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REVIEW

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Impact of SARS-CoV-2 on male reproductive system and fertility

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Abstract

Objective Evaluate the impact of SARS-CoV-2 on male fertility.

Design Comprehensive analysis of studies exploring virus presence, inflammation, and altered semen parameters.

Result(s) While some studies report absence of SARS-CoV-2 in semen, others highlight testicular injury, inflammation, and potential viral orchitis. Scrotal discomfort and altered sperm parameters indicate reproductive implications.

Conclusion SARS-CoV-2 may pose significant challenges to male fertility, necessitating further research for a comprehensive understanding of its long-term effects. Limitations include varied testing methods and sample sizes, emphasizing the need for confirmation and detailed post-COVID examinations.

Keywords SARS-CoV-2, Male fertility, Testicular injury, Viral orchitis, Semen parameters

Introduction

The World Health Organisation in 2019 calls the new coronavirus COVID-19. It first showed up in Wuhan, Hubei county, China, in December 2019. In this case, COVID-19 was caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first case was found because of a sudden rise in the number of unclear cases of pneumonia. When tests were first done on patients, they came back clear for common lung viruses but subsequent tests showed good results for a newly discovered coronavirus [3]. At the time Chinese health officials did everything they could to stop the virus from spreading by isolating the sick patients. But it quickly spread all over the world, within a few months [46] causing the COVID-19 outbreak that is still going on [20] but on the way out.

It is possible to be infected with SARS-CoV-2 without having any symptoms. Data shows that it spreads through drops or fumes [16]. The virus is thought to take 5 days to fully develop after exposure, but this period may vary from 2 to 14 days [35] [35]. Initially, it was thought to be associated with a range of mild to severe respiratory distress syndrome in individuals. Affected individuals exhibited symptoms such as dry cough, fatigue, fever, breathing difficulties, and muscle pain. These symptoms could progress to asthma, loss of smell and taste [2]. However, there is some evidence to suggest that COVID-19 could also have adverse effects on other organ systems apart from the respiratory system. This review will initally and briefly explore the negative impacts of COVID-19 on various body parts, including the heart, kidneys, digestive system, central nervous system, skin, but then predominantly discuss the virus effect on the reproductive system.

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Discussion

SARS-CoV-2 history and origin

SARS-CoV-2, which is an RNA virus, spread globally after the outbreaks of MERS-CoV and SARS-CoV in 2002 and 2012, respectively [29]. The first signs of SARS, which were consistent with the WHO definition, were observed in Foshan, China, on November 16, 2002. Many people contracted atypical pneumonia as a result, and by February 2003, more than 300 cases had been reported [59]. Those who were infected traveled to various countries, including Hong Kong, Vietnam, and Canada, spreading the disease worldwide [10, 15]. The WHO declared the SARS outbreak officially over after reports of 8,096 cases in 27 countries and 774 deaths. [48].

A man from Saudi Arabia, who was 60 years old, passed away due to acute pneumonia and kidney failure in a private hospital located in Jeddah. The MERS-CoV virus was found in his sputum culture after 10 years of the first case of SARS-CoV, according to a study by Zaki et al. in 2012. [57]. MERS-CoV spread to other countries outside of the Middle East because people who were infected travelled. For instance, a tourist who traveled back from the Middle East and developed a fever triggered a MERS outbreak in the Republic of Korea, as per a study by [21].

According to the World Health Organization (WHO), as of April 26, 2016, there have been 1728 cases of Middle East Respiratory Syndrome (MERS) recorded in 27 countries, resulting in 624 deaths [8]. Recent studies by Mohamadian et al. [29], suggest that MERS can be transmitted from animals to humans and from humans to other humans. While bats are believed to be the natural host of the coronavirus, Woo et al. [52] point out that it is difficult to establish their immediate role in the disease transmission since most patients have not been in close proximity to bats. However, Groot et al. [7] argue that it is more likely that a particular strain of the beta coronaviruses found in bats spread to a different animal host species and resulted in the accidental spillover to humans. So there was an accidental spill over into the human population [7].

SARS-CoV-2 molecular structure

There are four main types of coronavirus that can be distinguished based on genetic and viral tests. These are Alphacoronavirus, Beta coronavirus, Gamma coronavirus, and Deltacoronavirus. Alphacoronavirus and Betacoronavirus are known to infect mammals. Gamma coronavirus is known to infect birds, while Delta coronavirus is capable of infecting both birds and humans [25, 60]. The name coronavirus comes from the Latin word for crown because the virus's surface has S-protein spikes that resemble crowns and measure 80–160 nM in size [51]. SARS-CoV2, the virus responsible for the COVID-19 pandemic, is a single-strand RNA virus with an unsegmented coat. It has the largest genome of all known viruses, ranging from 27 to 32 kb in size [17, 25].

