SARS-COV-2 and Male Reproductive Health

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ABSTRACT

Critical challenges for the public and private health, research, and medical communities have been posed by the COVID-19 outbreak. Some of these challenges are related to the possible adverse effects of SARS-CoV-2 on male reproductive health, and whether other potential modes of transmission may occur, such as sexual transmission. Moreover, concerns have been raised in terms of whether the COVID-19 outbreak may have an impact on fertility worldwide. In this study, we will discuss the origins of SARS-CoV-2. We will further describe its mechanism of action, diagnosis, symptoms, and potential effects on the male reproductive system.

Keywords: Semen, Covid-19, SARS-COV-2, male reproductive.

Introduction

As of May 16, 2020, 4,434,653 confirmed cases and 302,169 deaths due to the novel coronavirus disease 2019 (COVID-19) – which is caused by the new, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – have been reported worldwide (WHO, 2020a). Although COVID-19 was first identified as a respiratory disease, it is now considered a systemic pathology, as it may affect different systems (Pan et al., 2020). New challenges are now emerging concerning the disease, such as associated reproductive implications and the consequences of assisted and natural conceptions in the presence of acute COVID-19 infection and following patient recovery (Eisenberg 2020).

In the last 20 years, there were two previous pandemics related to coronavirus, including the severe acute respiratory syndrome (SARS; 2002 and 2003) and the Middle East respiratory syndrome (MERS; 2012), which did not reach the number of cases and deaths associated with COVID-19. However, these previous pandemics have accelerated our understanding of the epidemiology and pathogenesis of SARS-CoV-2 (Jin et al., 2020), and an unprecedented number of research studies related to this disease have emerged. Further, over 500 clinical trials have been registered among different national and international clinical trial registry sites as of April 21, 2020, which aim to evaluate different possible therapeutic options (Thorlund et al., 2020). Nevertheless, until now, no specific and effective therapeutic strategies have been available to decrease the fatality rates of COVID-19, and it seems that quarantine, isolation, and social distancing remain the best strategies to deal with this novel pandemic (Hick & Biddinger, 2020). Thus, critical challenges for the public and private health, research, and medical communities have been posed by the COVID-19 outbreak (Fauci et al., 2020). Some of these challenges are related to the possible adverse effects of SARS-CoV-2 on male reproductive health, and whether other potential modes of transmission may occur, such as sexual transmission. Moreover, concerns have been raised in terms of whether the COVID-19 outbreak may have an impact on fertility worldwide (Cardona Maya et al., 2020).

In this study, we will discuss the origins of SARS-CoV-2. We will further describe its mechanism of action, diagnosis, symptoms, and potential effects on the male reproductive system.

SARS-CoV-2 history and origin

On December 31, 2019, Chinese health authorities announced dozens of pneumonia infections of unknown etiology in Wuhan city (Hubei province). The infectious agent was identified on 7 January 2020, and was classified as a novel coronavirus (2019-nCoV)(Abduljalil & Abduljalil, 2020). On January 30, 2020, the World Health Organization (WHO) decreed a public health emergency of international importance (Souza et al., 2020). Thereafter, on February 11, 2020, the WHO announced that this novel coronavirus pneumonia was classified as coronavirus disease-2019 (COVID-19)(WHO, 2020b). Due to its similarity with the causative agent, SARS, the novel coronavirus was named SARS-CoV-2 by the International Committee on Taxonomy of Viruses (Abduljalil & Abduljalil, 2020). Given the global involvement of COVID-19, the WHO declared a pandemic on March 11, 2020 (Souza et al., 2020).

SARS-CoV-2 is the seventh identified member of the coronavirus family to affect humans, and it is the third coronavirus to emerge in the human population in the past two decades. Many details related to its origin and its ability to spread among humans remain unknown (Munster et al., 2020). Coronaviruses are a large family of enveloped, single-stranded RNA viruses known to infect not only humans, but also other mammals and birds, leading to respiratory, hepatic, gastrointestinal, and neurologic diseases (Mungroo et al., 2020; Zhu et al., 2020). A genome-wide phylogenetic analysis indicated that SARS-CoV-2 shares 79.5% and 50% sequence identity with SARS-CoV and MERS-CoV, respectively (Jin et al., 2020). Although believed to originate from bats, it has been speculated that other animals, such as pangolins and snakes, served as intermediate hosts, allowing the spillover of SARS-CoV-2 as a distinct human virus (Abduljalil & Abduljalil, 2020). However, phylogenetic analyses of the virus and its closely related reference genomes indicate that the origin of the virus has yet to be determined (Zhou et al., 2020).

