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Review article

Male Infertility in infected patients with COVID-19: A Narrative Review

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Abstract

Background: Since the emergence of the pandemic of coronavirus disease (COVID-19) through severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019, we still have little knowledge about the mechanisms of pathogenesis of COVID-19. Surprisingly, early studies reported that men are more susceptible to COVID-19 compared to women. These findings raise the question of whether COVID-19 infection can negatively affect male fertility. Since angiotensin-converting enzyme-2 (ACE2) receptor, known as the entrance rout of virus into human cells abundantly on testicular cells, it is hypothesized that the virus can also have devastating effects male fertility.

Methods: The present study was conducted a narrative review of the literature on male infertility and COVID-19. We searched PubMed, Scopus, and Google scholar for papers. Full-text journal articles between the years 2019 and 2020 were reviewed for relevant articles.

Results: There is emerging finding, which provides support for the susceptibility of male reproduction health to COVID-19 infection. In the current review article, we documented an overview of male reproductive function manifestations and the possible male infertility mechanisms of COVID-19 infection. Certainly, clarifying the mechanism of these findings will lead to the timely management and treatment of infected patients.

Conclusion: This review suggests that male counseling about their fertility and the evaluation of their reproductive system function should be performed.

Keywords: Angiotensin-converting enzyme-2 (ACE2), COVID-19, Male infertility, Oxidative stress

Introduction

As a global pandemic, the 2019 novel coronavirus (COVID-19) with high contagious potential as well as almost 3352109 confirmed deaths as of 15 March 2021, has raised concerns in the global health community and significantly attracted the attention of many researchers. Coronaviruses (CoV) are known as members of the large family Coronaviridae, most of which, for example, hCoV-229E, hCoV-OC43, hCoV-NL63, and hCoV-HKU1, cause mild respiratory diseases in humans.

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But previous studies have shown that three other cases in this family, including syndrome coronavirus 2 (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and COVID-19, can cause acute respiratory syndromes or even death (1, 2). It is interesting that COVID-19, like SARS-CoV, connects to the angiotensin-converting enzyme 2 (ACE2) receptor on the membrane of human cells (3).

It is clear that in order to elucidate the mechanism of action of COVID-19 on male reproductive function, the effects of COVID-19 infection on testicular endocrine function and spermatogenesis should be carefully studied. However, the question arises as to why the prevalence of COVID-19 is significantly higher in men than in women and even it is associated with higher mortality rate. Therefore, in the current review, we discussed the proposed mechanisms by which COVID-19 infection can impair male reproduction health in infected patients with COVID-19.

Materials & Methods

The present study was conducted a narrative review of the literature on male infertility and COVID-19. We conducted a comprehensive search through PubMed, Scopus, and Google scholar for papers published in 2019 and 2020 using the following keywords: COVID-19, male infertility, angiotensin-converting enzymes 2, and oxidative stress.

Results

Recent findings suggest that ACE2 is preponderantly expressed in spermatogonia, Leydig, and sertoli cells (4). The results of a retrospective study of 1,099 infected cases with COVID-19 showed that about 60% of patients were male and that 55% of them were fertile by age (49 ~ 15 years) (5). Based on the evidences, concerns raised about the negative effects of the COVID-19 on the male reproductive function.

The question is whether SARS-CoV-2 is present in semen or not. There are conflicting opinions on this. A recent study reported that SARS-CoV-2 was found in semen samples from infected men (15.8%) and was even found in 8.7% of patients in the recovery phase (4). However, two other reports have shown that SARS-CoV-2 is not present in semen samples from male patients with COVID-19 during the recovery period (6, 7). In addition, it is important that viral infection associated with fever can have devastating effects on the male reproductive system in a variety of mechanisms through factors such as fever, inflammation, hypoxia, or even the use of medications during the treatment. The results of an autopsy of six patients who died of COVID-19 disease presented evidence of orchitis, although no COVID-19 virus was found in the testes (8).

Clinical manifestations in patients diagnosed with COVID-19 may range from common symptoms such as mild fever or dry cough to pneumonia as well as a wide range of multi-organ dysfunction (2, 9). Because the virus can reach the host cell by binding to the ACE2 receptor, it is expected that tissue cells that express ACE2 receptors on their own surface will be more susceptible to COVID-19 infection (10). The established ACE2 receptors are expressed in multiple tissues including lungs, brain, kidneys, testis and many others tissues (10-13). Interestingly, one of the major concerns about the pathogenicity of COVID-19 is the potential for negative effects of this virus on male reproductive function in patients with COVID-19.

