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Review

Male genital damage in COVID-19 patients: Are available data relevant?

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Abstract Over the past few weeks, we have observed increasing concern about the possible impact of coronavirus disease 2019 (COVID-19) which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus) on male fertility. Precise mechanisms of male reproductive damages are still unclear, but it seems that high temperature resulting from persistent fever and triggering a secondary autoimmune response leading to an autoimmune orchitis are the most likely involved mechanisms. Also, angiotensin conversion enzyme 2 (ACE2) plays a highly important role in cellular entry for SARS-CoV-2 and male genital system presents high ACE2 expression. All these preliminary findings suggest that COVID-19 could impact men's reproductive health. Thus, we examined available data including published and unpublished articles to assess the potential risk of COVID-19 in particular on the male reproductive system.
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1. Introduction

Many viruses such as mumps virus, hepatitis viruses B/C, herpes simplex virus, human papillomavirus, coxsackie virus, influenza, human immunodeficiency virus (HIV) and severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) could infect the male genital system and impair fertility [1,2]. Over the past few weeks, we have observed increasing concern about the impact of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on male fertility. Thus, we examined available data including published and unpublished articles to assess the potential risk of COVID-19 in particular on the male reproductive system.

2. Viral threat to male fertility

It is known that viruses could infect the testis directly [2]. Also, the male reproductive system has an immunosuppressive environment due to the blood–testis barrier which

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might protect seminal viruses from immune surveillance [1]. For example, mumps viruses has high tropism for the testes; orchitis develops in 20%—30% of cases and could destroy testicular parenchyma [1,2]. Main mechanisms of testis damage in mumps infection are unknown and remain to be clarified [1,3]. However, the most common hypothesis is that testis degeneration is attributed to an increase in testicular temperature as an indirect effect of the inflammatory milieu [1].

Also, Xu et al. [2] conducted a study on autopsy specimens of testis that were obtained from six patients who died of SARS-CoV-1 infection (SARS-CoV-2 is closely related to SARS-CoV-1 with above 85% identity [4]). All six cases had orchitis. Xu et al. [2] noticed a leukocyte infiltration in the SARS-CoV-1 testis that could affect the function of Leydig cells, damage the blood-testis barrier, and destroy directly the seminiferous epithelium. Furthermore, symptoms of orchitis in these patients were not observed or reported clinically.

Precise mechanisms of male reproductive damages in viral infection are still unclear [1], but it seems that high temperature resulting from persistent fever and triggering a secondary autoimmune response leading to an autoimmune orchitis are the most likely mechanisms of male reproductive system damage [1—3].

All this data suggest that male urogenital system may be a potential target of SARS-CoV-2.

3. Epidemiology

SARS-CoV-2 is the virus causing the disease named COVID-19 [5]. This virus is the seventh infecting humans member of the coronovirinae subfamily which are enveloped, single positive-strand RNA viruses [5]. It is listed in the World Health Organization (WHO) Blueprint list for priority pathogens for research due to its epidemic potential [5].

It is also the most contagious [6], and is now declared as a Public Health Emergency of International Concern by the WHO [7]. As of 11 Jun 2020, there have been 7 221 717 confirmed cases with 411 818 deaths [7]. Interestingly, COVID-19 has a lethality that continuously rises with age unlike other respiratory diseases that have a U-shaped lethality curve [5].

Limited data are available at this stage of the pandemic, concerning the involvement of male genital system in COVID-19 patients.

4. Clinical characteristics

Almost 58.1% of patients are males with a median age of 47—49 years and increased severity in the elderly [6,8,9]. Also, the complete clinical manifestation is not clear yet [8]. COVID-19 patients present a wide spectrum of clinical features [5]. They commonly report fever, respiratory symptoms, myalgia or fatigue [8,9]. Most patients present cytokine storm that might cause immune damage [10]. This uncontrolled reaction of the immune system can damage most vital organs and lead to acute kidney injury, various degrees of liver damage, acute cardiac injury, and multiple organ failure [10]. Previous exposure to non-SARS-CoVs in China could explain the disparity between the severity of cases observed in China and those outside China [5]. Male genital system involvement is not clear yet.

