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Narrative Review

The Effect of COVID-19 Infection on Male Fertility: A Narrative Review

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Abstract
The emergence of a new coronavirus, officially referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has challenged all healthcare workers and clinicians worldwide. The presence of the virus in biological fluids including the semen has raised some concerns about infertility treatment. There is evidence that SARS-CoV-2, which causes coronavirus disease 2019 (COVID-19), can damage the male reproductive system following the inflammatory process caused by the cytokine storm. However, the direct and long-term effects of SARS-CoV-2 on fertility and the reproductive capacity of the human testis are still open to controversy. The lasting presence of the virus, even after a complete recovery, can increase the risk of sexual transmission and adversely affect the male reproductive system, sexual function, and fertility. Therefore, there is a need for a careful assessment of reproductive organs and testicular function in male patients. This study aimed to evaluate the invasive effect of SARS-CoV-2 on the testis and male reproduction.
Keywords: SARS-CoV-2 , Male fertility, Sexual transmission, Semen, Pregnancy

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Introduction

Coronavirus disease 2019 (COVID-19) emerged in December 2019 in Wuhan, the capital city of Hubei in China, and rapidly spread throughout the world. The World Health Organization (WHO) called it a novel coronavirus on January 21, 2020 (1). Many studies have been conducted in the Hubei Province to diagnose, prevent, and treat SARS-CoV-2 infection on time. Information about SARS-CoV-2 is updated every day (2). Coronaviruses are a large family of viruses called *Coronaviridae* and can lead to many diseases, from a common cold to more severe diseases such as the severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19. Coronaviruses are single-stranded RNA viruses that look like a crown under an electron microscope. The subfamily *Orthocoronavirinae* includes four genera (from alpha to delta) with different tissue tropisms which can be transmitted to different species including humans (3). Recently, multiple coronaviruses have caused epidemics in different parts of the world, including SARS-associated coronavirus (SARS-CoV) epidemic in China (2002-2003), MERS-associated coronavirus (MERS-CoV) epidemic in Saudi Arabia (2012), and SARS-CoV-2 in Wuhan, China (2019), with over one million confirmed cases and more than 50 000 deaths globally (4). Similar to SARS in 2003 and MERS in 2012, COVID-19 causes a series of respiratory disorders suggesting the potential role of epithelial cells in the admitted patients. COVID-19 initially targets the respiratory system and is transmitted via droplets, aerosols, and contact. Coronavirus using transmembrane serine protease 2 (TMPRSS2) and the angiotensin-converting enzyme 2 (ACE2) receptor infects the host cells and the lungs. ACE2 can be expressed in many tissues, including the cardiovascular system, gastrointestinal tract, and liver (5). Of note is that ACE2 expression has also been found in the testis and different cell types (6). According to recent studies, SARS-CoV-2 can also be found in the blood and urine (7-9). However, serious urinary complications are also probable such as an acute kidney injury and damage to the reproductive system with significant changes in sex hormones and

sexual function (10, 11). Evidence suggests that SARS-CoV-2 can affect male reproductive system. Besides, an abnormal level of sex hormones and a lower sperm quality were observed in patients recovering from COVID-19 (12). Understanding the mechanisms through which SARS-CoV-2 can disrupt the reproductive system based on previous evidence may help better manage COVID-19 and prevent it in therapeutic programs. How SARS-CoV-2 infection disrupts the male reproductive system is an issue that needs further investigation. Therefore, the present study aimed to investigate the effects of the emerging SARS-CoV-2 on the male reproductive system.