Discussion

There are conflicting views on the hypothesis that COVID-19 disease, which originates from SARS-CoV-2, leads to dysfunction of the male reproductive system. Based on the previous reports about the virus' ability to enter host cells, the hypothesis that COVID-19 affects the male reproductive system has been strengthened. Since similar to the rest of SARS-CoV viruses, COVID-19 can also infect target cells via the interaction between the its viral spike (S) protein, ACE2, and transmembrane serine protease 2 (TMPRSS2) (14, 15). It is interesting that both ACE2 and TMPRSS2 are expressed in multiple tissues including the male genitourinary system. However, it has been shown that there is a more limited expression of these receptors in the testes (16). But with this evidence, there is a concern that the SARS-CoV-2 virus could be transmitted through sexual intercourse and affect male fertility in the long-term. There have been conflicting reports of the presence of SARS-CoV-2 in the semen of infected patients with COVID-19. A recent report found that this virus was found in semen samples from 34 men with a mean age of 42.2 years. Among them, 18 men were in the recovery phase from SARS-CoV-2 infection, 2 men had with acute COVID-

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19 infection, and 14 were Asymptomatic individuals with negative SARS-CoV-2 antibody. COVID-19 virus was not observed in the semen of recovered infected patient with COVID-19 43 days after a positive oropharyngeal swab (17). In another study on 38 men with COVID-19 who were infected or were on the recovering path, SARS-CoV-2 was confirmed in semen samples from six men (18). However, there have been several reports of no SARS-CoV-2 presence in the semen of infected patients (19-21). Although these conflicting results may be due to time differences in semen sampling in infected men, the presence of SARS-CoV-2 in semen on days 8 (21) and 14 (19) of the onset of the COVID-19 signs was not found in these reports. Although it has not been proven that SARS-CoV-2 can be transmitted through semen, the viral entry of COVID-19 into the male reproductive system can have adverse effects on spermatogenesis and male fertility. It is, however, clear that systemic viral infections such as mumps, human immunodeficiency virus, and herpes simplex virus have devastating effects on male reproductive function. It is also presumed that the increase in body temperature associated with viral infections can also inhibit the process of spermatogenesis. Interesting results from Holtman et al. showed that one in 18 men who recovered suffered from scrotal discomfort during his acute infection (22). This report was similar to the observations of Pan et al. In this study, 6 of the 34 men who recovered from the COVID-19 infection complained about scrotal discomfort (21). These reports hypothesize that COVID-19 can lead to orchitis in infected men in the acute stages of the disease.

Reports from Holtman et al. on the effect of COVID-19 infection on semen parameters showed that among the participants who had moderate SARS-CoV-2 infection, semen parameters such as sperm concentration, total sperm count, and progressive motility showed a significant decrease compared to the parameters of the control group (22). These results largely suggest that COVID-19 infection may have negative effects on spermatogenesis in patients with moderate COVID-19-related symptoms. In addition, the total number of motile sperm was significantly lower in participants who had fever. Also, other factors including sperm concentration and sperm count tended to decrease in these participants, but the results were not statistically significant.

Due to the incompleteness of the above-mentioned studies based on the reports that have been published so far, the small number of people examined, short follow-up time, and failure to examine semen samples before COVID-19 infection, it will be difficult to make a definitive assessment of the negative effects of the virus on sperm parameters. On the other hand, it is doubtful that the observed results are due to the effects of antiviral drugs such as hydroxychloroquine used during the treatment (17).

Previous studies have shown that other viruses, including HIV, Epstein-Barr, hepatitis, papilloma and mumps can present orchitis as a clinical manifestation, which can eventually direct to male infertility and even testicular tumors (8). An autopsy study of six male patients with the virus who died showed that the virus could lead to orchitis. The pathological results of six patients in this study showed spermatogenic cell apoptosis, germ cell destruction, low or no sperm in the spermatogenic epithelium, increase in basement membrane thickness and leukocyte infiltration in all six patients. Based on these findings, it can be claimed that the testes are affected in the COVID-19 disease (8). A recent study to evaluate gonadal function in 81 infected men with COVID-19 found that the ratio of testosterone to luteinizing hormone (T to LH) in people with COVID-19 was significantly higher than that of the healthy group. Serum T to LH ratio is a known criterion for male gonadal function. The results of this study indicated that SARS-CoV-2 had dysfunction of the gonads (23).

Several studies have shown that men are more likely to be infected with the COVID-19 than women. These studies have also reported that COVID-19 may adversely affect the male reproductive system, leading to male infertility (5, 24). Also, a recent cohort study from the United Kingdom on about 20,000 infected patients with COVID-19 has shown that about 60% of cases were male. Therefore, gender was identified as a risk factor for COVID-19 disease (25). The confirmation of these results in another study, a systematic review of recently published reports, found that men were more likely than women to develop COVID-19 complications and even had higher mortality rates (26). It is worth mentioning that most of these men were in their reproductive age and that their reproductive ability may have been affected as a result.