5. Pathogenesis: How could SARS-CoV-2 infect male genital system?

Angiotensin conversion enzyme (ACE) converts angiotensin I to angiotensin II in the renin-angiotensin-aldosterone system (RAAS) [11]. ACE2 is an endogenous counter-regulator of classic ACE system that deactivates the angiotensin II [11].

First, the SARS-CoV-2 enters into human cells using ACE2 as receptor which have very similar spike protein three-dimensional (3D) structures with strong binding affinity [12]. ACE2 is present with relatively high expression in respiratory epithelial cells, alveolar cells type I and II, oral cavity, kidney, testis, and intestines [11]. Thus, human cells with ACE2 expression are probably targets of SARS-CoV-2 infection [13]. However, it should still be noted that SARS-CoV-2 invasion is not just about ACE2 and there is probably other vulnerable organs [13]. It seems that high temperature resulting from persistent fever and triggering a secondary autoimmune response leading to an autoimmune orchitis are the most likely involved mechanisms.

6. SARS-CoV-2 and male genital system

Preliminary findings from studies that are, unfortunately, not peer-reviewed and published as preprints, are linking SARS-CoV-2 to male infertility [14—16]. But, it seems to us that it is premature to make definitive conclusions at present.

Ma et al. [14] conducted a study on 81 reproductive-aged men with SARS-CoV-2 infection and 100 age-matched healthy men. They found significantly elevated luteinizing hormone (LH) level, but decreased testosterone/LH and follicle-stimulating hormone (FSH)/LH ratios levels in 81 men with COVID-19 which is suggesting potential hypogonadism. But it seems to us that these findings cannot affirm whether this alteration is due to a direct or indirect effect of SARS-CoV-2 on the testes. Previous studies reported that high temperature contributed to germ cell destruction [2], and high fever in COVID-19 might have an indirect effect on testicular dysfunction. Furthermore, LH release is pulsatile and shows circadian rhythm. We think that there is a biased sampling in Ma et al. study [14]. Actually, COVID-19 patients and control group should be tested at the same time of the day, otherwise, widely varying average levels of LH will be observed.

Also, Fan et al. [15] and Shen et al. [16] found high ACE2 expression in testis (both germ cells and somatic cells) suggesting potential tropism of SARS-CoV-2 to testicular tissues. Shen et al. [16] performed bioinformatics tools to analyze scRNA-seq data of testis for three normal young males, two adult normal males, seven obstructive azoospermia and one nonobstructive azoospermia. They showed that the expression level of ACE2 was related to the age and the peak of positive rate was at 30 years old [16]. These findings are confirmed by the interesting study of Liu et al.

[17] on scRNA-seq data, including seven obstructive azoospermia (OA) donors and two normal donors in a total of 2854 single cells. They showed the existence of ACE2 in almost all testis cells and primordial germ cells with the highest expression in Sertoli cells. These ACE2 positive cells had high expressions of stress response and immune activation-related genes [17].

Despite these relevant findings, we think this tropism has to be proven by finding viral material in autopsy specimens of testis or testicular biopsies, especially since a previous study on SARS-CoV-1 reported no infected cells in testis despite the high expression of ACE2 [18].

Notably, only one study showed the presence of SARS-COV-2 nucleic acid in the urine specimen of 6.9% of patients even if it is known that the urinary and genital systems in males merge [19].

7. Conclusion

In conclusion, the available data are relevant and show that ACE2 plays a highly important role in cellular entry for SARS-CoV-2 and that male genital system presents high ACE2 expression [15,16]. All preliminary findings mentioned above suggest that COVID-19 could impact men's reproductive health inducing spermatogenic failure. In conclusion, even though it seems to us that it is premature to make definitive conclusions at present, this should alert to the possible impact of COVID-19 on the male reproductive system. This is particularly important for COVID-19 patients, as most of them are males [8,9]. Further investigations of the potential male genital damage are warranted.

Author contributions

Study concept and design: Youssef Kharbach, Abdelhak Khallouk.
Data acquisition: Youssef Kharbach.
Data analysis: Youssef Kharbach, Abdelhak Khallouk.
Drafting of manuscript: Youssef Kharbach.
Critical revision of the manuscript: Abdelhak Khallouk.

Conflicts of interest

The authors declare no conflict of interest.

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