Sexual Transmission of COVID-19

The rapid transmission of COVID-19 caused WHO to call it a pandemic (12). It is essential to identify the potential sources of infection and get aware of the ways the disease is transmitted to prevent the further spread of the disease. The source of SARS-CoV-2 is still unknown. The first confirmed cases were found in a seafood market in Huanan in southern China. The collected samples from this market were all positive for SARS-CoV-2 ; however, some later cases showed to be irrelevant to this market (13). With a rapid geographic spread and transmission rate, COVID-19 had clinical manifestations in patients (14). Therefore, serious measures were taken by governments and health officials to restrain the disease. Accordingly, researchers started to study the transmission pathways and validate the available diagnostic methods (14-16). Recent bioinformatic evidence suggests that ACE2 receptors, as the potential targets for COVID-19, are highly expressed in testes (17, 18). It seems that SARS-CoV-2 can strongly interact with ACE2 receptors in various tissues, including lungs, intestines, testes, and kidneys. Therefore, some other means of transmission are found besides the respiratory droplets (15). In fact, virus RNA also exists in other biological samples including feces, urine, and blood. In his study on COVID-19, Kashi affiliated with Shahid Beheshti University of Medical Sciences proclaimed that ACE2 receptors, which act as binding sites for SARS-CoV-2, are abundantly found in testicular tissues and reproductive organs. Hence, whether the disease can be transmitted through assisted reproductive treatments (ARTs) such as sperm donation needs to be clarified in the pandemic, since COVID-19 is expected to affect our lives for long (19). There are concerns about the presence of SARS-CoV-2 in other biological fluids such as the semen with regard to ARTs (20, 21). Chinese researchers showed that SARS-CoV-2 can remain in semen even after recovery from COVID-19 and this finding increases the possibility of sexual transmission. A research team conducted a study on 38 male patients in Shangqui Municipal Hospital at the peak of the pandemic. They found evidence for SARS-CoV-2 in semen. Their results showed that SARS-CoV-2 was present in 16% of the semen samples. In addition, approximately one-fourth of the patients were in the acute phase of infection and 9% were in recovery. In their research in a general army hospital in Beijing, Li et al suggested that SARS-CoV-2 can be present in the semen of acutely infected or even recovered patients. They also added that even if the virus is incapable of proliferation in the reproductive system, it may persist, most probably due to the immunity of testes. Such specific immunity implies the exclusion of testes from the attack of the virus by the immune system. Many viruses can escape the immune system in this way and remain in the male reproductive system. Ebola and Zika viruses have been found in the semen of male patients months after a complete recovery. However, it is still unclear whether SARS-CoV-2 can be transmitted via semen. The proven presence of the virus does not necessarily translate into infection. The control and prevention of COVID-19 in men and the possible risk of transmission have become a major concern. Few studies have been carried out on the sexual transmission of SARS-CoV-2 in men (22). Nevertheless, evidence on other coronavirus diseases such as SARS and MERS can contribute to our understanding of sexual transmission in male COVID-19 patients. If the sexual transmission of SARS-CoV-2 is proven in future studies, it can become an important part of the prevention programs and guide treatment strategies and sexual behaviors for COVID-19 in men.

Adverse Effects of COVID-19 on Men

Wang and Xu showed that ACE2 receptors are mainly expressed in testes and spermatogonia, Leydig, and Sertoli cells. ACE2-positive spermatogonia express more reproduction and transmission genes of the virus and fewer spermatogenesis-related genes than ACE2-negative spermatogonia. These findings show that testis is at a higher risk of SARS-CoV-2 infection that may result in spermatogenic failure (18). In addition, ACE2-positive Leydig and Sertoli cells express more cell junction-related and immunity genes and less mitochondria and reproductive genes. SARS-CoV-2 may also disrupt male gonadal function (Figure 1) (23). SARS infection in men can cause damage to germinal cells, some spermatozoa in the epididymis, and the basement membrane of the testis. However, whether the reproductive system is susceptible to SARS-CoV-2 infection is still unknown. Nevertheless, recent findings show that testis is at a high risk of SARS-CoV-2 infection which can result in spermatogenesis failure and that SARS-CoV-2 infection can affect male sex glands and disrupt reproductive function which can lead to male infertility (18). Studies have provided bioinformatic evidence for the possible vulnerability of testis to SARS-CoV-2 infection and suggested that due to the sensitivity of this organ and the probability of reproductive dysfunction, men recovering from COVID-19, especially younger men, should be monitored for orchitis (24). Leukocytes, CD3+ T-lymphocytes,