SARS-CoV-2 mechanism of action

SARS-CoV-2 has four key structural proteins, namely nucleocapsid (N), spike (S), small membrane (SM), and membrane (M) proteins. The S protein is required for the virus to fuse to the host cell through the receptor-binding-domain (Monteleone et al., 2020). The main path for SARS-CoV-2 entry into the cell is via the attachment of the S protein to the angiotensin-converting enzyme 2 (ACE2) that can be identified in type II alveolar cells, myocardial...
cells, proximal tubule cells of the kidney, ileum and esophagus epithelial cells, and bladder urothelial cells (Zhou et al., 2020). ACE2 can also be identified in the human testis, as it is highly expressed in Leydig and seminiferous tubules cells (Fan et al., 2020). Thus, it is hypothesized that SARS-CoV-2 may bind to ACE2 in testicular tissue, leading to alterations in testicular tissue and providing a site for viral infection (Cardona Mayora et al., 2020) Following membrane fusion, viral RNA is released into the cytoplasm, and viral replication begins (Monteleone et al., 2020).

It has been considered that the main path for SARS-CoV-2 transmission is from person to person through droplets and close contact (Chan et al., 2020). However, it has also been hypothesized that other transmission routes may be available, although they require further verification (Uddin et al., 2020; Halfmann et al., 2020). In reproductive medicine, special consideration has been paid as to whether vertical transmission (mother-to-fetus) (Simões e Silva et al., 2020) and sexual transmission may occur (Li et al., 2020).

COVID-19 diagnosis and symptoms

The most frequently occurring symptoms of COVID-19 include fever, cough, fatigue, shortness of breath, sputum production, headache, and myalgias. Patients may also complain of vomiting, diarrhea, anosmia, and also ophthalmologic and cutaneous manifestations (Segars et al., 2020). Interestingly, in a recently published study evaluating the presence of the coronavirus in the semen of infected patients, it was noted that although no SARS-CoV-2 was identified in semen samples, ~18% of infected men reported scrotal discomfort at the time of COVID-19 infection (Pan et al., 2020).

COVID-19 patients have been classified as asymptomatic, mild, severe, and critical types. Mild patients tend to experience mild pneumonia, while severe patients exhibit dyspnea and increased respiratory frequency within 24–48 hours. Critical patients suffer from respiratory failure, acute heart injury, septic shock, and multiple organ failure (Mungroo et al., 2020).

SARS-CoV-2 is a highly pathogenic virus that may be associated with uncontrolled cytokine release, known as a cytokine storm, that may lead to capillary leakage, tissue toxicity, edema, organ failure, and shock (Zhou et al. 2020). In COVID-19, a significant elevation of cytokines (interferon [IFN]-α, tumor necrosis factor [TNF]-α, interleukin [IL]-6, IL-10, IL-2, IL-1, and others) and lymphopenia are found. The clinical manifestation of the severe type in patients is significantly related to elevated IL-6 (Zhou et al., 2020).

Although the presenting symptoms and radiographic analysis of computed tomography (CT) scans may suggest the presence of COVID-19, a definitive diagnosis is achieved through virus detection via polymerase chain reaction (PCR). It is recommended by the U.S. Centers for Disease Prevention and Control (CDC) that a PCR be performed to diagnose acute infection. False-positive SARS-CoV-2 testing is rare, although false-negative results can occur due to inadequate sample collection or if it is performed early in the disease course. PCR may be performed with samples obtained from nasal swabs, trachea and nasopharynx extracts, and several primers used to detect SARS-CoV-2, which were established through realtime reverse-transcription (RT)-PCR. This enables fast and specific virus detection (Mungro et al., 2020; ASRM COVID Task Force, 2020). Serologic tests, evaluating the presence of immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies are not recommended for diagnosis of acute infection, although emerging evidence suggests that they may confer immunity or reduced risk of reinfection. When performed by ELISA, serologic tests present >95% specificity for disease diagnosis, but sensitivity may range from 60%-98% (ASRM COVID Task Force, 2020).