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On the other hand, COVID-19 is associated with fever, which may lead to impaired spermatogenesis. It has also been shown that elevated body temperature in viral diseases has a negative effect on sperm parameters (27). Previous studies have reported that sperm count and total motility in patients with COVID-19 decreased significantly on days 15, 37 after the fever period (27). Another study also showed that sperm DNA fragmentation and changes in sperm nuclear protein composition occurred after the fever period (28).

Studies have shown that SARS-CoV-2, like other viruses in the SARS-CoV family, infects host cells with the ACE2 receptor and TMPRSS2. In addition to lung epithelial cells, ACE2 is also expressed in other tissues such as the kidneys and bladder (11, 29, 30). It is worth noting that the testes showed the highest expression of ACE2 receptor (11). Excessive expression of ACE2 in the testicular cells raises the concern that COVID-19 could easily infect testicular cells and eventually cause damage. Wang et al., in a study to investigate the vulnerability of different testicular cells to SARS-CoV viruses, studied single-cell ACE2 receptor expression in different human testicular cells. The results showed that ACE2 expression was much higher in spermatogonia, leyding, and Sertoli cells, while spermatocytes and spermatids showed very little expression (4). TMPRSS2 expression is similar to ACE2, except that TMPRSS2 was high in spermatogonia and spermatids. Interestingly, ACE2-expressing spermatogonia cells are responsible for expressing genes that are also essential for virus reproduction and transmission, while Leydig and Sertoli cells expressing ACE2 are responsible for expressing genes involved in cell junctions and cell immunity.

Based on these findings, it can be concluded that COVID-19 can have negative effects on testicular cells as well as spermatogenesis growth. One study evaluated the function of the male gonads following COVID-19 disease. The results showed that testosterone (T) levels did not differ significantly between the affected and healthy groups. In addition to testosterone, luteinizing hormones (LH) and follicle stimulating hormone (FSH) were also examined. The results demonstrated that in the group of infected patients with COVID-19, the ratio of T to LH and the ratio of FSH to LH showed a significant decrease compared to the healthy group (23). These results could indicate the effect of COVID-19 on the testicular ability to produce sex hormones. However, more detailed research is needed to determine definitively the effects of this virus on testicular ability. Previous studies have shown that SARS-CoV can lead to orchitis (8). Given this similarity, it can be claimed that COVID-19 also has this manifestation in infected men.

However, there are several mechanisms by which SAR-CoV2 can impair male reproductive functions. Previous studies have shown that the virus is able to activate oxidative stress-sensitive pathways through inflammatory reactions, thus leading to oxidative stress (OS), which has been shown to be a common pathological pathway for dysfunction many physiological mechanisms. It is well-established that the male reproductive system is highly sensitive to OS-induced damage, as OS can be mediated through a variety of mechanisms, including intracellular oxidative damage to spermatozoa through sperm membrane lipid peroxidation, sperm DNA damage, and developing apoptotic pathways on sperm, which have negative effects on both its quality and morphology (31, 32). Previous studies have shown that SARS-CoV infections cause severe production of reactive oxygen species (ROS), which may induce the nuclear factor kappa-light chain-enhancer of activated B cells (NF-κB)-toll-like receptor (mostly TLR-4). These factors lead to increased secretion of cytokines, leading to an intensification of inflammatory responses (33). According to previous discussions, COVID-19 disease can cause orchitis and can also lead to oxidative stress through the mechanisms discussed. In addition to all these pathological mechanisms, SARS-CoV-2 infection causes psychological distress, which, in turn, can activate oxidative stress (34). On the other hand, drug therapy for COVID-19 includes antiviral drugs such as ribavirin, which have been shown to cause the disruption of male reproductive ability through a variety of pathways, including the induction of the oxidative stress, decreased serum testosterone levels, impaired spermatogenesis (35, 36). Previous studies have demonstrated that the therapeutic use of ribavirin can reduce sperm count (37) and increase sperm DNA fragmentation, (38) which continues for up to 8 months after stopping the treatment (34, 39).

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Conclusion

Although respiratory manifestations are the most common clinical sign of COVID-19, given the importance of fertility, the manifestations of the COVID-19 on the male reproductive system should be further investigated. It should be noted that the blood testicular barrier is not immune to COVID-19, and that the dysfunction of the gonads is associated with abnormal levels of sex hormones. Therefore, male patients of childbearing age should be counseled about their fertility and the evaluation of their reproductive system function.

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Conflicts of Interest

The authors of this manuscript declare no conflicts of interest related to this article.

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