Can COVID-19 Be Transmitted Sexually by Semen?

Ahmed E. Taha1,2

1Microbiology and Immunology unit, Department of Pathology, College of Medicine, Jouf University, Al-Jouf, Saudi Arabia.
2Medical Microbiology and Immunology Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt.

Abstract

Information on the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has amplified quickly since its spread; however, many issues remain unclear. SARS-CoV-2 is mainly transmitted through respiratory secretions. However, the potential for SARS-CoV-2 sexual transmission by semen is worthy of study. The cell-receptors of SARS-CoV-2, the angiotensin-converting enzyme-2 receptors, are highly expressed in human testis and may enable this virus to cause testicular tissue damage with bad effect on male fertility. SARS-CoV-2 presentation ranges from asymptomatic carriage to acute respiratory distress and fatal pneumonia, and elderly persons with underlying comorbidities usually suffer from a severe clinical picture. Asymptomatic individuals can spread the virus through their respiratory secretions and possibly through sexual transmission. SARS-CoV-2 can persist viable if cryopreserved in semen samples in sperm cryobanks. As far as I know, there is a gap in knowledge about SARS-CoV-2 transmission through semen, indicating the need for further research. This review attempts to understand the SARS-CoV-2 sexual transmission by semen. One recent study confirmed the theoretical risk of SARS-CoV-2 transmission by semen, but few studies negate this theory. Given that, an increasing number of asymptomatic and reactivated SARS-CoV-2 cases are being reported, attention to semen safety and SARS-CoV-2 transmission should be considered particularly in high-risk areas, to ensure the safety of male gametes for artificial reproduction and the general public. Avoiding cryopreservation of male gametes, condom use or even abstinence might be of paramount importance for these persons.

Keywords: Artificial reproduction, Infection prevention, Pandemic, SARS-CoV-2, Virus
INTRODUCTION

Sexually transmitted infections are mainly transmitted by sexual contact in humans. Recently, many viruses have been confirmed to be sexually transmitted by semen, although they were previously unknown to be transmitted by sexual contact, for instance, viruses as Zika and Ebola, which were detected in the semen of cases in both the acute and clinical recovery stages of the disease. However, the detection of viral genomes in semen does not confirm that the virus is sexually transmitted; examples of such viruses are certain flaviviruses, paramyxoviruses, and retroviruses. Though, such detection should raise the attention for the need for more infection prevention and control measures.

The pandemic of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), the causative organism of coronavirus disease (COVID-19), has aroused attention worldwide. The SARS-CoV-2 pandemic will result in numerous morbidities, mortalities and major cost impacts. It has been reported that the world lost more than $280 billion, and China lost about $62 billion in the first quarter of the year 2020.

The SARS-CoV-2 clinical presentation ranges from asymptomatic carriage to acute respiratory distress and severe pneumonia. Elderly persons with underlying comorbidities usually suffer from severe clinical picture compared to children and sexually active young adults who present with asymptomatic and mild cases. The number of COVID-19 cases in men is higher than that of women.

Although SARS-CoV-2 is mainly a respiratory virus, some studies have reported that the virus can be found in many human body fluids. The potential for sexual transmission by semen is worthy of study because many COVID-19 cases are asymptomatic or present mild symptoms. There is a potential risk for SARS-CoV-2 reactivation as mentioned by Ye et al., who reported that 9% of patients that were discharged from the hospital had presented SARS-CoV-2 reactivation confirmed by quantitative reverse transcription-polymerase chain reaction (qRT-PCR). In addition, Zhang et al. reported a discharged patient, after complete cure from COVID-19, who was retested positive for SARS-CoV-2 by qRT-PCR. The asymptomatic and reactivated cases are dangerous sources for transmission of this fatal virus and represent an infection control challenge, resulting in an increase in the number of cases. To my knowledge, there is wide controversy and big debate about SARS-CoV-2 sexual transmission by semen.

Breif Review of SARS–CoV-2 Structure

A review of the SARS–CoV-2 structure helps in understanding its pathogenesis while infecting the male reproductive tract. SARS–CoV-2 has an envelope, a helical nucleocapsid and a single-stranded RNA genome that encodes many proteins including; Spike (S), Membrane (M), Nucleocapsid (N) and Envelope (E) structural proteins. All these proteins are important for viral replication.