SARS-CoV-2 and the male reproductive tract

- Does the virus affect the male reproductive tract?

Until now, it is unknown whether or to what extent SARS-CoV-2 can affect male reproductive health (Wang & Xu, 2020; Esteves et al., 2020; Stanley et al., 2020). COVID-19 is primarily contracted through droplets; however, the virus has already been isolated in the urine (Guan et al., 2020), feces (Guan et al., 2020), and conjunctiva (Xia et al., 2020) of infected patients. Due to its mechanism of action – i.e., ACE2 receptor binding – it may compromise other tissues with ACE2 receptors, such as those of the reproductive system. Specifically, high ACE2 expression levels are found in testicular cells, mainly in seminiferous duct cells, spermagonia, and Leydig and Sertoli cells (Esteves et al., 2020).

- Testicle

Studies of SARS-CoV reveal orchitis as a possible clinical presentation of this virus, and there is evidence of deleterious effects on testicular tissues, including the presence of the virus on autopsy (Xu et al., 2006; Zhao et al., 2003). As in SARS-CoV, the ACE2 receptor plays an important role in the pathophysiology of SARS-CoV-2 infection, as it is used as the primary form of cell binding, leading the virus to infect the cell and replicate. Several studies have demonstrated a high concentration of ACE2 in testicular tissues, either in germ cells or somatic cells (Fan et al., 2020; Wang & Xu, 2020; Shen et al., 2020; Zhang et al., 2020). Thus, there is evidence that the testis is vulnerable to SARS-CoV-2 infection, so it is important to assess and monitor the reproductive functions of these patients. In addition, the presence of orchitis complaints was found in 19% of patients (Pan et al., 2020). However, a recent study evaluated patients with COVID-19 and showed a complete absence of SARS-CoV-2 in the semen and testes of infected men (Song et al., 2020). Therefore, more studies examining more patients are needed to confirm whether the virus is present in the testes.

- Prostate

Only one small retrospective study evaluated the presence of SARS-CoV-2 in prostatic aspirate samples (PS). A Chinese study evaluated the PS of 18 males diagnosed with COVID-19 and five suspected cases. The samples of all evaluated patients did not show evidence of the RNA expression of SARS-CoV-2 (Quan et al., 2020).

- Seminal sample

Although there is a protective blood–testicular barrier, more than 27 viruses can be found and transmitted through the semen, such as human immunodeficiency virus (HIV), mumps, influenza, Zika virus, coxsackievirus infection, Ebola, and hepatitis B and C. Two previous studies did not find SARS-CoV-2 in semen; however, these studies had low numbers of patients who were at different stages of infection and recovery (Pan et al., 2020; Song et al., 2020). The first study to evaluate the semen of males diagnosed with COVID-19 evaluated 34 Chinese males. Although six (19%) of these patients complained of scrotal discomfort due to viral orchitis, SARS-CoV-2 was not detected in the semen of any of these patients (Pan et al., 2020). The second study evaluated 12 patients in the recovery phase of COVID-19, and the semen evaluation of all patients showed no detectable SARS-CoV-2 RNA in the semen samples (Song et al., 2020).

The third study published evaluating the semen samples of men with COVID-19 featured 38 patients. The study
found that in six (15.8%) of these patients, SARS-CoV-2 was detected in the semen samples, even among those who were recovering. However, the study was not able to evaluate virus shedding, survival time, and viral concentration in semen. This study raises question of whether SARS-CoV-2 can be sexually transmitted, as this might represent a critical factor in transmission prevention (Li et al., 2020). Thus, as of May 15, 2020, data are available on the semen samples of 84 male patients with COVID-19, and it was found that SARS-CoV-2 was identified in six (7.1%).

There are no data in the literature regarding changes in the fertile potential of these men affected by SARS-CoV-2, although it is known that any feverish condition is capable of altering seminal quality (Carlsen et al., 2003; Jung & Schuppe, 2007). However, it is important to assess whether there are any such direct effects associated with this virus, as occurs in cases of mumps infection (Davis et al., 2010).

