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UNCERTAINTY BASED ON VIRUS REPORTS: WHAT IS THE EFFECT OF SARS-COV-2 ON MALE REPRODUCTION? (COVID-19 AND MALE REPRODUCTION)

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ABSTRACT

Background and objectives

Coronavirus disease 2019 (COVID-19) has become a pandemic. Preliminary data reported that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might not be found in the semen of patients in the early stages of COVID-19; however, the virus may be seen in the semen in the late, severe stages. To determine the effects of SARS-CoV-2 infection on the male reproductive system.

Materials and methods

We reviewed the relationship between previously reported infections with mumps virus (MuV), HIV, Zika virus, hepatitis virus B, hepatitis virus C, SARS-CoV, and influenza viruses that could possibly damage the male reproductive system, and then investigated whether SARS-CoV-2 infection could cause any damage to the male reproductive system.

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Results

There were various reports that viruses could impair male reproduction by entering into the testicular cells, inducing inflammation, or both. Regarding SARS-CoV-2, five recent independent studies showed no evidence to suggest that SARS-CoV-2 could be found in the semen and testicular tissues, suggesting that SARS-CoV-2 would not directly damage the blood–testis barrier (BTB) in the early stages of COVID-19 infection. However, a study found that viral RNA was found in 6 out of 38 patients. Three studies found that there were some changes in the sexual hormone levels.

Discussion and conclusion

There is a lack of substantial evidence to determine how SARS-CoV-2 affects male reproduction at this moment. Understanding of the relationship between SARS-CoV-2 and male infertility requires further research.

Keywords: *COVID-19; male reproduction; SARS-CoV-2; virus*

INTRODUCTION

Pneumonia was the primary manifestation of SARS-CoV-2 infection that appeared in Hubei Province, China, in December 2019. Researchers quickly discovered a new coronavirus that caused cause acute respiratory distress syndrome and severe pneumonia. The World Health Organization named it coronavirus 2019 (COVID-19).[1,2] Subsequently, COVID-19 caused a pandemic, with patients in 188 countries. To date, the total number of COVID-19 patients worldwide has reached an alarming 24,746,587, including 5,917,439 confirmed cases in the United States (Data from https://coronavirus.jhu.edu/map.html, 2020/8/29).

Medical professionals and researchers around the world are diligently working together to fight this pandemic, and a large number of COVID-19-related articles have been published in peer-reviewed journals. We found that COVID-19 was more common in men, and the conditions were mainly mild among those receiving treatment in the general ward. There was also a proportion of patients of reproductive age.[1–5]

In the past, viruses (e.g., mumps virus [MUV], human immunodeficiency virus [HIV], hepatitis virus B [HBV], and others) were shown to affect the reproductive function of male patients, and caused symptoms of testicular pain or abnormal semen quality. In addition, a large group of these men infected by SARS-CoV were of reproductive age. This raises concerns for the possible effect of SARS-CoV-2 on fertility. In the present study, we investigated the possible mechanisms of damage to male reproduction by MuV, HIV, Zika virus (ZIKV), HBV, HCV, and SARS-CoV, specifically focused on the impact of SARS-CoV-2 to attract the attention of medical staff and scientific researchers around the world.

Viruses related to male reproduction

Studies have found that some viruses can affect male fertility via various mechanisms. However, some viruses are suspected of causing damage to male fertility without compelling evidence, requiring more future research. Below, we have reviewed viruses related to the impairment of male reproduction and reviewed the literature of damage to the reproductive tract by the possible mechanisms. The specific methodology is showed in Table 1.

MuV

MuV is an enveloped negative-sense RNA virus that belongs to the genus Rubulavirus of the family Paramyxoviridae and can cause human testicular disease. Orchitis is a common complication of mumps in men after puberty, and it occurs in 20–30% of mumps cases.[6] MuV infection in some

TABLE 1 The Specific Methodology of Literature Related to MuV, HIV, Zika Virus, Hepatitis Virus B, Hepatitis Virus C, and SARS-CoV.