Viral genomes have a 5' and 3' end and are enclosed in a spiral capsid made of the nucleocapsid protein (N). [25]. The 5' end of the genome contains open reading frames that encode proteins necessary for virus replication. The structural proteins of the virus are located in the 3' end, including the membrane protein (M) and the envelope protein (E), which assist in assembling the virus. The M-protein is responsible for shaping the viral coat and is more common than the E-protein, which is the smallest structural protein and is produced heavily during the viral replication cycle inside the infected cell. [45]. The virus capsid also contains a spike protein (S) [25, 9].

The S-protein, which gives the coronavirus its spiked look, is also responsible for attaching and permitting the virus to enter the host cell. This protein is highly mutable and comprises type I membrane glycoproteins [17, 51]. According to Zhu et al. [60], the S-protein binds to cell receptors on the host cell to gain entry. The virus genome also includes the nucleocapsid protein (N), the envelope protein (E), and the haemagglutinin-esterase (HE) protein at the 3' end [45]. The HE protein helps the virus to recognize the host cell, while the N-protein aids in virus transcription and assembly by forming RNA complexes.

Mechanism of action/pathogenesis affecting male reproduction

The renin-angiotensin system (RAS), along with ACE2 and TMPRSS2, plays a significant role in how SARS-CoV-2 enters cells. The strong development of ACE2 in the male reproductive system makes this route even more crucial for COVID-19 cases [41]. In 2021, Seymen conducted a study called "RAAS ACE2," which has put forth many ideas, mostly in the field of andrology, about the biological similarities between SARS-CoV and SARS-CoV-2. Angiotensin Converting Enzyme-2 (ACE2) is a receptor that both viruses use to infect human cells [18, 36, 42]. Angiotensin Converting Enzyme-2 (ACE2) is a receptor that SARS-CoV and SARS-CoV-2 both use to get into human cells [18, 36, 42].

Numerous studies have demonstrated that ACE2 expression varies in different organs, with the kidney, heart, thyroid, fatty tissue, small intestine [50], and testes having the highest expression [23, 26]. This finding raises the curiosity of investigating the expression of ACE2 in these organs including neurological tissue and determining the possible contribution of neurological tissue damage to the morbidity and mortality caused by COVID-19 [1]. Because ACE2 receptors are present in Leydig and Sertoli cells of the testicles, it is believed that the virus may affect the testicles' function once it enters the body.

This notion also includes the idea that the virus's binding to the ACE2 receptor could cause an excessive amount of ACE2, leading to an inflammatory response that affects Leydig and Sertoli cell function [18].

COVID-19 diagnosis and symptoms

COVID-19 is a viral infection that can cause mild to serious illness [34]. Symptoms may appear anywhere from 2 to 14 days after exposure to the virus. Common symptoms include fever, cough, and muscle pain. Other less serious symptoms may include sore throat, chills, headache, nausea, loss of taste, coughing up blood, diarrhea, or vomiting. [4, 45]. Older adults or people with underlying health conditions such as high blood pressure, diabetes, chronic obstructive pulmonary disease, or heart disease, are at a higher risk of developing severe symptoms that can quickly worsen and lead to septic shock, acute respiratory distress syndrome, problems with blood clotting, and in some cases, death [16].

A study conducted by Pan et al. in 2020 examined the presence of COVID-19 in the semen of patients [32], The study found that, after one month of diagnosis, there were no signs of SARS-CoV-2 in the semen of patients who were recovering from COVID-19. However, even though the disease was not found in the sperm, 19% of patients experienced pain in their scrotum during their COVID-19 diagnosis, which could be a sign of viral orchitis. [32]. It is important to identify individuals experiencing fever, one of the main symptoms of SARS-CoV-2, as early as possible [30].

During the diagnosis process, a physical check is an important step that helps doctors determine whether a patient has a serious form of the disease. Some common symptoms of this type of disease are shortness of breath, wet rales in the lungs, fewer breath sounds, dull percussion, and either more or less physical speech trembling [53]. In addition to physical examination, radiographic tests such as CT scans and lung X-rays can also reveal the signs of SARS-CoV2.

In the early stages of pneumonia, a chest x-ray can show small spotty shadows and interstitial changes, especially around the edges of the lungs [3]. In more serious cases, there may be multiple ground-glass opacities on both sides, shadows that penetrate the lungs, and pulmonary consolidation, with pleural effusion occuring rarely [49, 53]. CT scans can provide more precise and distinct differentiation between pneumonia and any underlying lung pathologies or malignancy – something which may not be visible initially on chest X-rays. However, results depend on the patient's age, health, drug combinations, and the stage of the disease at the time of the scan. Some of the diseases that can be detected through CT scans include ground-glass opacity and segmental consolidation in both lungs, mostly around the edges of the lungs [5, 53]. RT-PCR is the most accurate way to diagnose SARS-CoV-2 as it directly targets the viral genome instead of relying on secondary signals such as antibodies or proteins [56]. This method can quickly and accurately identify the virus, and a nasopharyngeal or oropharyngeal swab is usually used to obtain a sample [19].