**Hormonal dosages**

There was an evaluation of gonadal function in some patients, which was achieved through hormone profile measurement. When compared to healthy patients, those infected showed a probable initial gonadotoxic effect (Zhang et al., 2020). However, more data are necessary to confirm the gonadotoxic effects of the virus.

**Conclusion**

There is the theoretical possibility that testicular damage and subsequent infertility may result following COVID-19 infection, and also the possibility of sexual transmission, as SARS-CoV-2 has been identified in the semen of infected patients. However, the available data and study findings are recent, based on small sample sizes, and present conflicting information. Thus, until now, there is not enough evidence to support the need for asymptomatic couples to avoid sexual intercourse to protect against virus transmission. Further research is needed to understand the long-term impacts of SARS-CoV-2 on male reproductive function, including its potential effects on fertility and testicular endocrine function. Before arriving at a definitive understanding of the impacts of potential viral attacks on the testis, more detailed physiological and pathological examinations of the male reproductive systems of COVID-19 patients after their recovery are needed.

**Conflict of Interest**

The author has no conflict of interest to declare.

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**REFERENCES**

Abduljalil JM, Abduljalil B M. Epidemiology, Genome, and Clinical Features of the Pandemic SARS-CoV-2: A Recent View. New Microbes New Infect. 2020, 35: 100672.  
PMID: 32322400 DOI: 10.1016/j.nmni.2020.100672

ASRM - American Society for Reproductive Medicine COVID Task Force. patient management and clinical recommendations during the coronavirus (COVID-19) pandemic. UPDATE #4. 2020 Available at: https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/covid-19/covidtaskforceupdate4.pdf

Cardona Maya WD, Du Plessis SS, Velilla PA. SARS-CoV-2 and the Testis: Similarity with Other Viruses and Routes of Infection. Reprod Biomed Online. 2020; S1472648320301887.  
PMID: 32362571 DOI: 10.1016/j.rbmo.2020.04.009

Carlsen E, Andersson AM, Petersen JH, Skakkebaek NE. History of febrile illness and variation in semen quality. Hum Reprod 2003;18:2089-92.  
PMID: 14507826 DOI: 10.1093/humrep/deg412

Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsui HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK, et al. A Familial Cluster of Pneumonia Associated with the 2019 Novel Coronavirus Indicating Person-to-Person Transmission: A Study of a Family Cluster. Lancet. 2020. 395: 514-23.  
PMID: 31986261 DOI: 10.1016/S0140-6736(20)30154-9.

Davis NF, McGuire BB, Mahon JA, Smyth AE, O’Malley KJ, Fitzpatrick JM. The increasing incidence of mumps orchitis: a comprehensive review. BJU Int. 2010; 105:1060-5.  
PMID: 20070300.  
DOI: 10.1111/j.1464-410X.2009.09148.x.

Eisenberg ML. Coronavirus Disease 2019 (COVID-19) and Men’s Reproductive Health. Fertil Steril. 2020; S0015028220303861.  
PMID: 32387274 DOI: 10.1016/j.fertnstert.2020.04.039

Esteves SC, Lombardo F, Garrido N, Alvarez J, Zini A, Colpi GM, Kirkman-Brown J, Lewis SE, Björndahl L, Majzoub A, Cho CL, Vendeira P, Hallak J, Amar E, Cocuzza M, Bento FC, Figuereira RC, Sciorio R, Laursen RJ, Metwalley AM, et al. SARS-CoV-2 Pandemic and Repercussions for Male Infertility Patients: A Proposal for the Individualized Provision of Andrological Services. Andrology. 2020.  
PMID: 32357288 DOI: 10.1111/andr.12809

Fan C, Li K, Ding Y,Lu W, Wang J. ACE2 expression in kidney and testis may cause kidney and testis damage after 2019-nCoV infection. MedRxiv. 2020  
DOI: 10.1101/2020.02.12.20022418

Fauci AS, Lane HC, Redfield RR. Covid-19 - Navigating the Uncharted. N Engl J Med. 2020; 382:1268-9.  
PMID: 32109011 DOI: 10.1056/NEJMep2002387

Guhan W, Ni Z, Hu Y, Liang W, Ou C, He J, Liu L, Shan H, Lei C, Hui DSC, Du B, Li L, Zeng G, Yuen KY, Chen R, Tang C, Wang T, Chen P, Jie Xiang J, Li S, et al. Clinical characteristics of 2019 novel coronavirus infection in China. N Engl J Med. 2020; 382:1708-20  
PMID: 32109013 DOI: 10.1056/NEJMoa2002032