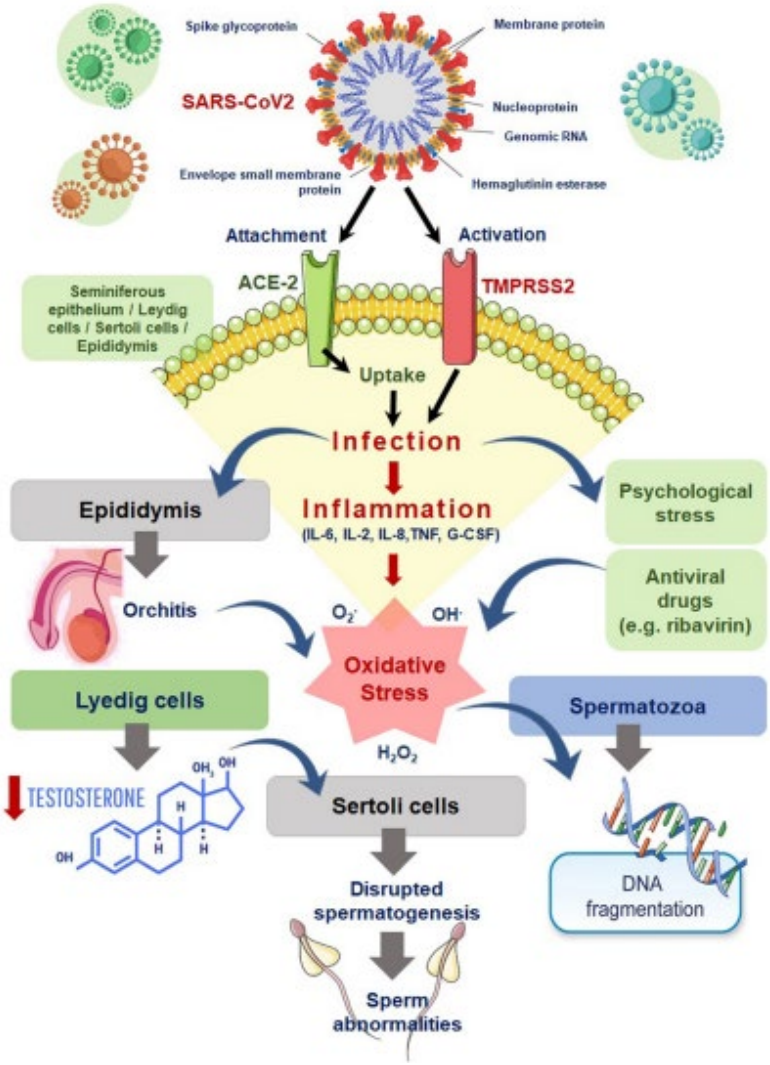

Figure 1. The Potential Mechanism of SARS-CoV-2 Affecting the Reproductive Function (23).

and CD68+ macrophages can infiltrate the interstitial tissue of the testes and produce interferons that may inhibit steroidogenesis and testosterone. Inflammatory cytokines that are locally or regularly produced by these cells can spontaneously activate the immune response which destroys the seminiferous epithelium resulting in autoimmune orchitis. The high production of cytokines after viral or bacterial infections, disease, or injury can exacerbate spermatogenesis and steroidogenesis, decrease sex hormones, and adversely affect fertility (25). Therefore, the persistence of SARS-CoV and MERS-CoV in urine and feces after discharge from hospital raises concerns about the spread of the virus when patients return to social activities. The same is true about the presence of the virus in semen and the serious complications in the reproductive system (9).

