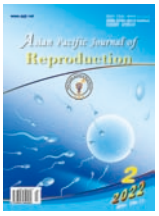

Review Article

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A scoping review of SARS-CoV-2 and male infertility: Concerns and future prospects

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been detected in the blood, urine, facial/anal swabs, semen, and vaginal discharge; all have been shown to contain SARS-CoV-2 RNA. Recent findings have highlighted the prospect of SARS-CoV-2 invading the genital system in addition to other tissues, which might give rise to reproductive concerns. This investigation sheds light on male reproductive tract vulnerability to invasion by SARS-CoV-2 and provides a foundation for further researches into male fertility. Males are infected with COVID-19 at a higher rate than females. As a result, some data suggest that this viral infection might affect the male reproductive system. The probable causes for male genital tract abnormalities in COVID-19 are: 1) high expression of angiotensin-converting enzyme 2 in the testes; 2) SARS-CoV-2 infection indirectly induces immune response in the testes; 3) SARS-CoV-2 directly damages male genital cells by virus-receptor binding activity; 4) fever in SARS-CoV-2 infected males may cause damages to testicular cells; 5) testosterone level decreased in SAR-CoV-2 infected males; 6) males are more susceptible to COVID-19 than females, which may be due to differences in the physiology of the genital tract. This review seeks to offer some insights into the potential causes of COVID-19 that affect the male reproductive system, as well as future prospect on this issue.

KEYWORDS: Infertility; COVID-19; SARS-CoV-2; Male reproductive system; Coronavirus; Genital tract abnormalities; Orchitis

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a coronavirus that causes severe acute respiratory syndrome. It is an RNA envelope with a positive polarity that belongs to the Coronaviridae family. Following SARS coronavirus and Middle East Respiratory Syndrome (MERS) coronavirus, SARS-CoV-2 looks to be the third very lethal human coronavirus to emerge in the last two decades[1]. Many organs in the body, particularly the lungs, are known to be damaged by SARS-CoV-2, but less is known about its effects on the reproductive system[2].

Angiotensin-converting enzyme 2 (ACE2) is found on the cell membranes of enterocytes in the small intestine and duodenum, proximal tubular cells in the kidneys, gallbladder glandular cells, as well as testis Sertoli cells and Leydig cells[3]. The ACE2 protein has a peptidase M2 domain at the *N*-terminus and a collectrin renal amino acid transporter domain at the *C*-terminus[4]. Some coronaviruses, such as HCoV-NL63, SARS-CoV (the virus that causes SARS), and SARS-CoV-2, employ ACE2 as a transmembrane protein as their major entrance route into cells[5]. This has led some to believe that lowering ACE2 levels in cells could aid in the fight against infection. ACE2 on the other hand, by boosting the production of the vasodilator angiotensin 1–7, has been found to protect against virus-induced lung injury. Furthermore, investigations on mice show that the interaction of the coronavirus spike protein with ACE2 causes a decline in ACE2 levels in cells due to internalization and destruction of the protein, which may contribute to lung injury[6].

Although the immune system serves a crucial antiviral role[7-9], excessive immune factor production can be harmful and lead to orchitis. The body's adaptive immune response after a SARS-CoV-2 infection is a massive release of inflammatory factors and chemokines, but it can also lead to uncontrolled inflammation, which results in a large decrease in the number of lymphocytes, as well as adaptive immune response dysfunction and low initiation efficiency. It's possible that this will result in secondary autoimmune orchitis[10].

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Sex hormones, such as testosterone, play a definite function in immune response modulation, providing a clue to the underlying causes of these consequences. A better knowledge of these epidemiological results allows for a more effective illness response[11].

Although epidemiological evidence suggests that men are at a higher risk of COVID-19-related morbidity and mortality[12–14], the impact on male reproduction and any causes are unclear. Male testes and sperm have been reported to contain a wide range of viruses, including Zika, Ebola, and Marburg[15]. As demonstrated in HIV or mumps-induced orchitis, virus-induced testis injury can affect gonadal hormone release and spermatogenesis[16].

This review intended to offer a comprehensive update on the effects of COVID-19 on male reproduction by identifying the likely causes of the disease in the male genital tract to COVID-19.

The databases of Scopus, EMBASE, PubMed, Science Direct, and Google were searched using the terms: COVID-19, male fertility, ACE2, spermatogenesis, and orchitis, to conduct a review article on the possible effects of SARS-CoV-2 on the fertility in the male reproductive system. We looked over all of the short and long articles published till October 2021.