Halfmann PJ, Hatta M, Chiba S, Maemura T, Fan S, Take-da M, Kinoshita N, Hattori SI, Sakai-Tagawa Y, Iwatsu S1472648320301887.  
PMID: 32357288 DOI: 10.1111/andr.12809

Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, Duan G. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. Viruses. 2020; 12: E372.  
PMID: 32230900 DOI: 10.3390/v12040372.
Jung A, Schuppe HC. Influence of genital heat stress on semen quality in humans. Andrologia. 2007; 39:203-15. PMID: 18076419 DOI: 10.1111/j.1439-0272.2007.00794.x.

Li D, Jin M, Bao P, Zhao W, Zhang S. Clinical Characteristics and Results of Semen Tests Among Men With Coronavirus Disease 2019. JAMA Netw Open. 2020; 3:e208292. PMID: 32379329 DOI: 10.1001/jamanetworkopen.2020.8292

Monteleone PA, Nakano M, Lazar V, Gomes AP, de H Martin, Bonetti TC. A review of initial data on pregnancy during the COVID-19 outbreak: implications for assisted reproductive treatments. JBRA Assist Reprod. 2020; 24:219-25. PMID: 32301600 DOI: 10.5935/1518-0557.20200030

Mungroo MR, Khan NA, Siddiqui R. Novel Coronavirus: Current Understanding of Clinical Features, Diagnosis, Pathogenesis, and Treatment Options. Pathogens. 2020; 9:E297. PMID: 32316618 DOI: 10.3390/pathogens9040297

Munster VJ, Koopmans M, van Doremalen N, van Riel D, de Wit E. A Novel Coronavirus Emerging in China — Key Questions for Impact Assessment. N Engl J Med. 2020; 382: 692–4.

PMID: 31978293 DOI: 10.1056/NEJMmp2000929

Pan F, Xiao X, Guo J, Song Y, Li H, Patel DP, Spivak AM, Alukap JP, Zhang X, Xiong C, Li PS, Hotaling JM. No Evidence of SARS-CoV-2 in Semen of Males Recovering from COVID-19. Fertil Steril. 2020: S0015028220303848. doi: https://doi.org/10.1016/j.fertnstert.2020.04.024.

Quan W, Chen J, Liu Z, Tian J, Chen X, Wu T, Ji Z, Tang J, Chu H, Xu H, Zhao Y, Zheng Q. No SARS-CoV-2 Infection in Spermatogonia, Leydig and Sertoli Cells. Cells. 2020; 9: 920.

PMID: 32283711 DOI: 10.3390/cells9040920

WHO - World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. 2020a Available at: https://covid19.who.int. Accessed on: May 16, 2020

WHO - World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. 2020b. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-19)-and-the-virus-that-causes-it

Xia J, Tong J, Liu M, Shen Y, Guo D. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. J Med Virol. 2020. PMID: 32100876 DOI: 10.1002/jmv.25725

Xu J, Qi L, Chi X, Yang J, Wei X, Gong E, Peh S, Gu J. Orchitis: a complication of severe acute respiratory syndrome (SARS)1. Biol Reprod. 2006; 74:410-6.

Zhang J, Wu Y, Wang R, Lu K, Tu M, Guo H, Xie W, Qin Z, Li S, Zhu P, Wang X. Bioinformatic Analysis Reveals That the Reproductive System Is Potentially at Risk from SARS-CoV-2. Preprints. 2020: 2020020307 DOI: 10.20944/preprints202002.0307.v1.

Zhao J, Zhou G, Sun Y. SARS coronavirus could cause multi-organ infection. Med J Chinese People’s Liberation Army. 2003; 28:697-8.

Zhou G, Chen S, Chen Z. Advances in COVID-19: The Virus, the Pathogenesis, and Evidence-Based Control and Therapeutic Strategies. Front Med. 2020; 14:117-125 PMID: 32318975 DOI: 10.1007/s11684-020-0773-x

Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. 2020. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020; 382: 727–33.

PMID: 31978945 DOI: 10.1056/NEJMoa2001017.