SARS-CoV-2 and the male reproductive tract

Numerous studies have suggested various ways in which the SARS-CoV-2 virus can enter different parts of the body such as the lungs, circulatory system, gut, and urine system, but it is still unclear whether it can infect the reproductive system [47]. The virus has been detected in the urine, faeces [14], and eyes [54] of infected individuals. Considering how SARS-CoV-2 operates, cells with ACE2 receptors may not be able to handle it effectively. The majority of the ACE2 in testicular cells is found in the seminiferous duct cells, spermatogonia, and Leydig and Sertoli cells [12]. ACE2 receptors are present in both male sexual systems, indicating a possible connection with sperm function [20].

Testicle

Numerous studies have explored the possibility of SARS-CoV-2 infecting the testes, which contain a significant amount of ACE2. However, a study by Yang et al. [55] found no signs of the virus in the testicular tissue of 90% of the 12 patients examined. Nonetheless, the same study did reveal that all patients had lower Leydig cell counts, higher Sertoli cell counts, mild lymphatic inflammation, and seminiferous tubule damage [55]. Another study by Song et al. [43] analyzed testicular biopsies from deceased COVID-19 patients, but the results showed no positive RT-PCR findings. However, this study only examined a small group of people [43].

Another study by Ediz et al. [11] found that hospitalized COVID-19 patients were more likely to experience testicular pain, although they did not exhibit any inflammation markers associated with epididymo-orchitis. [11].

Prostate

Expressed prostatic secretion (EPS), is a crucial component of semen, which is released by the prostate gland. It constitutes approximately one-tenth to one-third of the total ejaculate and plays a vital role in protecting and maintaining the health of sperm cells. Recent studies have examined the potential involvement of the prostate gland in SARS-CoV-2 infection. Zhang et al. [58] found no evidence of SARS-CoV-2 infection in the prostate tissues of ten COVID-19 patients. However, they did observe higher levels of inflammation biomarkers in these

patients. [58]. Similarly, Ruan et al. analyzed data from three studies and concluded that all 89 cases of prostate fluid tested negative for SARS-CoV-2. These findings suggest that the prostate gland may not be directly involved in the infection process [39]. A study conducted by Quan et al. on 18 COVID-19 patients and five potential cases and found that none of them had SARS-CoV2 present in their prostate fluids [37].

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Seminal sample / frozen samples

SARS-CoV-2, the virus responsible for COVID-19, has been detected in the sperm of infected patients, which raises the possibility of it being transmitted through physical contact [13]. However, there is not enough evidence to support this claim, as the studies that have been conducted are relatively new and have small sample sizes.. Some studies have found no evidence of the virus in semen samples of infected patients. For instance, a review conducted in October 2020 by Khalili et al. did not find any viral RNA in semen samples of 82 patients. In another study, conducted by Li et al., SARS-CoV-2 RNA was detected in the sperm of six out of 38 cases studied [24]. The study found that age, history of urogenital disease, and disease development did not affect the results. However, these studies are not conclusive, and more research is needed to understand the potential of SARS-CoV-2 transmission through semen.

According to several studies that examined a total of 120 patients, it has been discovered that the SARS-CoV-2 virus was found in the sperm of 6 COVID-19 cases. This means that the virus was present in the sperm of 5% of individuals who had contracted COVID-19, based on data from all 120 patients in these 6 studies.. However, in contrast Paoli et al. [33], found no presence of the virus in the sperm or urine samples of a 31-year-old COVID-19 patient. Similarly, Pan et al. [32] found no evidence of the virus in the sperm of 34 patients who were recovering from the disease. Song et al. [44] also discovered that the virus was not present in the testis of a patient who died from COVID-19 or in the sperm of twelve patients who were still recovering. [44].

Additionally, Kaspa et al. analyzed the results of 14 studies worldwide and found that all of the seminal fluid that was tested (293/299) was negative for the virus. However, most of these tests were conducted on patients who were still recovering from SARS-CoV-2 [12, 32].

Male reproductive hormones

The first study to find a link between changes to the male sex hormone and getting SARS-CoV-2 was by Ma et al. [28]. The study aimed to find differences in male sex hormones by looking at 81 men who had SARS-CoV-2 and 100 healthy men. It was found that COVID-19 cases with higher LH levels and a lower T to LH ratio may indicate hypogonadism. There was no statistical difference between the two groups of men in terms of blood testosterone. There was also a drop in the ratio of follicle stimulating hormone to LH [28]. A study conducted by Ma et al. in 2020 revealed that COVID-19 patients had significantly higher levels of luteinizing hormone (LH) and prolactin, as compared to healthy individuals. However, the amount of testosterone in the blood remained unchanged, as suggested by Illiano et al. in 2020. The authors of the study explained that this might be due to a slow, negative feedback loop between LH and testosterone.

