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-azoospermia 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/azoospermi a) 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 (Batha 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 (Batha 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.

References

Batha O, Al-Deeb T, Al-Zoubi E, Alsharu E. Impact of COVID-19 and other viruses on reproductive health. Andrologia 2020;52: e13791.

Bendayan M, Boitrelle F. COVID-19: Semen impairment may not be related to the virus. Hum Reprod 2021;36:2063–2064.

Ding Y, He L, Zhang Q, Huang Z, Che X, Hou J, Wang H, Shen H, Qiu L, Li Z. et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. J Pathol 2004;203:622–630.

Fu J, Zhou B, Zhang L, Balaji KS, Wei C, Liu X, Chen H, Peng J, Fu J. Expressions and significances of the angiotensin-converting enzyme 2 gene, the receptor of SARS-CoV-2 for COVID-19. Mol Biol Rep 2020;47:4383–4392.

Gacci M, Coppi M, Baldi E, Sebastianelli A, Zaccaro C, Morselli S, Pecoraro A, Manera A, Nicoletti R, Liaci A. et al. Semen impairment and occurrence of SARS-CoV-2 virus in semen after recovery from COVID-19. Hum Reprod 2021;36:1520–1529.

Meng T-T, Dong R-J, Li T-G. Relationship between COVID-19 and the male reproductive system. Eur Rev Med Pharmacol Sci 2021;25:1109–1113.

Sergerie M, Mieusset R, Croute F, Daudin M, Bujan L. High risk of temporary alteration of semen parameters after recent acute febrile illness. Fertil Steril 2007;88:970.e1–7/970.e7.

Stanley KE, Thomas E, Leaver M, Wells D. Coronavirus disease-19 and fertility: viral host entry protein expression in male and female reproductive tissues. Fertil Steril 2020;114:33–43.
Sir,

The paper ‘Andrological findings in infertile men with two (biallelic) cystic fibrosis transmembrane conductance regulator (CFTR) mutations: results of a multicentre study in Germany and Austria comprising 71 patients’ by Rudnik-Schöneborn et al. (2021) recently published in Human Reproduction recommends CFTR analysis in all men with unexplained azoospermia in the presence of normal gonadotropin levels. We have concerns whether this conclusion is correct based on the reported data.

Firstly, the authors selected patients with two variants in the CFTR gene, but do not provide information on what grounds and how many patients with azoospermia were screened for CFTR mutations to detect the described 71 patients. In the first group, the variants are both pathogenic or likely pathogenic. In the second group of just 15 men, only one pathogenic mutation in combination with a variant of unknown significance was detected which does not support the claim this is the origin of the azoospermia. Furthermore, most variants are suspected but not proven to be biallelic; for one combination of variants, it is even stated they often occur on one allele. Thus, it is doubtful whether these variants are the cause of the azoospermia.

Furthermore, while andrological variables are evaluated, none of them were assessed in the complete group of 71 patients. The most important information for evaluation of azoospermia in congenital bilateral absence of the vas deferens (CBAVD) (ejaculate volume, pH, physical examination and transrectal ultrasound of the seminal vesicles) was available in only 19 patients. It is unclear how the authors corrected for this substantial amount of missing data, and whether some information was missing in many patients, or many information parameters were missing in some patients.

In the patients whose seminal vesicles were examined 21% had normal seminal vesicles. This is contradictory to the finding that less than 5% of the men had semen pH, semen volume and semen fructose levels that are compatible with normal seminal vesicles.

Currently, the European Association of Urology (2020) only recommends CFTR mutation diagnostics when patients are diagnosed with CBAVD (3% of the azoospermic patients). The authors are right that it is sometimes hard to confirm CBAVD due to the clinical variations. Therefore, the combination of semen parameters together with the other clinical parameters such as laboratory findings and ultrasound assessment will select those patients where CFTR mutation testing is relevant rather than to recommend this analysis for all patients with an unexplained azoospermia in the presence of normal gonadotropin levels.

The fact that one in 30 middle European men carry one CFTR mutation, screening of all men with unexplained azoospermia in the presence of normal gonadotropin levels will certainly lead to detection of CFTR mutations not causal to the clinical picture. This will result in pendency for the patients and unnecessary costs for the society.

Therefore, we oppose the proposition made by the authors that CFTR analysis should be offered to all patients with unexplained azoospermia in the presence of normal gonadotropin levels, but should be performed only in those men who have azoospermia combined with other clinical aspects indicating CBAVD.

Conflict of interest

None declared.

References

Rudnik-Schöneborn S, Messner M, Vockel M, Wirleitner B, Pinggera G-M, Witsch-Baumgartner M, Murtinger M, Klesch S, Swoboda M, Sänger N et al. Andrological findings in infertile men with two