Coronavirus S protein is a large protein that projects from the envelope as a trimer giving the virus its characteristic crown-like appearance when examined by electron microscopy. Functionally it binds to the specific receptor during the viral entry inside the cell at the beginning of the infection. Furthermore, it determines the host range and tissue tropism and it is a vital immunodominant protein that can induce immune response of the host.

The ectodomain in the S protein of all coronaviruses is divided into two (S1 and S2) domains. The S1 helps in binding to host cell receptor by the receptor-binding domain (RBD) while the S2 helps in the fusion between the virus and membranes of host cells to allow the viral genome to penetrate the host cells.

The M proteins are the most abundant proteins present in the viral particle and play an important role in the viral assembly. The N proteins enhance the viral transcription and facilitate M protein role during assembly. Although the E proteins are the smallest among the structural proteins, they are important for viral assembly, release, tropism and pathogenesis.

Pathogenesis of SARS–CoV and SARS–CoV-2 Infection of Male Reproductive Tract

Data learnt from SARS–CoV, helps inform knowledge of tissue-specific SARS–CoV-2 pathogenesis. Many receptors for coronaviruses were detected on human cells including angiotensin-converting enzyme-2 (ACE2), Ezrin, CD26 and cyclophilins receptors. In SARS-CoV and SARS-CoV-2, the RBD of S1 protein interacts with the ACE2 receptor. Antibodies, vaccines
or therapeutics targeting this interaction can prevents its entry inside the cell\textsuperscript{25,26}.

D\textsuperscript{o}u\textsuperscript{g}las et al.\textsuperscript{27} suggested that coronaviruses might impact the men’s reproductive tracts either directly (because ACE2 receptors are expressed selectively by the Leydig cells of adult testes) or immunologically after inoculation of the viral RNA within the testicular tissue. It was reported in 2005 that postmortem testicular tissue focal atrophy was detected in eight SARS–CoV deceased patients, but the viral RNA was not detected in testicular biopsy\textsuperscript{28}. Furthermore, in 2006 Xu et al.\textsuperscript{29} reported sever orchitis cases caused by SARS–CoV with massive germ cell destruction, immunoglobulin G precipitation and leukocyte infiltration in testicular tissues.

The SARS–CoV-2 infection of human male reproductive tract needs more clarification. During the current COVID-19 pandemic, it was reported that the cell-receptors of SARS-CoV-2 (ACE2 receptors) are highly expressed in human testis and could enable the virus to cause testicular tissue damage with bad effects on men’s fertility all over the world. SARS-CoV-2 may be presented by orchitis, consequently, it is reasonable to consider the possibility of its transmission by semen. Additional studies on male reproductive tract infection by coronaviruses are necessary, especially among recovered persons\textsuperscript{30}.

Effects of SARS–CoV-2 ON Human Male Gametes

Information on SARS-CoV-2 has amplified quickly since its spread; however, many issues remain unclear regarding its impact on male reproduction. ACE2 receptors are much more expressed in the reproductive systems of males than females. As discussed above, the SARS–CoV-2 virus attaches to the ACE2 receptors within the adult Leydig cells in the testis to enter inside the cells. It was reported that ACE2 plays an important role in spermatogenesis. Therefore, spermatogenesis could be affected\textsuperscript{31,32}. Furthermore, fever can affect spermatogenesis. Sperm count and motility may be decreased for 72–90 days following fever\textsuperscript{33,34}.

We must deal with gametes of patients infected by some other viral diseases, such as hepatitis and human immunodeficiency virus, with special care to reduce exposure of non-infected partners and cross-contamination of within the assisted reproductive technology (ART) laboratories\textsuperscript{35}. The Society for Assisted Reproductive Technology (SART) and the American Society for Reproductive Medicine (ASRM) have warned prospective parents, gamete donors, ART patients and gestational carriers from pregnancy or participation in fertility programs in case of fulfilling the diagnostic criteria for COVID-19\textsuperscript{36}. The Center for Diseases Control and Prevention (CDC) has not excluded the possibility of SARS-CoV-2 transmission by non-respiratory body fluids, including semen, from infected persons\textsuperscript{37}.