Animal experiment	(9), (12–13), (40–41), (43–44), (46), (63), (73–76)
Human cell or tissue experiment	(14), (15), (20–25), (29–30), (33–34), (38–39), (42), (45), (47), (50), (59–60), (64–65), (67–68), (70), (72)
Human examination or observation	(7), (10–11), (18), (26), (35–36), (49), (51–58), (61), (71)

patients may transiently reduce the number of sperm and change the sperm morphology. Bilateral mumps orchitis accounts for 18.2% of cases (2/11 patients) and usually leads to infertility associated with testicular atrophy.[7]

The mechanism of how MuV infection impairs testis was elaborated in some animal experiments. MuV induces innate immune responses in mouse Sertoli cells via activation of toll-like receptor 2 (TLR2), which induces the expression of pro-inflammatory cytokines TNF-α and IL-6 and chemokines MCP-1 and CXCL10.[8] Under inflammatory conditions, TNF-α can be upregulated, and it can inhibit the production of testosterone by impairing the Leydig cells.[9–11] TNF-α produced by Sertoli cells after MuV infection induced apoptosis in male germ cells.[12] Another study confirmed the mechanism of MuV-mediated disruption of the blood–testis barrier (BTB) and the impairment of spermatogenesis through the activation of TLR2 signaling.[13] Other studies demonstrated the harmful effects on the production of testosterone and spermatogenesis caused by infection with the MuV, which targets Leydig cells as a site of replication within the testes.[14,15] Nevertheless, the lack of human samples limits the opportunity to study the pathogenesis of mumps in patients. Therefore, information can only be obtained through animal models.

HIV

Acquired immune deficiency syndrome (AIDS) is a potentially deadly infectious disease caused by infection with HIV. HIV is a virus that can attack the body's immune system, especially $CD4^+$ T lymphocytes, as the main target of attack, ultimately severely compromising the immune function. HIV-infected patients are susceptible to various diseases with high case fatality rates,[16,17] while there are some people living with HIV (PLW-HIV) (there is a lack of reports on reproduction in the literature, so the corresponding discussion will not be carried out below). HIV is classified into two types, HIV-1 and HIV-2. HIV-1 is the main cause of most HIV infections while HIV-2 is rare; there are only a few relevant studies. HIV-1 can be detected in the semen.[18] A number of studies reported that the virus damages male infertility in a number ways, as described below. Several studies mentioned that HIV-1-positive men suffer from testicular injury and endocrine disorders, which manifest as chronic orchitis or progressive hypogonadism.[19,20] Surprisingly, testes mostly showed atrophy in AIDS, probably due to germ cell loss, interstitial fibrosis, or lymphocytic infiltrate,[21] and HIV-1 DNA was detected in male germ cells.[22,23] In some studies, testicular changes in patients who died from AIDS were divided into five categories (Figure 1).[24,25] An article reported that serum testosterone levels in AIDS patients were low, while LH and FSH levels were high, suggesting that testosterone synthesis was impaired.[26] HIV-1 damages male reproduction by killing various types of testis cells. The mechanism that causes male infertility may include damage to germ cells and Sertoli cells, causing widespread inflammation, or Leydig cells causing testosterone abnormalities. Nevertheless, further mechanisms remain to be clarified.

Human papillomavirus

Human papillomavirus (HPV) infection is one of the most common sexually transmitted diseases (STD) worldwide. It often infects reproductive-age men and women. There is controversy regarding

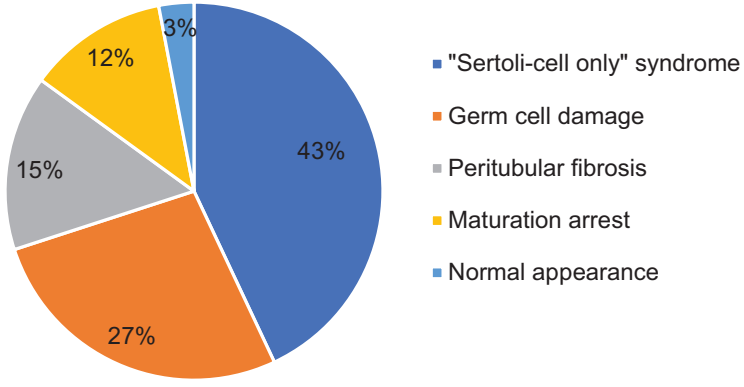

FIGURE 1 The categories of testicular changes in patients who died from acquired immune deficiency syndrome.

whether HPV can cause infertility in infected patients. Some studies suggested that the virus damaged the sperm quality and caused poor pregnancy outcomes.[27–31] Other scholars hold different views regarding the detection methods of HPV in the semen and the effect of HPV infection on the semen parameters.[32–35] The four possible biological mechanisms by which HPV infection causes male infertility are as follows.[32] HPV could combine with the sperm head tightly, leading to a decrease in sperm motility;[33,36] HPV may jeopardize the integrity of sperm DNA and lead to apoptosis of spermatozoa; HPV infection may induce the generation of anti-sperm antibodies, resulting in interference with sperm motility and sperm-oocyte binding; finally, HPV could be transferred into blastocysts, causing adverse pregnancy outcomes. All these mechanisms require further research and confirmation.

