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human reproduction LETTER TO THE EDITOR

Reply: COVID-19: semen impairment may not be related to the virus

Sir,

We read the letter by Bendayan and Boitrelle, regarding our recent paper reporting the impact of COVID-19 on male fertility, with interest (Bendayan and Boitrelle, 2021).

As correctly stated in the letter, we found a high proportion of men showing oligo-crypto-azoo-spermia about 1 month after recovery from the disease (Gacci *et al.*, 2021). In our paper, we evidenced the need for a careful evaluation of the fertility status of men recovering from COVID-19.

The official website of government of Hubei Province posted a bulletin suggesting that men infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) should undergo fertility checks (Meng *et al.*, 2021). On the other hand, SARS-Cov-2 infection can damage several organs besides lungs, including the testis. Moreover, COVID-19 predominantly affects male patients: therefore, the possible impact on male fertility should not be ignored (Ding *et al.*, 2004).

In particular, several evidences demonstrated that SARS-CoV-2 uses the angiotensin-converting-enzyme 2 (ACE2) receptor to enter cells and this could cause pathological injuries in multiple organs, including testes which show a high expression of ACE2 receptor(Wang and Xu, 2020). Therefore, it seems mandatory to assess whether the virus can infect the human reproductive tract and affect male fertility (Fu *et al.*, 2020; Stanley *et al.*, 2020).

In our manuscript, we demonstrated that semen impairment (oligo/crypto/azoospermia) and signs of genital tract inflammation (elevated semen levels of IL-8 and leukocytospermia, both signs of male genital tract inflammation) were related to Covid-19 severity (Gacci *et al.*, 2021).

Overall, our data are in agreement with those reported in a recent systematic review based on 70 studies (23 quantitative 47 qualitative) (Tur-Kaspa *et al.*, 2021). The Authors tested the male and female reproductive tracts of 404 adult COVID-19 patients with the aim to determine if COVID-19 is an STD or not, and to evaluate its possible effect on fertility. They concluded that COVID-19 may cause inflammation of the testes, in 5–10% of male patients of reproductive age and that this orchitis is highly correlated to the severity of the disease. They also conclude that there is no evidence to support that COVID-19 can be considered as a STD.

Several viral infections including HPV, HSV, HBV, HCV challenges reproductive health and must be considered as a risk factor for male infertility. All these viruses have been detected in semen and can impair testicular function (Batiha *et al.*, 2020). Some viruses such as MuV, HIV and SARS-CoV can affect testicular cells, resulting in severe orchitis, which can result in male infertility (Xu *et al.*, 2006).

Bendayan and Boitrelle, in their letter, suggest that even fever alone—a symptom observed in over 80% of patients infected by COVID-19—could have a negative impact on the physiological scrotal heat regulation, with the consequent semen impairment (Boitrelle and Bendayan, 2021). Actually, COVID-19 patients, such as those affected by influenza, suffer from fever, which may affect sperm production. It is well demonstrated that febrile status can have a negative impact on semen quality (Batiha *et al.*, 2020), including an induction of DNA damage (Xu *et al.*, 2006). However, it should be noted that both sperm count and motility were temporarily reduced more than one month after fever episode, before going back to normal several weeks after fever (Sergerie *et al.*, 2007).

In addition to fever, COVID-19 patients underwent severe cycles of medications, were hospitalized and may have a prolonged abstinence period, as correctly indicated in the letter by Bendayan and Boitrelle (2021). All these conditions may be involved in producing testicular damage. However, at present, whether testicular damage is produced by virus infection in the testes or is due to the associated pathological condition, medications, etc. remains to be defined. Similarly, it is not known, at present, whether testicular damage may persist for long time.

In such a situation, we fully agree with Bendayan and Boitrelle (2021) regarding the need for a re-evaluation of men that have been affected by COVID-19 at least 3 months following complete healing, which is presently under investigation in our laboratory.

Conflict of interest

The authors have nothing to disclose.

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