La Marca et al.\textsuperscript{38} reported that Italian authorities are mandating interviewing of all gamete donors regarding COVID-19 respiratory symptoms and/or their recent travel history to high-risk places. If COVID-19 respiratory symptoms are presented, they should postpone gamete donation for two weeks after clearance of symptoms and/or returning from a high-risk place.

Most viruses can be stored dried at ultralow temperatures in suitable protein concentrations\textsuperscript{39}. Both SARS-CoV-2 and influenza viruses are RNA enveloped viruses. Cryopreserved influenza viruses can persist infectious even after 40 years\textsuperscript{40}. Similarly, SARS-CoV-2 could persist viable if cryopreserved in semen samples in sperm cryobanks\textsuperscript{41}.

Interestingly, a recent study reported the importance of a transmembrane serine protease 2 (TMPRSS2) protein during the virus–cell fusion process\textsuperscript{42}. Nevertheless, this protein is rarely expressed within tissues of the testis\textsuperscript{43}. Consequently, vulnerability of the testis to SARS-CoV-2 may be doubtful.

In this context, further investigations are necessary to pledge the safety of male gametes and ART. Therefore, the present review aimed to study the gap in knowledge about SARS-CoV-2 transmission through semen until August 2020. PubMed and other related databases were reviewed using the keywords (ACE2, Artificial reproduction, COVID-19, SARS-CoV-2, semen, sexual). Original articles, confirming or excluding presence of SARS-CoV-2 in semen, were included in this review. This review is highlighting the possibility of semen to be a vehicle for transmission of SARS-CoV-2. Some recent studies negate the presence of SARS-CoV-2 in semen\textsuperscript{44-52} and only one study proves its presence\textsuperscript{53}. 
Reports Excluding Possibility of SARS-CoV-2 Transmission by Semen

Song et al.\textsuperscript{44} reported that SARS-CoV-2 was not detected by qRT-PCR in testicular samples of one patient who died during the acute phase of COVID-19 and in semen samples collected from 12 infected men at the recovery phase (the period after two consecutive negative respiratory qRT-PCR tests or a significant resolution on chest CT scans with many symptoms). They excluded possibility of sexually transmitted SARS-CoV-2 by semen. Furthermore, they excluded the possibility of SARS-CoV-2 infecting the male genital tract. Limitations of their study were the small number of cases that were tested and the insubstantial number of semen samples that could be collected from the cases while they were sick. They recommended that more patients, more semen samples, and more pathological and physiological examinations of the male genital system are needed to confirm their findings.

Similarly, Paoli et al.\textsuperscript{45} reported that SARS-CoV-2 was not detected by qRT-PCR in a semen sample collected from a 31-year-old man (voluntary participant) who was found positive for SARS-CoV-2 in a pharyngeal swab eight days before collecting the semen sample. The patient’s symptoms were mild fever, anosmia, and myalgia. The limitation of their study was that it involved only one case and one semen sample that was collected on the 8\textsuperscript{th} day after the first positive pharyngeal swab, this was obligatory owing to poor health condition of that patient during the peak of the disease. They formulated two hypotheses: the first is that SARS-CoV-2 was present in semen, at the peak of the infection, but cleared with the progressive clinical recovery of the patient during the eight days; the second is that SARS-CoV-2 was never present in the semen at the time of testing. Furthermore, they recommended that more semen samples (if possible) should be collected from more patients with more severe symptoms, especially during the acute phase when virus shedding can be detected in the semen.

Furthermore, Pan et al.\textsuperscript{46} collected a single semen sample from 34 adult Chinese males. The cases were diagnosed with SARS-CoV-2 by confirmatory qRT-PCR from pharyngeal swabs. Semen was collected after a median of 31 days from COVID-19 confirmation. SARS-CoV-2 was not detected in the semen. Pan and his team concluded that although they did not detect the virus in the tested recovering patients, they cannot definitively exclude its presence in the semen during an acute SARS-CoV-2 infection with severe symptoms. In addition, the study reported presence of orchialgia in some tested cases that indicate possibility of testicular damage. Moreover, they recommended the need to further research for understanding the SARS-CoV-2 long-term effect on male fertility, reproductive and testicular endocrine functions.

