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The jury is still out: COVID-19 and male reproduction



There are many unanswered questions about the reproductive health implications of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Naturally, there is tremendous interest in the impact of COVID-19 on male reproduction based on prior knowledge about the viral entry mechanism into host target cells. Similar to SARS-CoV 2002, viral entry into target cells by SARS-CoV-2 is likely mediated by the interaction between the viral spike (S) protein and cellular angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2). ACE2 and TMPRSS2 expression occurs in many different organ systems including the male genitourinary tract, although their expression seems relatively limited in the testes. With an opportunity for SARS-CoV-2 to enter cells of the male genitourinary tract, there is a legitimate concern about viral transmission through alternative routes (sexual transmission) and the long-term male reproductive implications.

Recently, there have been conflicting reports about the presence of SARS-CoV-2 in the semen of patients who were previously diagnosed with COVID-19. In this issue of *Fertility and Sterility*, Holtmann et al. (1) report their series of 34 men (average age 42.2 years) at the university hospital in Duesseldorf, Germany, including 18 men recovered from SARS-CoV-2 infection, 2 men with acute SARS-CoV-2 infection, and 14 asymptomatic men as controls who were SARS-CoV-2 antibody negative. The SARS-CoV-2 virus was not detected in the semen of recovered or acutely infected men with SARS-CoV-2 after a mean of 43 days after a positive oropharyngeal swab. This finding is consistent with several recent reports where SARS-CoV-2 was not detected in the semen (2–4).

However, Li et al. (5) detected SARS-CoV-2 in semen samples of 6 of 38 men either recovering or with acute SARS-CoV-2 infection (days 6 to 16 from onset of COVID-19 symptoms). Although this inconsistency may be due to the time between the onset of COVID-19 symptoms and obtaining the semen sample, SARS-CoV-2 was not detected in the semen in the series from Pan et al. (4) as early as day 8 and the series from Song et al. (2) as early as day 14.

Although it is uncertain whether SARS-CoV-2 may be transmitted in the semen, viral entry of SARS-CoV-2 into structures of the male reproductive tract may also have implications for spermatogenesis and male reproductive function. The male reproductive tract has been involved in other systemic viral infections including mumps, human immunodeficiency virus, herpes simplex virus, and cytomegalovirus. Acute febrile illness and elevated body temperatures can hinder spermatogenesis. It is interesting that Holtmann et al. (1) reported one man (out of 18) among the recovered participants who had scrotal discomfort at the time of his acute infection. This clinical observation is consistent with the report from Pan et al. (4) where 6 out of 34 men recovering from SARS-CoV-2 infection had scrotal discomfort. This suggests that SARS-CoV-2 may contribute to orchitis as a clinical manifestation in acutely infected males.

Holtmann et al. (1) are also the first to report the effect of SARS-CoV-2 infection on semen parameters. In recovered participants who reported moderate symptoms at the time of SARS-CoV-2 infection and required hospitalization, there was a statistically significant negative effect on semen parameters—including sperm concentration, total sperm count, and total number of progressive motility—when compared with controls. This novel finding suggests that SARS-CoV-2 infection may impact spermatogenesis in the short term in patients with moderate symptoms associated with COVID-19. When the cohort was categorized by presence of fever as a symptom of acute COVID-19, only total motile sperm count was statistically significantly lower in those participants with a reported fever. Sperm concentration and sperm count were trending toward being lower in participants who reported fever, but these findings were not statistically significant. It is difficult to draw more definitive conclusions given the small sample size, short follow-up period, lack of semen analyses before the SARS-CoV-2 infection, and only a single semen analysis performed after infection. Additionally, these findings may be confounded by the medications used to treat COVID-19, including certain antivirals and hydroxychloroquine; three of the four patients with moderate symptoms of COVID-19 were treated with these medications in the current study.

The current report further questions whether SARS-CoV-2 can be transmitted in the semen. Additionally, it is one of the first reports about SARS-CoV-2 and effects on semen parameters, although there are several limitations. Larger-scale community-based testing for SARS-CoV-2 and semen analyses in both symptomatic men with a wide range of COVID-19 severity and asymptomatic men are needed before we can better understand whether sexual transmission can occur and the effects of SARS-CoV-2 on semen parameters.

Although the implications of sexual transmission are debatable when considering respiratory droplet transmission due to close contact in an acutely infected or recently infected individual, there are unique considerations for artificial reproductive technologies, and specifically for intracytoplasmic sperm injection (ICSI). We do not know whether SARS-CoV-2 can be transmitted through ICSI. As many fertility centers resume treatments for infertile couples, we do not know the implications of SARS-CoV-2 on embryonic development or fetal organogenesis. Data from future studies will provide additional knowledge and direction on this rapidly evolving issue.

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