furthermore, the ablation of the Leydig cells by a specific toxin, ethane dimethane sulphonate (EDS), eliminated ACE2 immunoreactivity from the interstitium, indicating the Leydig cells to be the main testicular source of this protein in rats. The ACE2-positive cells increased constitutively with increasing number of Leydig cells during recovery after EDS treatment (Douglas et al., 2004). Interestingly, the inhibition of LH and testosterone levels by the use of testosterone implants did not significantly alter the expression of ACE2 activity in the testis, suggesting that this enzyme is not regulated hormonally (Douglas et al., 2004). Overall, this study demonstrated that ACE2 is a constitutive product of adult-type Leydig cells and may regulate testicular function by yet unknown mechanism (Douglas et al., 2004).

As the newly identified coronavirus (SARS-CoV-2) shares the same receptor as SARS, it raises the possibility of testis being a potential target for SARS-CoV-2 infection. In our recent transcriptome sequencing studies, we found ACE2 expression in spermatocytes and round spermatids (our unpublished data). We also found the presence of ACE2 transcript in our recent transcriptome sequencing of human spermatozoa, further validating its expression in germ cells (our unpublished data). We also retrieved the published transcriptome studies to figure out ACE2 expression in testicular cells. Transcriptomic analyses of human testicular germ cell subtypes obtained from pools

of 500 individually laser-capture microdissected cells by RNA-Seq revealed the presence of ACE2 transcripts in human spermatogonia, spermatocyte and spermatids (Jan et al., 2017). Similarly, another RNA-Seq study also reported the presence of ACE2 transcripts in mouse testis (Soffientini et al., 2017). Single-cell RNA-Seq transcriptomes for >62,000 individual spermatogenic cells from adult male mice revealed the presence of ACE2 transcripts in mouse spermatogonium and spermatid population (Hermann et al., 2018).

Recently, the analysis of ACE2 expression in adult human testis by single-cell transcriptome sequencing revealed that ACE2 expression is chiefly limited to the Leydig and Sertoli cells in the human testis (Wang & Xu, 2020). Furthermore, using Gene Set Enrichment Analysis (GSEA) they showed that ACE2-positive spermatogonia display a higher number of genes related to viral reproduction and transmission, and a comparatively lower number of genes associated with spermatogenesis compared to ACE2-negative spermatogonia. Likewise, ACE2-positive Leydig and Sertoli cells showed a higher number of genes related to cell-cell junction and immunity, and a lower number of genes associated with mitochondria and reproduction (Wang & Xu, 2020). With this study, the authors concluded that testis is a high-risk organ vulnerable to SARS-CoV-2 infection that may lead to spermatogenic failure (Wang & Xu, 2020).

Recently, single-cell RNA-Seq of adult human testis showed that ACE2 is expressed by both germ and somatic cells. The Sertoli cells, spermatogenic stem cells and Leydig cells are the majority cluster with significant enrichment of ACE2 expression (90% of cells) in Sertoli cells (Shen et al., 2020). Moreover, a higher number of cells were ACE2 positive in infertile men compared to fertile men, suggesting that an over-activation of ACE2 might affect spermatogenesis (Shen et al., 2020). They also showed that ACE2 expression was related to the age of men, with highest number of ACE2-positive cells in 30-year-old men compared to 20-year- and 60-year-old men (Shen et al., 2020).

As the incidence and severity of SARS-CoV-2 are reported to be higher in males than females, Shastri et al. performed a study to determine the time to viral clearance after infection in a total of 68 individuals (48 males and 20 females) with median age of 37 years (Shastri et al., 2020). They observed that females were able to achieve viral clearance significantly earlier than males. Furthermore, a serial follow-up evaluation of three families with both male and female patients demonstrated that female members of the same household cleared the SARS-CoV-2 infection earlier in each family (Shastri et al., 2020). In order to determine the reason for delayed clearance in males, they also checked the expression of ACE2 in tissue-specific repositories. It was found that testicular tissues were one of the tissues showing ACE2 expression in 3 independent RNA expression databases (Human Protein Atlas, FAMTOM5 and GETx). Interestingly, the ovarian tissue showed very low expression of ACE2 (Shastri et al., 2020).