In Renmin hospital of Wuhan university of China, Ning et al.\textsuperscript{47} excluded the presence of SARS-CoV-2 in semen of 112 COVID-19 confirmed male patients. All semen samples were negative for the ORF1ab and N genes. Orchidoptosis was detected in three severe COVID-19 patients (2.7%). Another report from China negated the presence of SARS-CoV-2 RNA in semen of tested 23 men (11 patients were tested negative and the other 12 patients were still positive in sputum and fecal samples)\textsuperscript{48}.

In Germany, Holtmann and her colleagues\textsuperscript{49} performed a pilot cohort study during which they obtained 18 semen samples from recovered men (8–54 days after clearance of symptoms), two semen samples from active COVID-19 patients and 14 semen samples from control persons. No SARS-CoV-2 RNA was detected in any semen sample by RT-PCR. They concluded that mild SARS-CoV-2 infection is doubtful to affect the testis, whereas moderate infection could impair the semen parameters.

Similar results were reported from USA by Rawlings et al.\textsuperscript{50} when SARS-CoV-2 RNA was not detected in semen of six COVID-19 male patients (6–17 days after the symptoms onset) in spite of associate shedding in oral secretions. Furthermore, the results of a Turkish study supported the believe that sexual transmission of SARS-CoV-2 through semen does not has a vital role after they did not detect its SARS-CoV-2 RNA in semen of 16 patients although all the semen samples were collected during the acute phase of the disease while the tests of nasopharyngeal swabs were positive\textsuperscript{51}.

In Italy, Pavone et al.\textsuperscript{52} reported that no evidence of SARS-CoV-2 in semen of nine Italian males recovering from mild COVID-19 in spite of prolonged positivity of nasopharyngeal swabs. Despite the limited size of this study,
they outweighed low probability of SARS-CoV-2 sexual transmission by men recovering from mild symptoms. However, they did not rule out the presence of SARS-CoV-2 in the semen of severe acute cases. They recommended larger scale studies to analyze serial samples collected from the start of symptoms till complete recovery of the disease.

**Reports Approving Possibility of SARS-CoV-2 Transmission by Semen**

Surprisingly, a recent study by Li et al. confirmed the presence of SARS-CoV-2 in semen samples collected from 6 patients by qRT-PCR. The study included 38 participants, of which 15 were in the acute phase of the disease and 23 were in the clinical recovery phase. Among the 6 positive patients, 4 were in the acute phase and 2 in the recovery phase, which is predominantly noteworthy. They outweighed that SARS-CoV-2 could be seeded and persist in the testes and semen even after clinical recovery due to inflammation (systemic and local), imperfect blood-testes/deferens/epididymis barriers and the privileged immunity of testes. This study was limited by the small sample size and the short follow-up period. The study recommended that further researches should focus on SARS-CoV-2 shedding, survival time, and infectious dose in the semen.

**CONCLUSION**

In conclusion, there is a gap in knowledge about SARS-CoV-2 in the semen, which shows that further researches are required. Given that, an increasing number of asymptomatic and reactivated SARS-CoV-2 cases are being reported, attention to semen safety and SARS-CoV-2 transmission should be considered particularly in high-risk areas to ensure the safety of the general public and cryopreserved male gametes for artificial reproduction. More attention should be considered when dealing with patients suffering from COVID-19 severe clinical picture. This study might provide new information about COVID-19 prevention and control.

**Recommendations**

While we do not currently have all the answers regarding possibility of SARS-CoV-2 transmission by semen, I suggest that SARS-CoV-2 sexual transmission should be considered during prevention and control of this fatal virus depending on the findings suggesting that it could be found in the semen of recovering patients who might be young and sexually active. Furthermore, this may happen in patients during the incubation period or with no or mild symptoms who can practice sex or cryopreserve their gametes. When dealing with a couple in which the man has been diagnosed with COVID-19, avoiding cryopreservation of male gametes, condom use or even abstinence might be of paramount importance for these persons.

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**DATA AVAILABILITY**

All datasets generated or analyzed during this study are included in the manuscript.

**ETHICS STATEMENT**

This article does not contain any studies with human participants or animals performed by the author.

**REFERENCES**