2. Expression of ACE2 in the testis

The carboxypeptidase ACE2 attaches to endothelial cells and is abundantly expressed in a variety of human organs, including the lungs, heart, gastrointestinal system, testes, and so on[17]. ACE is a critical component of the renin-angiotensin-aldosterone system, which regulates blood pressure and body fluids[18,19]. Testicular ACE2 expression is extensive in these organs, with the majority of it localized in testicular spermatogonial cells, interstitial cells, and supporting cells, all of which are linked to male reproductive function[2].

Although the specific mechanism in male reproductive function was not determined, ACE2 expression was discovered in mature Leydig and Sertoli cells of the human testis in 2004[20]. Further research revealed the importance of the ACE2 Ang1-7 Mas receptor axis in regulating spermatogenesis in rats: Ang1-7 receptor blockade resulted in a decrease in testis and seminal vesicles weight, seminiferous epithelium, daily sperm production, overall spermatogenesis rate, and an increase in apoptotic cells in the seminiferous epithelium[21,22].

The ACE2-producing Ang (1–7) and its receptor Mas were found in the testis, mostly in the interstitial compartment and cytoplasm of Leydig cells. The people with significant spermatogenesis impairment have lower levels of ACE2, Ang-(1–7), and Mas than fertile persons, demonstrating the importance of ACE2 in the male reproductive system. Following then, additional research investigations in this sector have just recently surfaced as a result of the COVID-19 pandemic, as follows[23]. ACE2 receptor expression was present in the testicles of 68 middle-aged males who tested positive for the virus, even at protein levels[24].

The four primary structural proteins of coronavirus particles are the spike (S), membrane, envelope, and nucleocapsid proteins[25]. The S protein connects the virus to the host receptors; it is split into two distinct peptides labeled the S1 protein and S2 protein, which form the receptor-binding domain of the S protein and the stalk of the spike, respectively, by a host cell enzyme. Spike proteins are used by all coronaviruses to infect other cells. To mediate infection, the S1 proteins attach to cellular receptors, completing the virus's invasion process. The functional components of the S2 proteins assist the virus in interacting with the target cell membrane[26]. SARS-CoV-2 genomic data reveal that its S1 protein has certain unique modifications that boost affinity of SARS-CoV-2 for human ACE2; this might explain why COVID-19 has spread so broadly[27]. Furthermore, among 31 standard human tissue samples, the testis, along with the small intestine, kidney, heart, and adipose tissue, had the greatest amount of ACE2 mRNA expression[28].

Shen *et al*[29] found that ACE2 was expressed in both germ cells and somatic cells, including Sertoli cells, spermatogenic stem cells, and Leydig cells, among others. Furthermore, they discovered that infertile men's testes had a greater rate of ACE2 positivity than normal men's, indicating that SARS-CoV-2 may induce reproductive diseases *via* a route triggered by ACE2, and that men with reproductive abnormalities are more likely to be infected by SARSCoV-2. Furthermore, they discovered that ACE2 expression levels were related to a man's age, with a peak positive rate at 30 years, indicating that young men are more likely to be infected with SARS-CoV-2[29].

It is impossible to rule out the possibility of a direct effect of this virus on follicles/oocytes and spermatozoa. Given that SARS-CoV-2 operates *via* the ACE2 receptor[30], ACE2 receptors have recently been discovered on human Leydig cells[31], suggesting that the virus may have a direct effect on the male reproductive system. Another recent study indicated that testicular ACE is important for embryo development in the early stages[32], since ACE has been proven to play a role in sperm function. Furthermore, ACE has been linked to either decreased or complete failure of fertilization[33]. Angiotensin-(1–7) has been found in detectable concentrations in the follicular fluid, and ACE2 receptors have been shown to be present in human ovaries[34]. Considering these facts, it is possible that SARS-CoV-2 has a direct effect on spermatozoa or follicles/oocytes, but additional molecular or cellular research is needed to confirm this[35].

ACE2 has an essential role in sperm protection, and it may also play a key role in the pathogenesis of COVID-19 in the male reproductive tract by facilitating viral entrance into cells.

3. Immune response in the testes to SARS–CoV–2 infection

SARS-CoV infection can still cause serious immunological damage to the testes and extensive reproductive cell death[2].

