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human reproduction LETTER TO THE EDITOR

# Does SARS-CoV-2 have influence on male reproductive system?

Sir,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been found to infect lungs, organs of gastrointestinal tract and urogenital organs, and is correlated with high expression of angiotensin-converting enzyme 2 (ACE2) and TMPRSS2 in the affected tissues (Lukassen *et al.*, 2020; Wang *et al.*, 2020; Zhang *et al.*, 2020). Whether it is able to infect the male reproductive organs will be dictated by expression of ACE2 and the protease expression. Analysis of different human testis scRNA-seq datasets carried out by three groups revealed that *ACE2* is highly expressed in spermatogonia, Leydig and Sertoli cells (Fan *et al.*, 2020; Liu *et al.*, 2020; Wang and Xu, 2020). Although *TMPRSS2* was expressed in most of the cell types, it was not co-expressed with *ACE2* in all of them (Liu *et al.*, 2020; Wang and Xu, 2020). Liu *et al.* (2020) reported that Sertoli cells have high *ACE2* expression level and low *TMPRSS2* expression level, whereas the opposite is true in spermatogonial stem cells. The expression of ACE2 in Leydig and Sertoli cells was found at the protein level as well (Douglas *et al.*, 2004). Thus, the testes are likely to become infected with SARS-CoV-2. However, single-cell analysis carried out by Pan *et al.* (2020) on different datasets revealed that *ACE2* and *TMPRSS2* are expressed at low levels in different cells of the testes, and there is no overlapping gene expression between the two. The underlying reasons for the conflicting findings warrant further research.

Two individual clinical studies did not detect SARS-CoV-2 from semen or testicular biopsy of coronavirus disease 2019 (COVID-19) recovered or the active cases (Pan *et al.*, 2020; Song *et al.*, 2020). Besides, using RT-PCR, no evidence of virus was found in most of the testes of individuals who died of the disease (Song *et al.*, 2020; Yang *et al.*, 2020). Conversely, a study carried out by Li *et al.* (2020) revealed that SARS-CoV-2 was found in the testes of infected, as well as recovered, cases using RT-PCR. Thus, it can be assumed that in some but not every COVID-19 infected or recovered person, SARS-CoV-2 gains access to the male reproductive system. However, the virus-induced systematic effect may have consequences on the reproductive system. Testicular discomfort was reported in the COVID-19 recovered cases even when the testes were SARS-CoV-2 negative as detected by RT-PCR (Pan *et al.*, 2020). Although no signature traces of SARS-CoV-2 genome were found in testes in most of the cases, however severe devastation to the testicular parenchyma was reported (Yang *et al.*, 2020).

Hormonal profiling of SARS-CoV-2 infected men carried out by Ma *et al.* (2020) revealed an increase in serum LH levels, as well as the ratio of FSH to LH, whereas the ratio of testosterone to LH decreased. However, no nucleic acid based viral detection of semen or testicular biopsy was carried out, and a direct linkage of SARS-CoV-2 in testes with altered hormones could not be established. Although the clinical studies give us a clue about the effect of COVID-19 on the male reproductive system, the studies have been limited by their sample sizes. A large sample size of varying severity, subsequent follow up, the titer of virus in testes, assessment of hormonal profiling, sperm quality and sperm quantity would give us a clearer picture about how far the male reproductive system is influenced by SARS-CoV-2 infection.

## Conflict of interest

None.

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