3 | DISCUSSION

Viruses are much more penetrative than we understand, and they are known to affect male fertility since long. A classical example of

virus-induced infertility comes from the mumps virus. There were several large epidemics of mumps during 1914–18 and 1939–45. In one of the credible classic reports on the effect of mumps on fertility, Ballew and Masters (1952) evaluated 79 individuals with family case histories of prior mumps infection, finding a total of 19 (23%) cases of mumps orchitis (Ballew, 1954). Of the 19 males with mumps orchitis history, 12 (63%) had the involvement of bilateral testes and 11 (58%) were found to be azoospermic on repeated examinations. An article by Benard in 1927 stated that Sterility following adult mumps is a myth (Benard, 1927). This myth was cleared by yet another study on mumps induced infertility. Scott (1960) found that 21.4% of infertile husbands attending his infertility clinic had a history of mumps in childhood, and 1.8% had mumps after puberty. From an extensive review of 25,000 cases, Scott reported that about 20% of mumps cases have orchitis, and about 15% have bilateral involvement (Scott, 1960).

The male reproductive tract turned out to be a subject of great interest in virology following the upsurge of human immunodeficiency virus (HIV) infections in the 80's (Stekler et al., 2008). HIV is one of history's deadliest and most detailed studied viruses. HIV has infected 75 million people and caused about 32 million deaths. Globally, 37.9 million people were living with HIV at the end of 2018 ('WHO | Number of Deaths Due to HIV/AIDS', 2019). Since numerous HIV-infected persons worldwide are of reproductive age, pregnancy and desire for reproduction have arisen as clinically relevant problems in this population (Khawcharoenporn & Sha, 2016). Many HIV/AIDS-related disorders comprise orchitis, acute epididymitis and other pelvic inflammatory disorder induced by opportunistic bacteria and sexually transmitted infection (STI) acquired by a near-HIV transmission route (Brookings, Goldmeier, & Sadeghi-Nejad, 2013). At the same time, certain antiretroviral medications are noxious to mitochondria of the cells and can distress spermatozoa (White, Mital, Taylor, & John, 2001). Impairments in sperm development and sperm generation, including reduced ejaculatory volume, number of spermatozoa and progressive motility, have been found in HIV-infected people (Bujan et al., 2007; Nicopoulos, Almeida, Vourliotis, & Gilling-Smith, 2011; White et al., 2001). Among other cases, the people diagnosed with HIV were found to be oligozoospermic with viscous semen and few round cells (Kushnir & Lewis, 2011). Furthermore, a study on testicular autopsy reported the gradual destruction of germ cells in extended AIDS survival (Shevchuk, Pigato, Khalife, Armenakas, & Fracchia, 1999). Males who used more advanced immunosuppressants had reduced levels of total serum testosterone, caused by secondary hypogonadism (Gomes, Aragüés, Guerra, Fernandes, & Mascarenhas, 2017), and the latter is one of the significant endocrine disorders causing infertility in men with AIDS (Wong, Levy, & Stephenson, 2017).

3.1 | BTB is not limiting to viruses

The blood-testis barrier (BTB) is not impermeable to viruses, particularly with the onset of systemic or local inflammation or viraemia.

Eventually, some viruses could be found in semen (Li, Wang, & Han, 2012; Salam & Horby, 2017). In mammals, viruses such as parainfluenza virus, Japanese encephalitis virus, foot and mouth disease virus and Paravaccinia virus were detected in semen long ago (Kahrs, Gibbs, & Larsen, 1980). More than 27 viruses have been found in semen to date (Salam & Horby, 2017). The scientists have found evidence after analysing more than 3,800 research papers that at least 11 viruses live in the testis, including those causing pneumonia, dengue and extreme acute respiratory syndrome (Salam & Horby, 2017). Regardless of the way they enter, viruses have been recognised in the human ejaculate, though the degree to which infection and reproduction occur inside the spermatozoa or germ cells stay indistinct (Mansuy et al., 2016). In addition, some viruses, such as HIV/AIDS, Zika and hepatitis virus, can be transmitted via semen (Atkinson et al., 2017). Zika virus can be found inside spermatozoa and might be transferred to the oocyte at the time of fertilisation. It is suggested that sexual transmission of ZIKA virus will prompt an ascent in the number of infected people in the endemic territories (da Silva, 2018).