SARS-CoV infection can still cause serious immunological damage to the testes and extensive reproductive cell death. These pathological alterations might be generated directly by local replication of SARS-CoV-mediated cytopathic effects, or indirectly by a detrimental immunological and cytokine response to a viral infection, or systemic toxicity from respiratory failure[36].

The surface spike (S) glycoprotein of the virus, which binds to the ACE2 cellular receptor, mediates viral-host cell fusion[37]. The cellular membrane serine protease TMPRSS2, which cleaves S protein into S1 and S2 and leads to viral endocytosis, translation, and replication, initiates the process[38]. ACE2 internalization results in a decrease in ACE2 levels at the cell surface, leading in decreased angiotensin 2 (Ang2) breakdown to angiotensin 1–7 (Ang1–7), indicating detrimental lung damage, inflammation, and fibrosis. As a result, the ACE2 receptor serves as a cell-protective barrier on one hand and an admission gate on the other[38]. Interleukin (IL)-4 plays an eminent role in the activation of the JAK-STAT pathway and leads to the disturbing pro-inflammatory cytokine as well as further damages male fertility. The disturbed IL-4 decreases the level of the ACE 2 with the inflammation. This further leads to male infertility in COVID-19 patients[39].

In comparison to control, Hajizadeh Maleki and Tartibian discovered increased ACE2 enzyme activity in seminal plasma, increased seminal inflammation [IL-1, IL-6, IL-8, IL-10, transforming growth factor, tumor necrosis factor (TNF), interferon], oxidative stress (increased reactive oxygen species) and reduced superoxide dismutase, and increased seminal apoptotic markers activity (caspase-8)[40].

Macrophages in the testicular mesenchyme can release tumor necrosis factor, interleukins, and other cytokines[41–43], which can have a paracrine or autocrine role in the local control of testicular function. Leukocyte infitration is a characteristic hallmark of SARS-CoV-infected testes. ACE2 is expressed by macrophages and leukocytes, and it can impact testosterone synthesis by testicular interstitial cells, causing the blood-testicular barrier and spermatogonial cells to be destroyed. Furthermore, the inflammatory cytokines produced by these cells may trigger an autoimmune response in the seminiferous tubules, resulting in the formation of autoantibodies. The vas deferens epithelium, including some degenerated germ and supporting cells, has been revealed to have a substantial quantity of IgG deposition. This finding implies that SARS-CoV does not infect the testes directly, but rather generates an immunological reaction. SARS orchitis, like other viral orchitis, is an autoimmune orchitis[44].

Patients recovering from COVID-19 had considerably lower sperm concentrations and significantly higher seminal IL-6, TNF, and monocyte chemoattractant protein-1 (MCP-1) levels than controls, according to Li *et al*[45]. In addition, 39.1% of patients exhibited oligozoospermia, and 60.9% showed an increase in leucocytes. Immune orchitis was also identified in this group of individuals[45].

The testes have their own anti-infection defense mechanism, which mostly relies on the blood-testis barrier's function. The blood-testis barrier protects the testes against autoimmune cell death, which makes them immune-privileged[2]. The composition of blood-testis barrier includes its physical and immunomodulatory components. The immunomodulatory components are mostly made up of testicular cells' constitutive production of anti-inflammatory substances, most notably transforming growth factor beta[46,47]. Because of the high expression of ACE2 on Sertoli cells, the physical barrier of blood-testis barrier is sensitive to viral assault. When cells are assaulted by viruses, the testicular immune response is triggered, causing immune cells including T-lymphocytes and macrophages to congregate in the testes.

4. SARS–CoV–2 and testis damage

There is currently no clear proof that SARS-CoV may infect the testicle directly; however, this possibility cannot be ruled out. A research comparing sperm parameters and immunological variables, among other features, between semen specimens from rehabilitated COVID-19 patients and those who died provides concrete evidence for the effect of COVID-19 on male reproductive function. When compared to age-matched controls, epididymides from decreased COVID-19 patients showed noticeable differences, such as the presence of interstitial edema and congestion in both the testes and epididymides, as well as thinning of the seminiferous epithelium, demonstrating that SARS-CoV-2 can significantly impair spermatogenesis. Furthermore, compared to age-matched control men, patients with COVID-19 had considerably lower sperm concentrations[45].