Clinical Implications

Considering the effect of SARS-CoV-2 on male reproductive health and its long-term persistence in the international community, it is essential to take the required clinical precautions for preventing the disease. Given the persistence of SARS-CoV-2 in semen, sperm donation at ART clinics should be delayed until further investigations.

ART clinics in Iran have stopped admitting new patients during the pandemic. Studies in the near future can facilitate decision-making in this respect and set standards of protective equipment required in ART clinics and laboratories working on semen samples (19). The existing literature shows that they can be used in the clinic. These standards include the use of contraceptives before sex. Condoms can be used to prevent COVID-19 from transmission. It can limit the possible adverse effects of the disease through sexual transmission. Future studies should focus on monitoring the growth process of fetuses in COVID-19 patients. Additionally, according to previous evidence and studies on ACE2 expression in the male reproductive tract of COVID-19 patients, precautions should be taken to prevent viral transmission during cryopreservation and ART procedures (Table 1) (26). Therefore, avoiding contact with the saliva and blood

Table 1. Hypothesis and Evidence for the Possible Sexual Transmission of SARS-CoV-2 and Its Effect on Natural Pregnancy, Assisted Reproduction and Cryopreservation

Sexual Transmission	Natural Pregnancy	Assisted Reproduction	Cryopreservation
Detection of SARS-CoV-2 virus in semen samples from 5% of men with active disease or in convalescence may indicate the possibility of sexual transmission, though this assumption warrants further investigation.	The effect of SARS-CoV-2 on pregnancy appears to be less severe than other coronaviruses. Preterm delivery is among the most common implication of SARS-CoV-2	ART during the SARS-CoV-2 pandemic may be conducted after incorporating risk assessment and mitigation strategies and when measures are taken to maximize the safety of patients and staff.	The SARS-CoV-2 may present a major risk of cross-contamination during cryopreservation.

ART: assisted reproductive technique.

of COVID-19 patients is not sufficient, because the persistence of SARS-CoV-2 in the semen of recovered patients can also transmit the disease. Moreover, male COVID-19 patients planning to have a child or maintaining sexual activities are suggested to regularly evaluate their sex hormones and semen quality and ascertain the health of their reproductive organs. Studies have demonstrated that SARS-CoV-2 infection can cause sexual dysfunction and the testosterone to luteinizing hormone (LH) ratio is decreased in COVID-19 patients compared to healthy controls at the same age (25). Due to uncertainty about the transmission of the virus via semen, further research is needed to safely perform ARTs. In addition, most studies have evaluated semen specimens taken after recovery and 14 days of quarantine. Future studies should assess semen samples within the first two weeks of infection so that potential adverse effects can be avoided.

Therefore, anti-inflammatory therapies can help treat acute orchitis and prevent potential factors involved in future infertility. Therefore, all follow-up and pre-pregnancy counseling during the COVID-19 pandemic is essential. At present, precautions are recommended for performing a safe ART procedure without the risk of transmitting the virus to ensure the prevention of possible complications and the long-term and serious effect of SARS-CoV-2 on the reproductive system.

Conclusion

The findings of the present study point to the destructive effect of SARS-CoV-2 on male reproduction. The most important effect appears to be on the testes following a cytokine storm. Severe secondary inflammation caused by the virus causes blood-testis barrier (BTB) damage and orchitis. In addition, the virus infection has a negative effect on germ cells and interstitial cells, as well as spermatogenesis and sex hormones. However, studies on the potential effect of COVID-19 on the testis and infertility, mediated by a viral attack, a secondary immunological response, or an inflammatory response show that the same process may adversely affect fertility.

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Authors' Contribution

ET, MJH, AH, ANA, ML conceived the ideas and SF wrote the manuscript.

Conflict of Interest Disclosures

The authors declare no conflict of interest.

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Informed Consent

The study was a review and thus required no informed consent from the participants.

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