ZIKV

ZIKV is a positive-stranded RNA virus belonging to the Flavivirus family. It can be sexually transmitted from man to woman, and it is frequently detected in the semen of infected men.[37,38] ZIKV RNA lasts longer, and in most cases, its levels in the semen are higher than those in blood.[39] Govero et al. showed that ZIKV caused epididymitis, reducing sperm motility.[40] Uraki et al. found that Leydig cells served as targets and reservoir cell types for ZIKV within the testes and may be impaired by ZIKA virus, thereby reducing the serum testosterone levels.[41]

Other researchers found that Leydig cells were highly sensitive to Zika virus infection in human and mouse models.[42,43] Other studies found that ZIKV caused testicular atrophy, infected Sertoli cells, and modulated the integrity of the BTB in an in vitro model by inducing inflammation.[44–47] Nevertheless, there is no compelling evidence of ZIKV-reduced fertility in humans, limited to two case reports of hematospermia.[48,49]

Hepatitis viruses

Hepatitis viruses are divided into five types; they are mostly RNA viruses, except for HBV, which is a DNA virus. Both HBV and HCV have been found in the semen and may be sexually transmitted, while HCV loads are lower than those of HBV.[50] Studies have found that both viruses injure the semen parameters, thereby reducing male fertility, including sperm counts, motility, and morphology[51–57] (Table 2). HBV and HCV were suspected of damaging the sperm by causing increases in reactive oxygen species (ROS) and subsequently inducing apoptosis, thereby causing abnormal semen

TABLE 2 Review of the Literature on the Influence of Hepatitis Virus B and Hepatitis Virus C Semen Infection on Sperm Parameters.

Type of Hepatitis viruses	References	Sperm count	Motility	Normal morphology
Hepatitis virus B	Vicari et al., 2006[52]	↓	↓	↓
	Lorusso et al., 2010[51]	↓	↓	↓
	Zhou et al., 2011[53]	↓	↓	
Hepatitis virus C	Durazzo et al., 2006[54]	N.D.	↓	↓
	Lorusso et al., 2010[51]	↓	↓	↓
	Safarinejad et al., 2010[57]	↓	↓	↓
	Hofny et al., 2011[55]	↓	↓	↓
	La Vignera et al., 2012[56]	↓	↓	↓

N.D.: No difference.

parameters.[58–61] Other studies reported hormone abnormalities, including lower total serum testosterone levels, meaning that the Leydig cells may be damaged.[55,57]

SARS-CoV

The global outbreak of severe acute respiratory syndrome (SARS) in 2003 infected more than 8000 patients, and 774 of them died, mostly in China.[62] Studies confirmed that SARS-associated coronavirus (SARS-CoV) was the causative agent of SARS.[63–68] In the follow-up research, researchers found that the angiotensin-converting enzyme 2 (ACE2) is the functional receptor for SARS-CoV, which is present in the testis. However, no SARS-CoV RNA has been detected in the testis,[69,70] suggesting that SARS-CoV might not damage the testis by entering these cells directly. SARS-infected testes demonstrated extensive germ cell destruction, with few or no spermatozoa in the seminiferous epithelium or the lumen, caused by probable leukocyte infiltration. Immunohistochemistry demonstrated abundant IgG precipitation in the seminiferous epithelium of SARS testes, suggesting possible immune responses as the cause for the damage.[70] The question as to whether SARS-CoV impairs male infertility requires further validation.