There were 12 researches that looked at the presence of SARS-CoV-2 RNA in human seminal fluid, with just two of them finding the virus in sperm. SARS-CoV-2 RNA was found in the semen samples of four acute stage patients and two recovery phase patients among 38 male patients who tested positive for COVID-19[48]. Only one patient in a group of 43 sexually active males recovering from COVID-19 had evidence of SARS-CoV-2 RNA in seminal fluid and tested negative on a nasopharyngeal test the same day, according to Gacci *et al*[49]. The presence of viral RNA was found in one case of mild infection, but the remaining 11 cases (moderate infection) were negative, according to Ma *et al*[50].

During the recovery phase, Pan and colleagues examined 34 male adult patients' semen samples for SARS-CoV-2 detection in the first cohort trial. RNA profiling tests revealed no virus, but 19% of scrotal pain was recorded. In addition, ACE2 and TMPRSS2 were sparsely abundant in testicular cells[51].

Direct harm has been hypothesized in the first place *via* virus-receptor binding; however, this damage is also contingent on the virus's ability to replicate and stabilize within the target[52–54]. Song *et al* recently collected 12 semen samples from SARS-CoV-2 infected patients during the recovery phase in order to diagnose COVID-19 using a polymerase chain reaction (PCR)

assay; however, no positive samples were found[18]. In 2006, Xu and colleagues observed no positive testis staining in SARS-CoV infected orchitis patients[44]. That was considered as an immunological disorder[55]. Surprisingly, a recent cohort research in China found four positive SARS-CoV-2 samples in COVID-19 patients during the acute phase of the disease, and two positive samples during the recovery period, out of a total of 38 semen samples from infected individuals[48].

Holtmann *et al*[56] examined 34 men's sperm as well as a blood sample. Reverse transcription-polymerase chain reaction (RT-PCR) revealed no RNA in the semen, including semen samples from two individuals with acute COVID-19 infection. In comparison to men recovering from a mild infection and the control group, patients with a moderate infection had a statistically significant impairment in sperm quality (sperm concentration, total number of sperm per ejaculate, total number of progressive motility, and total number of complete motility).

Because the virus may not be entirely isolated by the blood–testis barrier, it may seed into the male reproductive system. The goal of Kayaaslan *et al* was to look for SARS-CoV-2 RNA in the sperm of patients who had a positive nasopharyngeal swab test for SARS-CoV-2 in the acute stage. The study comprised sixteen individuals, and all semen samples tested negative for SARS-CoV-2 RT-PCR[57]. On the one hand, viral load has been suggested as a significant role in consequences such as testicular injury[3], and on the other hand, adaptive and innate immune response activation to combat the virus[58-61].

There were two researches that looked at the influence of SARS-CoV-2 infection on sperm quality. In a hospital-based case-controlled cross-sectional investigation, Li *et al*[45] looked at 23 patients recovering with COVID-19 infection. Patients recuperating from COVID-19 had considerably lower sperm concentrations, according to this study. Immune orchitis was also identified in this group of individuals. Hajizadeh Maleki and Tartibian [40] compared 84 patients recovering from COVID-19 to 105 healthy controls in a case-controlled longitudinal research, with assessments at 10-day intervals with a maximum follow-up of 60 days. Semen volume, sperm concentration, progressive motility, and sperm morphology were all shown to be significantly reduced. Inflammation of the male reproductive system is recognized as a major cause of infertility[62].

In COVID-19 infections, there were two investigations that mostly reported testicular clinical signs. Testicular discomfort and epididymo-orchitis were assessed in 91 COVID-19 patients ranging in age from 18 to 75 years old. Only one patient was clinically diagnosed with epididymo-orchitis, despite the fact that 11 percent of patients complained of discomfort[63]. Kim *et al*[64] described a 42-year-old adult male who presented to the emergency hospital with acute abdomen and testicular discomfort but no respiratory symptoms and was diagnosed with COVID-19. Pan *et al*[65] found a 19% incidence of symptoms suggestive of orchitis in a group of 34 male patients recovering from COVID-19.

5. Fever in SARS-CoV-2 infected males may cause damages on testicular cells

We know that temperature affects cell growth and development, and the ideal temperature for cell growth is 37 ℃. Almost all SARS-CoV patients, on the other hand, have a prolonged fever[66-68]. Changes in testicular temperature occur when the human body is in a condition of high fever for an extended period of time, and germ cells are destroyed and degenerate[36]. The ideal temperature for sperm production and survival is 1 ℃-2 ℃ below body temperature in normal conditions. Cell apoptosis has been linked to high temperatures[69].

