



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Coronavirus disease 2019 and men's reproductive health

As the coronavirus disease 2019 (COVID-19) pandemic rages across the world, the scientific community continues to study the pathophysiology of the SARS-Cov-2 virus to provide guidance on disease transmission, susceptibility, and treatment. The disease is a respiratory infection and is known to lead to the expected symptoms, including fever, cough, and shortness of breath (1). A highly contagious virus, SARS-Cov-2 is detected in the nasal secretions, sputum, feces, and rarely in the blood (1%) of infected individuals although not in the urine (2). Cardiac, ocular, and neurologic symptoms of COVID-19 have been reported, but the reproductive implications of coronavirus infection remain unknown.

As the reports have documented higher rates of infection, morbidity, and mortality among male patients, attention has shifted to potential male genetic susceptibility. Scientists have identified the main path for coronavirus entry into the cell—namely via the viral spike (S) protein attaching to the angiotensin-converting enzyme 2 (ACE2) and employing the cellular serine protease (TMPRSS2) for S protein priming, both of which are known to be present in the testis (3). Thus, concern has arisen regarding infection of the testes and possible sexual transmission.

In their current report, Pan et al. (4) address these separate but related questions regarding the possible testicular manifestations of COVID-19. Among the 34 men studied, no detectable SARS-Cov-2 was identified in the semen via reverse-transcription polymerase chain reaction. This is reassuring regarding possible viral transmission or lack thereof. However, it is important to note that the men studied were often several weeks removed from acute infections, and many had had only mild symptoms, so it is conceivable that earlier time points or higher viral loads could lead to different results. But given the normal time course of semen turnover, that appears less likely.

Given the known mechanisms of SARS-Cov-2 entry into cells and the requirement for dual expression of ACE and TMPRSS2 proteins, the authors used their existing single-cell RNA seq cellular data to show that only 4 of 6,490 (<0.1%) testicular cells contain RNA for both proteins. Thus, it appears unlikely that SARS-Cov-2 can enter into any cells in the testis (e.g., germ cells, Leydig cells, or Sertoli cells) as has been hypothesized.

Next, the authors reported another interesting and novel clinical observation: 6 (17.6%) of 34 men reported scrotal discomfort at the time of COVID-19 infection. Previously reports on the symptoms of COVID-19 centered on the

stigmata of severe systemic or respiratory illness. This novel scrotal observation should be confirmed, but it may improve future screening and should be further studied to understand the pathophysiology as well as the reproductive sequelae in men. Indeed, the current report was not able to assess any changes in semen quality among the participants, so it remains unknown how or whether the fecundability of infected men is impaired.

Prior data from other febrile illnesses have demonstrated that acute illness and elevated body temperatures (i.e., fevers) can temporarily lower spermatogenesis. Whether COVID-19 follows this model remains to be elucidated. In addition, more than 80% of those who are infected by the COVID-19 are asymptomatic, so the reproductive implications for these men would likely be favorable but remain unknown.

Nevertheless, the current report represents the first exploration of the association between SARS-Cov-2 and human fecundability. How women are affected and what the consequences are for assisted and unassisted reproduction in the face of acute COVID-19 infection or recovery remain to be studied. But given the current impact of the pandemic on the world, the likelihood the virus will remain for some time, and the birth of over 100 million babies every year, the reproductive implications of SARS-Cov-2 should be further studied.

Michael L. Eisenberg, M.D.

Department of Urology and Department of Obstetrics and Gynecology, School of Medicine, Stanford University, Stanford, California

<https://doi.org/10.1016/j.fertnstert.2020.04.039>

You can discuss this article with its authors and other readers at <https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/65807-30246>

REFERENCES

1. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;323:1061–9.
2. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA* 2020; <https://doi.org/10.1001/jama.2020.3786>.
3. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271–80.
4. Pan F, Xiao X, Guo J, Song Y, Li H, Patel DP, et al. No evidence of SARS-CoV-2 in semen of males recovering from COVID-19. *Fertil Steril* 2020, in press.