It has been suggested that during the early stages of testosterone production, LH may be released, which can help maintain stable testosterone levels for a short period of time. However, if this condition persists, it can lead to clinical hypogonadism [18],Daniel et al. 2022). A recent study conducted by Rastrelli et al. [38] aimed to investigate the relationship between testosterone levels and SARS-CoV in a group of patients admitted to the lung intensive care unit. The study found that individuals who had recovered from COVID-19 had low levels of total testosterone, which were associated with high levels of CRP. Moreover, low levels of total testosterone were observed in severe cases of the disease [20]. Although sexual transmission remains unlikely in recovered men, moderate to severe COVID-19 infection can lead to germ cell and Leydig cell depletion, leading to decreased spermatogenesis and male hypogonadism [6].

A study conducted in Germany compared male Covid-19 patients to those with coronary heart disease (CHD) and healthy individuals. The study found that most men with COVID-19 had lower levels of testosterone and dihydrotestosterone compared to men with CHD and HC. Based on these findings, hypogonadism may be considered a risk factor for COVID-19, resulting in higher rates of illness and death [40]. However, Ruan et al. [39] showed in a study of 66 blood samples that hormone levels did not significantly change. Hormones such as FSH, LH, testosterone, and estrogen were found to be within normal ranges [20, 39].

Sexual transmission implications

As we discuss the impact of COVID-19 on male fertility, it is also important to consider its effect on the sexual transmission of viruses. According to the data presented, there is no evidence supporting the claim that SARS-CoV-2 can be transmitted through physical contact. However, since other bacterial and viral diseases can be spread through physical contact, further research is necessary in this area. Chlamydia, gonorrhoea, and syphilis are all examples of bacterial infections [27] that are sexually transmitted. Human papillomavirus (HPV), herpes (also known as herpes simplex virus), HIV/AIDS, and hepatitis B are all viruses that can cause illness [27]

Gender differences in patients with COVID-19

Studies have revealed that common coronaviruses like SARS-CoV-1 and MERS-CoV have also affected men and women differently in the past. Men are more susceptible to contracting these viruses and when they do, they tend to experience more severe symptoms as compared to women. [31]. This aligns with the results of clinical trials conducted on mice which showed that oestrogen can reduce the risk of contracting SARS-CoV and alleviate the severity of the infection. [22]. It has been observed that female mice without eggs were more prone to get sick and the disease also spread faster. Although there may be differences between how men and women respond to SARS-CoV-2, there haven't been many epidemiological studies that have compared the numbers of SARS-CoV-2 to the numbers of COVID-19 cases and deaths. Therefore, it is still unclear whether the disease caused by SARS-CoV-2, including how fast it spreads and its mortality rate, affects men and women differently.

Conclusion

Studies show that COVID-19 can affect male reproductive health, with uncertain long-term complications. The semen characteristics of patients with COVID-19 are also altered, and there is an increase in the number of spermatozoa with DNA fragmentation. Even though the virus was not found in semen, prostatic secretions, or testicular tissues, the findings suggest that SARS-CoV-2 infection could result in significant reproductive difficulties. It's unclear whether the virus directly infects testes cells, but inflammation could play an indirect role. Patients with COVID-19 show high levels of seminal cytokines, apoptosis markers, and impaired antioxidant activity. This inflammation could trigger an autoimmune response and reach the semen through the blood-testis barrier. Administering antioxidants and drugs to counteract the effects of the cytokine storm can help prevent testicular injury and preserve fertility.

The impact of a SARS-CoV-2 infection on semen quality is still under investigation. Recent studies suggest that these effects could be temporary. This finding is critical for couples seeking assisted reproductive technology (ART) and for the cryopreservation of male gametes.

This review highlights the need for further research to understand the long-term effects of the virus on male fertility and testicular function. However, as these are only primary studies, there are limitations in the testing methods and sample sizes. It is also important to note that further confirmation and detailed examinations and testing methods should be performed post-COVID. Furthermore, another limitation could be the fact that functional baseline status and medical history of the participants, for example obesity, may not have been considered in analysis, which may have affected their reproductive function prior to a particular study.

Continued research into the sexual transmission and long-term reproductive health of individuals who have recovered from SARS-CoV-2 is crucial and could lead to changes in public health policies and provide useful prevention guidelines.

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SGS did the literature search and wrote the full manuscript, YS conceived the ideas and was an major contributor in writing the manuscript. editing and proof reading. Other authors helped with literature search and editing the manuscript. All authors read and approved the final manuscript.

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