SARS-CoV-2 infected males were compared to healthy men of reproductive age in China to see how their sex hormone levels changed. As a result of the decrease in testosterone: luteinizing hormone (LH) ratio, hypogonadism and Leydig cell death have been suggested. It's worth mentioning that the possible impact of certain treatments, such as corticosteroids, on the hypothalamic–pituitary–gonadal axis must be considered[70]. In another research, fever was linked to testicular injury due to the loss of germ cells in a high-temperature environment, as well as leukocyte infiltration caused by the demise of Leydig cells and a drop in testosterone levels[44]. High temperature contributed to germ cell destruction, and high fever in COVID-19 might have a potential indirect effect on testicular dysfunction.

6. Sex-related hormones changes in SARS-CoV-2 infected males

Testosterone has a variety of affects on the immune system, which raises the important topic of how testosterone levels affect COVID-19 in males. Sex hormones, such as testosterone and estrogen, are a key cause of physiologic differences between males and females, and they are likely to have a role in the COVID-19 pattern of outcomes[11]. Furthermore, a few studies have revealed that sex steroid abnormalities may have a role in the severity of symptoms and poor prognosis among COVID-19 patients[71,72].

For viral detection and semen characteristics study, Ma *et al*[70] collected semen specimens from 12 COVID-19 male patients. They examined the levels of sex-related hormones in 119 reproductive-aged males infected with SARS-CoV-2 and 273 age-matched controls. The group that tested positive for COVID-19 had greater blood LH and a lower testosterone to LH ratio. In 81 males with COVID-19, they discovered substantially higher LH levels, but reduced testosterone/LH and follicle-stimulating hormone (FSH)/LH ratios, indicating possible hypogonadism. However, these data are insufficient to determine whether this change is due to a direct or indirect action of SARS-CoV-2 on the testes[70].

Rastrelli *et al* looked at 31 people who had recovered from SARS-CoV-2 pneumonia. In comparison to the other groups, the severe/deceased group had much lower total and free testosterone and

significantly greater LH. These individuals also had higher *C*-reactive protein, procalcitonin, and neutrophil counts, as well as less lymphocytes[73].

Kadihasanoglu *et al* conducted a case-controlled cross-sectional research on 89 individuals with confirmed COVID-19 who were hospitalized. When compared to non-COVID-19 infections and control groups, testosterone was considerably lower and LH and prolactin were significantly higher in the COVID-19 cohort, with no changes in FSH. In patients with COVID-19 infection, testosterone was likewise inversely connected with hospital length of stay and positively correlated with oxygen saturation, but not in the non-COVID-19 infection group. When testosterone was compared to neutrophil count, lymphocyte count, or C-reactive protein, no associations were seen. The testosterone levels in four of the COVID-19 patients who died were lower than the COVID-19 cohort's median[74]. Reduced testosterone may weaken respiratory muscles, even further lowering lung function metrics like forced expiratory volume[75].

In a COVID-19 outpatient clinic, Okçelik *et al* studied 44 individuals. Patients who tested positive for COVID-19 had similar levels of testosterone, LH, and FSH to those who tested negative. In the pneumonia group, testosterone levels were considerably lower than those in the control group[76].

On a cellular level, Rastrelli and colleagues discovered that hypogonadal males infected with SARS-CoV-2 had greater neutrophil-to-lymphocyte ratios[73]. Neutrophilia has been linked to cytokine storms in the past[77,78], which might explain why this cellular profile is linked to poorer outcomes in these males. Furthermore, because the androgen receptor is found on the majority of white blood cells, testosterone may be directly modulated[79]. As a result, the putative function of testosterone in modifying the sex-specific immunological response has received a lot of attention. Testosterone has been demonstrated to reduce the action of IL-6 and TNF by inhibiting the protein complex nuclear factor-B, which is required for cytokine synthesis[80]. By increasing expression of IL-10 and transforming growth factor-β, testosterone also enhances the anti-inflammatory response *via* androgen receptor signaling[81].

COVID-19 patients presented an abnormal sex hormone secretion, suggesting that attention should be given to the reproductive function evaluation in the follow-up. Concentration of testosterone may influence the mortality of COVID-19 patients.

7. Males are more susceptible to SARS–CoV infection

The 1918 influenza pandemic in the United States resulted in greater death in males than females, and this sex-specific effect of viral pandemics is not unique to the twenty-first century[82]. Males had worse clinical results than females in several nations afflicted by the COVID-19 pandemic. Prior coronavirus epidemics, such as SARS and MERS coronavirus outbreaks, showed a similar pattern of consequences. There are other illnesses that affect men more than women[82,83]; the causes behind susceptibility of males to be infected with certain diseases more than females may be not fully understood[84–87].

