

#ESHREjc report: does SARS-CoV-2 affect male fertility?

Mina N. Mincheva¹, Claudia Massarotti  ², Zoya Enakshi Ali³,
Munevver Serdarogullari⁴, Jim Hotaling⁵, Jordan Best  ⁶,
Ranjith Ramasamy⁶, and Julia Uraji  ^{7,*}

¹Centre for Tumour Microenvironment, Barts Cancer Institute, Queen Mary University of London, London, UK ²Academic Unit of Obstetrics and Gynecology, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOOGMI), University of Genova, Genova, Italy ³R& D Department, Hertility Health Limited, London, UK ⁴Department of Histology and Embryology, Faculty of Medicine Cyprus International University, Northern Cyprus via Mersin 10, Turkey ⁵Division of Urology, Department of Surgery, University of Utah, Salt Lake City, UT, USA ⁶Department of Urology, University of Miami, Miami, FL, USA ⁷IVF Laboratory, MVZ VivaNeo Kinderwunschzentrum Düsseldorf, Düsseldorf, Germany

*Correspondence address. IVF Laboratory, MVZ VivaNeo Kinderwunschzentrum Düsseldorf, Völklinger Str. 4, 40219 Düsseldorf, Germany. Tel: +49-1742345266; E-mail: julia.uraji@gmail.com  <https://orcid.org/0000-0002-1441-4074>

The outbreak of the coronavirus disease 2019 (COVID-19) global pandemic posed healthcare challenges across medical fields, including the management of ART treatments. Accumulating studies and discussions have begun to describe the short- and long-term impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on male reproductive health. Concerns that SARS-CoV-2 may affect male fertility stem from the premise that viruses such as mumps, HIV and Zika have been detected in semen and can lead to testicular damage (Patel *et al.*, 2021). Among the outstanding questions about the impact of SARS-CoV-2 infection on male fertility are whether the virus targets the testis and how it affects semen quality. Current worldwide published information argues against the hypothesis that testicular and germ cells transmit SARS-CoV-2, with no detection of the virus during or after infection (Patel *et al.*, 2021; Tur-Kaspa *et al.*, 2021).

Few studies have evaluated the effect of COVID-19 on sperm parameters. The February 2021 edition of the ESHRE Journal Club (#ESHREjc), a monthly Twitter-based Journal Club (European Society for Reproductive Biology, 2021), featured a study published in *Human Reproduction* evaluating semen quality of 43 sexually active men with proven recovery from SARS-CoV-2 infection (Gacci *et al.*, 2021). This study demonstrated that while there was no viral RNA present in semen in the study subjects, 25% of men studied were oligo-cryptazoospermic and that this was significantly related to COVID-19 severity.

Participants in this edition of the #ESHREjc agreed that a systematic approach to assessing testis function and long-term follow-up are key to determining the impact of SARS-CoV-2 on male fertility. Repeated semen analysis, reproductive hormone profile and examination for testis damage (e.g. orchitis) would provide a more complete picture of whether COVID-19 has a permanent or transient effect on reproductive health. It is still unclear whether reported alterations of testicular

function are the result of a generalised severe inflammation, secondary to SARS-CoV-2 infection, or if they are pertinent to SARS-CoV-2 specific mechanisms.

Indeed, participants of February's #ESHREjc were more than enthusiastic to design the perfect study to answer precisely this question. Ideally, a study built to prospectively evaluate the effect of SARS-CoV-2 on male fertility should be conducted on a national or international level to ensure an adequate sample size. However, two challenges were mentioned that will likely stand in the way of this: first, the lack of standardisation of semen evaluation and second, finding patients with a baseline pre-infection semen analysis. Interestingly, fertility clinics may just be the perfect setting to overcome these challenges: a large cohort of men with baseline semen analyses and hormonal evaluations combined with experienced semenologists motivated to understand the short- and long-term effects on fertility. This would allow comparison of, not only semen parameters, but also testosterone and LH levels, DNA fragmentation and, ideally, data about potential epigenome modifications. Results should be stratified by time from infection and its severity (asymptomatic, mild and severe cases). As for the time interval between samples, the most commonly proposed timeline was once during infection and then every three months thereafter. We would expect to see some effect during the first three months as a consequence of generalised inflammation. If SARS-CoV-2 does not permanently damage testes, a return to baseline would be expected by six months. Another interesting cohort mentioned during the Journal Club was those with obstructive azoospermia. Matched cryopreserved testicular biopsies pre- and post-COVID-19 would allow for detailed morphological and immunohistochemical analysis to rule out potential testis damage incurred by SARS-CoV-2.

Another topic of importance during this #ESHREjc was how to improve the management of male infertility patients during the COVID-

19 pandemic. Critically, patient history should include previous infections with SARS-CoV-2 and, as mentioned above, sperm parameters should be tested with any such infections in mind. Additionally, Journal Club participants agreed that since fertility treatment generally affects the patient's psychology as a whole, counselling should be performed in routine practice.

Potential effects of COVID-19 on fertility of men not actively seeking fertility treatment cannot be excluded. For this reason, Journal Club participants pondered how the possibility of COVID-19 to influence sperm parameters might influence the decisions of couples trying to conceive naturally. The Journal Club's expert participants were of the opinion that, based on current data, the transmission of COVID-19 through semen was unlikely and thus the risk of sexual transmission is likely negligible—but more research is needed. Since the data on the potential impact of SARS-CoV-2 on offspring is limited, we should be cautious about both ART and natural conception equally. Journal Club participants concluded that counselling for patients should be based on their individual risk of exposure and touch upon recovery timelines, the optimal time for conception, the potential impact of sperm quality and vaccinations.

Finally, participants and experts of this month's #ESHREjc debated the best ways to address misinformation in times of a pandemic—specifically regarding SARS-CoV-2, vaccines and fertility. While the clinical and scientific evidence continues to build the picture that currently available vaccines against COVID-19 do not affect female or male fertility, this has done little to counter vaccine hesitancy in the public and the continuous spread of misinformation online. Journal Club participants agreed that data should continue to be collected to further improve our understanding but, perhaps more importantly, these findings must be easily accessible and communicated to the public by credible sources. Critically, information should be available in languages other than English, as vaccine hesitancy appears to be a worldwide issue. Experts, medical practitioners and science communicators should aim to use all channels, in particular social media, to be transparent about

the current evidence, thereby increasing understanding and trust in the public.

Acknowledgements

The authors thank all the participants of the ESHRE Journal Club on Twitter.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

No conflicts of interest to declare.

References

European Society for Reproductive Biology (2021). *ESHRE Journal Club*. <https://www.eshre.eu/Publications/Journals/JC> (23 April 2021, date last accessed).

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.

Patel DP, Punjani N, Guo J, Alukal JP, Li PS, Hotaling JM. The impact of SARS-CoV-2 and COVID-19 on male reproduction and men's health. *Fertil Steril* 2021; **115**:813–823.

Tur-Kaspa I, Tur-Kaspa T, Hildebrand G, Cohen D. COVID-19 may affect male fertility but is not sexually transmitted: a systematic review. *F S Rev* 2021; **2**:140–149.