The deleterious effects of viruses include overt damage to testis, spermatozoa, irregular sex-hormone expression and inflammatory cytokine dysregulation (Puggioni et al., 2018). Initially, it was believed that viruses do not usually reproduce in the male reproductive tract, but can be retained for years within cells or in secretions as free particles (Murray et al., 2010); however, a study exposed that the bluetongue virus could reproduce inside the testis in the endothelial cells of the peritubular regions, eliciting increased type-I interferon reaction, diminished Leydig cell testosterone formation and even destruction of the Sertoli cells (Ma, Zhang, & Zheng, 2017; Puggioni et al., 2018). The testes are made primarily of seminiferous tubules and intratubular tissue. The seminiferous tubule is the place where spermatozoa are produced, composed of sperm-producing cells (spermatogonia) and the supporting Sertoli cells (Puggioni et al., 2018). Under LH regulation, the interstitial Leydig cells are accountable for the production of testosterone. Since Leydig and Sertoli cells are bathed by blood, the effect of virus on these cells is enough to cause infertility, even if the BTB were impermeable to viruses.

3.2 | Effect of SARS Coronaviruses on testes and semen parameters

As discussed above, only two studies have analyzed SARS-CoV-2 presence in semen samples. In one of these, 38 participants provided a semen specimen, of which 23 participants (60.5%) had achieved clinical recovery and 15 participants (39.5%) were at the acute stage of infection. The results of semen testing found that 6 patients (15.8%) had results positive for SARS-CoV-2, including 4 of 15 patients (26.7%) who were in the acute stage of infection and 2 of 23 patients (8.7%) who were recovering, which is particularly noteworthy (Li, Jin, et al., 2020). Nevertheless, in another similar study from China, the virus was not detected in the semen samples of 34 COVID-19 patients after a median of 31 days (Pan et al., 2020).

Only two studies have looked for the presence of SARS-CoV-2 in semen samples and present contrasting findings. Therefore, further studies are required before the virus presence in semen samples and hence chances of sexual transmission can be ascertained. However, none of these studies mentioned whether the virus was analyzed in washed spermatozoa, seminal plasma or in neat semen samples. Assuming that it was done in neat semen samples, its analysis in washed sperm remains an attractive proposal, as the latter can guide the use of semen samples in assisted reproduction.

While no study to date has analysed the influence of SARS-CoV-2 on testis, data from previous coronavirus outbreak provide critical information about the possible impact of SARS-CoV-2 on male fertility. A lone study on testicular samples had shown a significant impact of the SARS coronaviruses on the reproductive system (Xu et al., 2006). In this study, the authors inspected the pathological variations in the testis of six patients who deceased of SARS and compared it with controls. They found that SARS caused orchitis, and the testis showed widespread damage of germ cells with very few or no spermatozoa in the seminiferous tubules. The seminiferous tubules had thickened basement membrane and showed significant leucocyte infiltration and macrophage staining, suggesting the impact of immune response on the testis. However, SARS genome sequences were not spotted in the affected testis, further suggesting that the impact on the testis was due to the immune response. This study clearly suggested that SARS coronaviruses cause orchitis and may lead to infertility even if they do not enter the seminiferous tubules or are not detected in semen samples (Xu et al., 2006).