The current epidemiology in China and Italy revealed that men are more likely than women to get SARSCoV-2[88]. COVID-19's impact on males was likely exacerbated by men's high infection rate and susceptibility rate. Men make up 60% of COVID-19 patients, according to a large-scale prospective cohort research undertaken in the United Kingdom[88].

Despite researches that imply a female preponderance or no sex discrepancy for COVID-19 morbidity and death, there is growing evidence of a male predominance[89] as well as a variety of other illnesses[90–93]. In a meta-analysis, Peckham *et al*[94] found no difference in confirmed infections between male and female gender, except that males had a 2.84 greater risk of intensive care treatment and a 1.39 increased risk of mortality[95]. In Europe, China, and Korea, increasing sex disparities in COVID-19 mortality have been documented[96].

As a result, it is been suggested that androgens may have a role in COVID-19 etiology. Due to the action of oestrogen in stimulating T cells, lower production of inflammatory cytokines, and increased antibody synthesis in B-lymphocyte humeral immune response, female patients may be less vulnerable to viral infections in general. Male patients had greater ACE2 expression in the renal system than female patients, which might explain the gender disparity.

The all above-mentioned possible causes of infertility in COVID-19 are presented in Figure 1.

8. Conclusions

SARS-CoV-2 is still spreading, and it is unknown why males have disproportionately greater infection and fatality rates. This might be because the reproductive system has yet to be identified as a possible target for SARS-CoV-2 infection. Further investigations of the potential male genital damage are warranted. Even though it appears to us that it is too early to draw clear conclusions at this time, this should raise awareness of COVID-19's potential influence on the male reproductive system.

Taking all the findings together, although most of the studies reported the absence of SARS-CoV-2 in the semen and prostatic secretions, as well as testicular tissues, which may reduce the possibility of transmission through this route, it is evident that there is testicular injury and inflammatory viral infiltration; orchitis may occur as patients experienced scrotal discomfort; there is altered semen parameters; and the number of spermatozoa with DNA fragmentation is increased. These findings imply that SARSCOV-2 infection may cause reproductive problems.

In patients with COVID-19, a clinical assessment of the male reproductive tract, seminal parameters, and reproductive hormones is advised, especially in males undertaking fertility therapy.

