Journal of Reproduction & Infertility
Volume 22, Issue no. 1
http://dx.doi.org/10.18502/jri.v22i1.4989

Editorial

Is Male Reproductive System More Vulnerable to SARS-CoV-2 Than Female's?

Coronaviruses are the largest family of viruses with RNA genome and more than 30 identified members. Coronavirus disease-2019 (COVID-19) caused by SARS-CoV-2 was initially identified with extensive respiratory symptoms such as chest pain, pulmonary edema, dyspnea, heavy breathing, shortness of breath, and dry cough. Following spreading of the pandemic worldwide and increasing the number of patients with severe disease, multiorgan failures including fever, fatigue and myalgia, sore throat, diarrhea, nausea, dizziness, headache, rhinorrhea and vomiting in addition to respiratory manifestations were reported. At the same time, ACE2 was identified as a receptor for spike protein (S) of SARS-CoV-2, which facilitates virus entry into target cells. ACE2 was known to be expressed in more than 30 organs, such as the kidneys, testes, heart, gallbladder, small intestine, colon, thyroid, and adipose tissue, *etc*. which are potentially targets of SARS-CoV-2 and may be the cause of several organ failures following COVID-19 infection (1).

Notwithstanding the persistent increase of our knowledge about pathogenesis, clinical manifestations and complications of the disease, there are still many unresolved questions, especially about the effects of COVID-19 on the reproductive system and fertility, including probability of its existence in semen, cervical mucus, vaginal discharge, follicular fluid and also its transmission through sexual contact; moreover, it is not clear whether the susceptibility to fertility failure after COVID-19 infection is the same among males and females or not. According to preliminary data, there is a significant difference between men and women in terms of prevalence and severity of COVID-19. Therefore, susceptibility and vulnerability of men is much higher than women of the same age. In addition, severe respiratory symptoms with a relatively high probability of death are more frequent among men who need intensive care unit services (2).

ACE2 expression is higher in testis and male genital tract in comparison to ovaries and female genital tract, reflecting the fact that male fertility is much more vulnerable than fertility of females in COVID-19. However, in human tissues, co-expression of TMPRSS2 as an essential metalloprotease with ACE2 is essential for SARS-CoV-2 infection. ACE2 is highly expressed in spermatogonia, spermatids, Sertoli, and Leydig cells, although co-expression of TMPRSS2 in all of these cells has not been confirmed with ACE2. For example, Sertoli cells have high levels of ACE2 expression and low levels of TMPRSS2, while spermatogonia have high levels of TMPRSS2 and low levels of ACE2 expression. Leydig and Sertoli cells have ACE2 at the protein level, but no overlapping of expression for these two target viral molecules has been reported in these cells. Thus, the inconsistent findings cannot confirm the direct effects of the virus on spermatogenesis and testicular damage following SARS-CoV-2 infection (3).

In addition, most clinical studies did not detect SARS-CoV-2 RNA in seminal fluid or testicular biopsy in cured or acute positive cases of COVID-19. In addition, there is no evidence of virus existence in the testes of adult men who have died from COVID-19. However, inconvenience in testicles is one of the complaints of patients after COVID-19 recovery, even in the absence of the virus genome in testicular biopsy. Semen is composed of several components and secretion by seminiferous tubules provides less than 10% of semen and seminal vesicle and prostate secretions make up more than 90% of semen. This evidence leads to the hypothesis that semen could not be a route of SARSCoV-2 transmission and there is low risk of viral transmission through assisted reproductive techniques (ARTs) during COVID-19 outbreak. Eventually, severe destruction of the testicular tissue is quite evident in histopathological examinations despite the above finding (1, 4).

So, it seems another mechanism is at work for indirect involvement of virus in testicular damages and male fertility. The most probable mechanism is the systemic effects of the virus on other organs, which has a wide variety of consequences on the reproductive system in different individuals. Male fertility problems, at first glance, could be induced by immune system. The testis is an immune privileged organ with blood-testis barrier (BTB) that protects spermatogenic cells against a wide range of pathogens, but BTB is not a complete barrier for protection of spermatogenic cells under systemic or local inflammation with cytokine storm due to SARS-CoV-2 virus infection. Inflammatory cytokines can provoke leukocytes infiltration into testicular tissue, which is characteristic of orchitis. It has also been shown that high levels of IL-6 disrupt the integrity of BTB, which facilitates virus infiltration and probably direct damages to spermatogenic cells. In fact, this may be the reason for the various reports on orchitis-like syndrome in COVID-19 patients (1, 5).

Immunohistochemical examination on slides of testicular tissue of dead men from COVID-19 showed orchitis-like syndrome with a large amount of IgG deposition in the seminiferous epithelium and also destroyed spermatogenic and Sertoli cells. This may be a key factor for secondary autoimmune response to SARS-CoV-2 virus, thereby leading to exacerbation of testicular damage with autoimmune orchitis (1).

SARS-CoV-2 may directly affect the hypothalamic-pituitary- gonadal axis and subsequently impair Leydig cells' functions, testosterone production, and significantly increase serum LH and prolactin. Based on the available data, cells of the nervous system extensively express ACE2 receptors, which may be a possible explanation for the neurological symptoms of COVID-19 and consequent SARS-CoV-2 damage on the hypothalamic-pituitary-testis axis. Thus, the production of pituitary and testicular hormones and male fertility are affected. In addition, elevated ROS production, oxidative stress and sperm DNA fragmentation due to long-term fever are another mechanism for destruction of male fertility by SARS-CoV-2 virus (3, 4).

The SARS-CoV-2 pandemic has raised concerns about male fertility over the past 10 months, and a comprehensive review of studies with controversial evidence necessitates more investigations on the relationship between COVID-19 and fertility. Despite the lack of conclusive findings for preventing its effects on the reproductive system, this is a starting point for further research into the effects of COVID-19 disease on male fertility. There has always been concern about a gradual decline in sperm quantity and quality and thus male fertility over time, with some studies reporting a 50% reduction in semen quality over less than half a century. Though the causative factors have not been identified yet, lifestyle and environmental factors seem to be the fundamental influences. Due to above clinical features of COVID-19, the SARS-CoV-2 may also exacerbate this process; therefore, assessing the effects of the virus on spermatogenesis and male fertility is an exigency which requires serious attention and further studies in future.

References

1. Huang C, Ji X, Zhou W, Huang Z, Peng X, Fan L, et al. Coronavirus: a possible cause of reduced male fertility. Andrology. 2020 Sep 22;10.1111/andr.12907.
2. Khalili MA, Leisegang K, Majzoub A, Finelli R, Panner Selvam MK, Henkel R, et al. Male fertility and the COVID-19 pandemic: systematic review of the literature. World J Mens Health. 2020;38(4):506-20.
3. Khan RIN, Malla WA. Does SARS-CoV-2 have influence on male reproductive system? Hum Reprod. 2020;35(11): 2626-7.
4. Navarra A, Albani E, Castellano S, Arruzzolo L, Levi-Setti PE. Coronavirus disease-19 infection: implications on male fertility and reproduction. Front Physiol. 2020;11:574761.
5. Li H, Xiao X, Zhang J, Zafar MI, Wu C, Long Y, et al. Impaired spermatogenesis in COVID-19 patients. EClinical Medicine. 2020;28:100604.

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