SARS-CoV-2 is known to use angiotensin-converting enzyme 2 (ACE2) as the receptor for gaining entry into the host cells (Hoffmann et al., 2020). The virus enters the human body through the respiratory organs, but once inside the body, it could gain entry into various cells expressing ACE2, which may explain its multi-organ impact. Single-cell transcriptome studies have revealed that Sertoli cells, spermatogonia and Leydig cells express ACE2 enzyme abundantly and are therefore highly vulnerable to SARS-CoV-2 infection (Fan, Li, Ding, Lu, & Wang, 2020; Wang & Xu, 2020). Gene Set Enrichment Analysis (GSEA) suggested that categories of gene ontology associated with viral replication and transmission are distinctly enriched in ACE2-positive spermatogonia, whereas related terms for male gamete generation are down-regulated (Wang & Xu, 2020). Taken together, we can infer that SARS-CoV-2 can also pose a high risk of injury to the testicular cells.

3.3 | Effect of SARS Coronaviruses on fertility via impact on brain

Most viruses enter human body through the nasal and oral routes and travel through the brain by increasing and dispersing through olfactory bulbs; the lingual nerve near the jawline and through the tongue; or the vagus nerve that goes through the neck and thorax (van den Pol, 2009). Viral particles may break the blood-brain barrier

(BBB) legitimately or by endothelial cell entrance while communicating with the sensory system, or by contaminating monocytes that blow the barrier before duplicating and overflowing white blood cells once inside the brain. Conversely, certain viruses do not cross the BBB, but induce an immune reaction that can activate breaching of the divide by cytokines or chemokines (Chai, He, Zhou, Lu, & Fu, 2014). Numerous viruses have been detected in the brain, including influenza, poliovirus, measles, mumps, rubella, HIV, SARS-CoV and SARS-CoV-2 (Cai et al., 2020; Sarrazin, Hézode, Zeuzem, & Pawlotsky, 2012). Inflammation may occur in various anatomical locations within the CNS, such as meninges, brain and spinal cord, or at the same time in multiple regions that could result in meningitis, encephalitis and myelitis or even more severe conditions like meningoencephalitis and encephalomyelitis.

It has been documented that the brain cells express ACE2 receptors that were observed over glial cells and neurons, making them a possible target for SARS-CoV-2 (Zhao et al., 2016; Zhou et al., 2020). A recent study showed that the SARS-CoV-2 genomic sequence is similar to the previous SARS-CoV virus (Yu, 2020), particularly the SARS-CoV receptor-binding domains being structurally identical to that of the SARS-CoV-2 (Lu et al., 2020). It suggests that SARS-CoV and SARS-CoV-2 share the receptor ACE2, which could be the reason why SARS-CoV and SARS-CoV-2 could invade the same location in the human brain. Previous experiments have shown SARS-CoV's capacity to induce neuronal death in mice by entering the brain through the nose around the olfactory epithelium (Hamming et al., 2004; Netland, Meyerholz, Moore, Cassell, & Perlman, 2008). The neurological damage was also observed in the SARS-CoV and MERS-CoV infections (Arabi et al., 2017; Desforges et al., 2019).

The very first case of SARS-CoV-2-associated meningitis/encephalitis observed upon brain MRI of a 24-year-old man (Moriguchi et al., 2020) revealed hyperintensity along the right lateral ventricle wall and hyperintense signal shifts in the right mesial temporal lobe and hippocampus, indicating the possibility of SARS-CoV-2 meningitis. An analysis of 214 patients showed that 78 out of 214 patients had severe neurological symptoms (Mao et al., 2020). These patients displayed symptoms of the central and the peripheral nervous systems. Other reports, such as fatigue, nausea and diarrhoea could be digestive or neurological symptoms (Li, Bai, Bai, & Hashikawa, 2020; Mao et al., 2020). After conducting the CT scan and MRI, a patient diagnosed with SARS-CoV-2 reported an unusual type of encephalopathy that has yet to be shown as caused by SARS-CoV-2 infection (Poyiadji et al., 2020). SARS-CoV-2's micro-invasive ability may play a role in COVID-19 patients' respiratory failure due to the linking of the synapse-connected route from the mechanoreceptors and chemoreceptors in the lung and lower airways to the medullary cardio-respiratory core (Li, Bai, et al., 2020). Expanding proof shows that the coronaviruses are not just constrained to the primary organs of entry, for example, the respiratory system, but can likewise enter the central sensory system and the reproductive tract. The central nervous system may have a major role in COVID-19 morbidity and mortality.