Influenza

Influenza is a respiratory virus that causes disease, primarily manifesting as respiratory symptoms. Various viruses have been reported in the literature, and some scholars detected the impact of flu on sperm quality. As a febrile illness, flu may affect the semen quality because of the impact on the semen parameters and sperm DNA integrity caused by fever.[71] Evenson et al. studied the characteristics of human sperm chromatin structure after influenza and high fever and found that influenza may alter sperm chromatin structure.[72] Some studies of animal models found that influenza damaged the sperm quality, leading to infertility.[73–76]

COVID-19

With the global pandemic of COVID-19, the general symptoms of the disease are gradually being known. Patients with COVID-19 mainly present with cough, fever, and dyspnea, as well as abnormal findings on the chest CT.[1–3] Some patients presented with gastrointestinal symptoms or blood system abnormalities, with or without cardiac and arrhythmic complications.[77,78] In addition to these patients with obvious symptoms, there are many asymptomatically infected patients with abnormal imaging findings, worthy of our attention.[79]

As studies continue to report more patients who present asymptomatically or atypically, Kim et al. reported the first case with the initial symptom of abdominal and testicular pain resulting from SARS-CoV-2 infection.[80] Pan et al. reported testicular and scrotal pain in 17.9% of SARS-CoV-2-positive patients in their recent study.[81] Holtmann et al. found that the semen parameters of some SARS-CoV-2-infected patients were impaired[82] The levels of serum luteinizing hormone (LH) in men with COVID-19 were significantly increased; by contrast, testosterone (T)/LH and the ratio of follicle-stimulating hormone (FSH) to LH was significantly reduced in comparison to age-matched healthy men.[83] Some studies returned results consistent with these sexual hormone changes.[84,85] These findings raised our concerns about whether SARS-CoV-2 could affect the reproductive function of male patients, just as other viruses that have been demonstrated to affect male fertility. The relationship between SARS-CoV-2 and male fertility deserves our close attention.

After studying the confirmed or suspected mechanism of various viruses on male reproduction, we divided them into two types:

I. Direct viral injury: Viruses impair male reproduction by entering testicular cells, affecting the sperm integrity of DNA, or transferring into blastocysts to reduce the secondary inflammation, leading to impaired spermatogenesis and poor semen parameters (e.g., HIV, HPV, ZIKV, hepatitis virus…).
II. Indirect viral injury: Viruses are unable to enter cells generally, but can damage testicular cells and sperm by inflammation (MuV, SARS, Influenza…).

We can also roughly divide the methods of viral injury to the initially damaged cells, including Leydig cells, Sertoli cells, germ cells, and sperm; however, SARS-CoV-2 usually impairs male fertility by various methods (both I and II types).

SARS-Cov-2 has a 79% similarity to SARS-Cov-1 based on genomic sequencing. Thus, it is not surprising that angiotensin-converting enzyme 2 (ACE2), previously known as the receptor for SARS-CoV, has been confirmed as an essential receptor for SARS-CoV-2 to enter cells.[86–89] High expression levels of ACE2 in testicular cells (i.e., germ cells, Sertoli cells, and Leydig cells) have been found, especially in this Leydig cells, and this was alarming to researchers.

ACE2 is a homolog of carboxypeptidase. It is the active peptide of the renin-angiotensin system (RAS). ACE2 is a dominant-negative regulator of RAS, which can balance the multiple functions of ACE. Angiotensin-converting enzyme (ACE) is a crucial protease that cleaves angiotensin I to produce angiotensin II. Angiotensin II is a potent vasoconstrictor and stimulant of aldosterone release; it can also enhance inflammation, oxidative stress, and increase coagulation in some experimental and clinical models.[90–93] However, ACE2 can reduce the adverse effects of angiotensin II by degrading angiotensin II and generating angiotensin,[1–7] which is the opposite result of angiotensin II.[94]

ACE2 is downregulated by entering into cells that have bound SARS-CoV-2.[95–97] As a result, the degradation of angiotensin II is impaired, and the product of angiotensin[1–7] disappears, which may cause subsequent effects induced by angiotensin II (i.e., enhanced inflammation, enhanced oxidative stress, and increased coagulation).