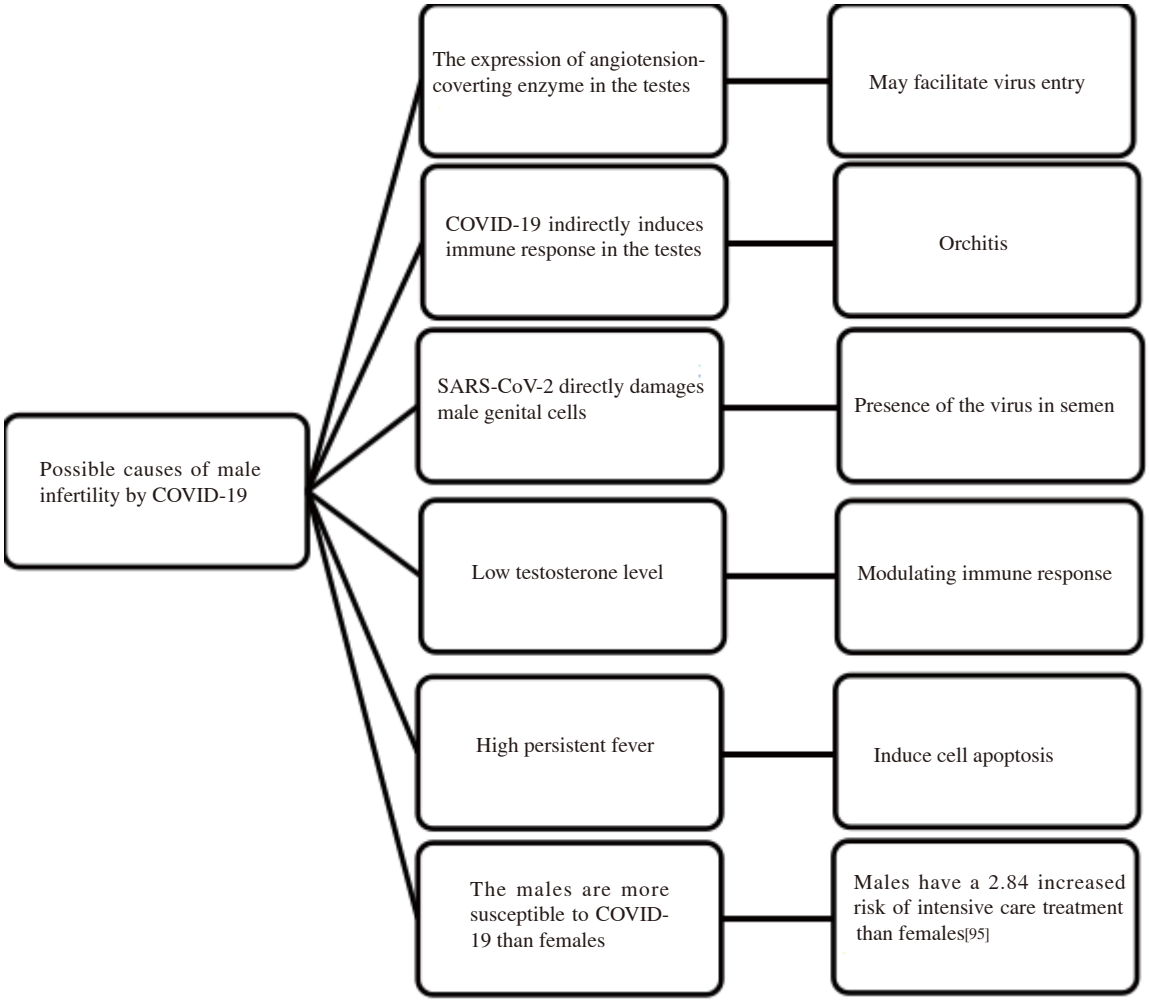

Figure 1. Possible causes of infertility in COVID-19.

Any long-term negative influence on male reproduction is still unknown, but it is something to think about in the future.

Although there is no clear evidence that testosterone causes higher vulnerability in males, testosterone may play a role in activating ACE2 and TMPRSS2 to allow viral entrance and fusion. The inflammatory response of the body is thought to be the cause of negative results. While testosterone appears to promote SARS-CoV-2 virus entry and fusion, it also appears to protect against immunological dysregulation. As a result, males with low testosterone may be more prone to have a harmful inflammatory reaction to the virus, and testosterone replacement therapy may be beneficial. Furthermore, laboratory data such as sex hormone levels and semen analysis should be evaluated to detect sperm dysfunctions and consequent reproductive difficulties in patients and those who recovered from COVID-19 over short and long periods of time.

9. Future prospects

Future research on ACE2 and its contributions to male genital tissues will require more research. Overall, the data provided in this review suggest that the testis is the organ in the human male reproductive tract most sensitive to SARS-CoV-2 infection, owing to its high ACE2 expression. Angiotensin-converting enzyme 2 receptors are found in spermatogonia, seminiferous tubules, Sertoli, Leydig, and prostate epithelial cells, yet their function is unknown.

As a result, infected males should be tested for fertility as soon as possible after recovery, especially if they are married and desire to start a family. Furthermore, precautions should be made to protect the reproductive health of males infected with COVID-19, and these individuals should be screened. Although no cases of infertility have been reported as a result of SARS-CoV-2 infection, current clinical evidence suggests that SARS-CoV-2 has an effect on the male reproductive system. To treat male reproductive system difficulties and fertility concerns, genital examination and laboratory testing should be explored.

More patients' evaluation and examination, more semen samples collected at different stages of the disease, extra hormonal function analysis, and more research in both RNA and protein expression levels are all needed to solve this issue.

Comparing the rate of fertility before, during and after COVID-19 pandemic may give interested information about the impact of this disease on the fertility in difference periods, which gives us an idea to manage any future problems regarding this issue.

There is no data that the COVID-19 vaccines may cause infertility and no credible scientific theories for how the COVID-19 vaccine may cause male infertility. Therefore, more information must be available for different types of vaccines, especially, for mRNA vaccines that may cause the body to attack itself by similar proteins in the body that shares a small piece of genetic code with the spike protein of the coronavirus.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Authors' contributions

Falah Hasan Obayes AL-Khikani and Aalae Salman Ayit wrote, revised and proofread the manuscript.

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