The central nervous system plays a vital role in the onset and endocrine control of spermatogenesis. The hypothalamic-pituitary-gonadal axis exerts a critical role in the pubertal growth and reproduction. Neurons releasing gonadotropin hormone (GnRH) secrete GnRH, the pulsatile release of which is critical to gonadotropin synthesis and release, the dysregulation of which results in infertility (Singh, Agrawal, Verma, & Singh, 2017). A controlled and pulsatile release of GnRH from the hypothalamus activates the release of the follicle-stimulating hormone (FSH) and the pituitary gland luteinising hormone (LH). Low level of GnRH causes decrease in FSH and LH secretions, resulting in impaired development and functioning of the Sertoli and Leydig cell, which may result in infertility. Altered operation of the GnRH pulse may also disturb the levels of estradiol and prolactin, which are known to relate to infertility. Therefore, apart from its direct impact on testes, SARS-CoV-2 may affect pubertal development and fertility indirectly by its impact on the central nervous system.

3.4 | Effect of SARS Coronaviruses on fertility via impact on prostate

The prostate gland is a male genital organ whose primary function is to secrete prostate fluid, one of the main seminal components (Verze, Cai, & Lorenzetti, 2016). The prostate gland muscles also help in pushing this seminal fluid through the urethra during ejaculation (Aaron, Franco, & Hayward, 2016; Verze et al., 2016). Prostate-excreted fluid accounts for around one-third of overall semen volume and includes numerous proteins, calcium and citric acid (Lu et al., 2020; Ricardo, 2018). The prostate is known to express ACE2 in normal and healthy prostate hyperplasia, so it is more likely to get SARS-CoV-2 infection, which may affect its secretions. Notwithstanding the respiratory tract fluid, the researchers effectively recognised SARS-CoV-2 in the patient's urine, saliva and conjunctiva (Guan et al., 2020; Xia, Tong, Liu, Shen, & Guo, 2020). It suggested that the virus may have different courses of transmission. The entirety of the above information suggests that the respiratory system, digestive system and urogenital system are all SARS-CoV-2 target organs. Hence, COVID-19 patients' testis and prostate are also vulnerable to SARS-CoV-2. A recent study reported that 18 cases of COVID-19 patients did not have SARS-CoV-2 in mediated prostatic secretion (Quan et al., 2020). So far, no other study is available to validate whether or not the prostate is actually affected.

4 | CONCLUSION

From the evidence cited above, it is plausible that SARS-CoV-2 can affect multiple reproductive organs, raising the possibility of its effect on fertility. Particularly in the case of young children who are undergoing puberty, SARS-CoV-2 infection could significantly affect the sexual development and fertility due to its impact on testicular and prostate development apart from its impact on the

neuroendocrine axis that regulates the pubertal development and the onset of spermatogenesis. Among the adult male population, the viral infection may cause significant damage to the testicular tissue, particularly the Sertoli cells, which can impair spermatogenesis. Out of two studies on semen samples, one reported virus presence and one denied it, raising doubts about its very presence in semen. If the virus is present in semen, it would be interesting to investigate its source. Since prostatic secretions have been found virus negative, the virus may be secreted in semen from other organs, including testis. Since co-morbidities have a significant impact on the overall outcome of SARS-CoV-2 infection, individuals with significant oxidative stress and other infertility predisposing factors are even more vulnerable to SARS-CoV-2-induced infertility. While under such life-threatening infections, lifesaving is a major concern, the impact of SARS-CoV-2 on fertility could be studied in the recovered patients. Since the impact of this viral disease is long-lasting, and spermatogenesis takes 70–75 days to completion, SARS-CoV-2 recovered patients are ideal subjects for studying its impact on spermatogenesis and fertility. We suggest that SARS-CoV-2 should be given a high priority to study its correlation with orchitis and infertility. Inclusion of a clause of SARS-CoV-2 infection history in infertility workup in future would help in consolidating these speculations.

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CONFLICT OF INTEREST

The authors declare to have no conflict of interest.

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