It is unclear as to whether SARS-CoV-2 damages male fertility by using the ACE2 receptor through testicular cells with subsequent cell apoptosis and inflammatory reactions, and whether SARS-CoV-2 could be sexually transmitted. Therefore, it is critical to examine the SARS-CoV-2 RNA in the semen samples collected from patients at all stages of COVID-19 infection and obtain testicular samples from autopsy. There are five studies showing no detection of SARS-CoV-2 RNA in the semen samples,[81,82,98–100] while Li et al.[101] found that there was virus RNA in 6 out

of the 38 patients (four patients in the acute stage of infection and two patients who had recovered). Pan et al. tested ejaculated semen samples from 34 adult male patients after a median of 31 days from COVID-19 diagnosis, but SARS-CoV-2 was not detected.[81] Holtmann et al. studied 18 semen samples from recovered men and two semen samples from patients with active COVID-19 infection; no RNA was detected using reverse-transcription polymerase chain reaction (RT-PCR).[82] Song et al. did not detect SARS-CoV-2 RNA in the semen samples of 12 recovered patients and testicular samples from one patient who died of COVID-19 during the acute phase.[98] Paoli et al. found no SARS-CoV-2 RNA in the semen and urine samples.[99] Ning et al. also did not find SARS-CoV-2 RNA in the semen samples of 17 patients with fertility needs.[100] We cannot conclude as to whether SARS-CoV-2 is sexually transmitted or not. However, current studies have many limitations. First, recent reports providing evidence of SARS-CoV-2 in the semen or testis were too small and immature, and therefore we cannot rule out the existence of SARS-CoV-2 in the semen or testis cells of other infected patients. Second, the absence of virus RNA in the semen analysis does not mean that SARS-CoV-2 cannot invade and damage testicular cells directly. The production of the sperm often takes time to complete spermatogenesis. Furthermore, Sertoli cells and Leydig cells generally do not appear in the semen. Third, there have been few severely infected patients, but viral loads may be too low to be detected. Fourth, patients did not undergo multiple semen tests, and this may increase the possibility of false negatives.

In addition to directly entering the cell, viruses like HIV, MuV, HBV, and SARS-CoV can also cause damage to the testicular cells by inducing inflammation and autoimmune reactions. The BTB, which is formed by adjacent Sertoli cells near the basal membrane of the seminiferous tubules, plays a critical role in maintaining the microenvironment essential for the function of the testes.[102] The BTB is created by several junctions between Sertoli cells, including tight junctions, adhesion junctions, and other junction complexes.[103] Some viruses cause the active receptor to induce the expression of pro-inflammatory cytokines and chemokines. Following upregulation of pro-inflammatory cytokines and chemokines, the BTB is destroyed and then the leukocytes infiltrate. More importantly, these testicular cells and their related products, inflammatory cytokines, may activate the autoimmune response and autoantibody development, leading to impaired testicular cells, resulting in reduced testosterone production and spermatogenesis disorders. SARS-CoV-2 might possibly trigger a secondary autoimmune response and cause viral orchitis by these mechanisms. In these patients, leukocytes, lymphocytes, macrophages, or IgG might be found in testicular tissues. Nevertheless, there remains a lack of research on this subject.

Therefore, studies provide only the "tip of the iceberg" regarding the potential impacts of SARS-CoV-2 on male reproduction. The research suggested that SARS-CoV-2 could both enter the testis and destroy the BTB, potentially causing damage to testicular function and male fertility, and possibly resulting in sexual transmission.

FUTURE RESEARCH DIRECTIONS

As the pandemic of SARS-CoV-2 rages worldwide, more studies are needed to understand its impact on male fertility.

First, a more significant series of semen samples from patients from all stages of COVID-19 should be collected and there should be an extended duration of semen collection. If possible, tissues from the testis of patients should be collected for testing.

Second, both primary testicular cell damage and subsequent spermatogenesis requires time; therefore, we need long-term monitoring and follow-up of the semen status and sex hormone levels in COVID-19 patients to determine how SARS-CoV-2 affects male fertility. If there are abnormalities,

intervention should be made in advance to preserve fertility.

Third, due to the ethical limits of human research, more animal models of COVID-19 are needed to determine meaningful outcomes, including studying the possibility of sexual transmission.

CONCLUSIONS

Many viruses cause direct or indirect impact and damage to male reproduction. With the pandemic of SARS-CoV-2, the issue of whether COVID-19 damages male reproduction needs to be further evaluated with greater attention. Although limited evidence might complicate the process of determining whether there is SARS-CoV-2 in the semen and the testicular tissues of COVID-19 patients, the impact of how SARS-CoV-2 affects the testicular cells, seminal fluid, and testicular pain at all stages of the infection needs to be further investigated. Notably, the possibilities of SARS-CoV-2 as a STD should be carefully studied.

CONFLICTS OF INTEREST

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

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