

COVID-19 in men: With or without virus in semen, spermatogenesis may be impaired

Sir,

We would like to congratulate you for the review recently published in *Andrologia* entitled 'Could SARS-CoV-2 affect male fertility?' (Vishvkarma R, & Rajender S, 2020). In just a few months, several million humans have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This brutal pandemic, called coronavirus-19 disease (COVID-19), disproportionately affects men and may have lasting impacts relating to aspects such as fertility. Some of these impacts are described in the literature, and others may be published in the coming months. Today, the literature focuses on whether the virus is present in semen, a possibility that is causing significant panic in the media and the public because the presence of the virus in the ejaculate would make COVID-19 an sexually transmitted infection (STI). However, beyond the answer to this question, there are symptoms of COVID-19 (e.g. fever) with the known andrological impacts that should be highlighted.

1 | PRESENCE OR ABSENCE OF VIRUS IN SEMEN?

The SARS-CoV-2 virus uses angiotensin-converting enzyme 2 (ACE2) receptors to enter human cells, and the spike protein (protein S) is primed by transmembrane serine protease (TMPRSS2). The male reproductive system is believed to express both the ACE2 and TMPRSS2 receptor in the testes (spermatogonia, Sertoli and Leydig cells) and in prostate epithelial cells (for a review, see Hamdi et al., 2020; Vishvkarma R, & Rajender S, 2020). If receptors for the virus are present at different stages of the male reproductive system, it is not unreasonable to think that the virus could be found in semen either by alteration of the blood-testis barrier but also by excretion into prostatic fluid. To date, five studies have identified no virus in the semen of 91 patients total infected with COVID-19 (Guo et al., 2020; Holtmann et al., 2020; Pan et al., 2020; Paoli et al., 2020; Song et al., 2020). While these data were reassuring, a manuscript mentions the presence of virus in the semen of six patients infected with COVID-19 (4 in the acute phase of the disease and 2 cured) (Li et al., 2020). Some authors have questioned the conditions of sperm collection or the detection limits of the quantitative reverse transcription-polymerase chain reaction (qRT-PCR) tests used. It should be noted that the diagnostic accuracy of many commercial quantitative reverse transcription-polymerase chain reaction (qRT-PCR) kits available for the detection of SARS-CoV-2 has a sensitivity and/or

specificity <100%. PCR inhibitors are also present in semen (Schrader et al., 2012). Therefore, both false positive and false negative results could be obtained. Although it is not expected that SARS-CoV-2 clings to sperm, this has not yet been evaluated. For infertile men utilizing assisted reproductive technologies (ARTs), is there not a risk of inoculating the oocyte with the virus during intracytoplasmic sperm injection (ICSI) or the woman's uterus during intrauterine insemination (IUI)? If these questions remain unanswered, ART activities in infertile men must take these factors into account.

1.1 | DEREGULATION OF SPERMATOGENESIS

Beyond the presence or absence of a virus in semen, it is clear that COVID-19 can be accompanied by the deregulation of spermatogenesis.

1.2 | SERTOLI CELLS AND SPERMATOGENESIS

As Sertoli's cells have receptors for SARS-CoV-2, it is not unreasonable to think that they could be infected by the virus and thus see their functions altered (Shen et al., 2020; Verma et al., 2020). Sertoli's cells play a key role in spermatogenesis and altering them could alter spermatogenesis. Future research would be interesting. It would be possible to study the in vitro impact of SARS-CoV-2 on Sertolian cell lines or more simply to explore in vivo Sertolian hormonal secretions (Anti-Müllerian hormone, inhibin B) in COVID-19 positive patients. This research would allow to assess, if they exist, the potential impacts of the virus on the functions of Sertoli cells.

1.3 | FEVER AND ALTERED SPERMATOGENESIS

Fever is a symptom observed in over 80% of patients infected with COVID-19. This fever alone can have a negative impact on the physiological mechanisms of scrotal heat regulation, which are overwhelmed when body temperature rises by even one degree Celsius. Therefore, even a fever of limited duration can decrease sperm count and/or motility and may alter sperm DNA integrity. The return to the basal state of the sperm parameters can take a long time, sometimes nearly three months (Sergerie, Mieuisset, Croute, Daudin, & Bujan, 2007; Carlsen et al., 2003; Lazarus & Zorogniotti, 1975). Fever

induced by COVID-19 can therefore alter sperm parameters even in the absence of virus in the semen. In infertile men with altered sperm parameters in the basal state, this fever could have a more deleterious impact. For this reason, it has recently been recommended to monitor sperm parameters and to delay ART management for three months in men who have been diagnosed with COVID-19 and developed a fever (Hamdi et al., 2020).

1.4 | COVID-19 AND TESTOSTERONE: A POSSIBLE HORMONAL DEREGULATION OF SPERMATOGENESIS?

The links between androgens and COVID-19 are complex. Some authors have described a promoting effect of testosterone on the risk of COVID-19 infection (Pozzilli & Lenzi, 2020). Conversely, one study detected possible primary hypogonadism in patients with severe forms of COVID-19, while the balance of andrological hormones observed in patients with milder symptoms was normal (Rastrelli et al., 2020). Is hypogonadism a cause or a consequence of the severity of COVID-19 symptoms? Is this association between hypogonadism and severity of COVID-19 linked to a confounding factor (e.g. patient age) or simply due to chance? What impact could hypogonadism have on sperm parameters and for how long? Moreover, if it were proven that an infection with SARS-CoV-2 could induce hypogonadism, what would be its pathophysiology? It could be hypothesised that damage to Leydig cells and/or the gonadotropic axis (and more precisely hypothalamic GnRH neurons) could be observed with coronaviruses; however, the primary or secondary character of COVID-19-related hypogonadism (if it exists) cannot be formally established in the current state of knowledge, and more large cohort studies are needed. Regardless of the nature of the relationship between testosterone and COVID-19, an andrological examination, an assessment of sperm parameters and a hormonal evaluation at the time of diagnosis of COVID-19 and several months later are necessary.

2 | CONCLUSION

SARS-CoV-2 can have negative impacts on spermatogenesis and male fertility. Even in cure patients, the presence of the virus in semen is not impossible, and apart from the presence of virus in semen, spermatogenesis can be impaired by COVID-19-related fever. Therefore, as a precautionary measure, clinical, hormonal and semen parameter evaluations of patients diagnosed with COVID-19 are recommended at the time of infection and during follow-up appointments (3 and 6 months), especially in severe forms. For infertile men, a postponement of ART activities to three months post-infection is advisable.

KEYWORDS

Covid-19, fever, SARS-CoV-2, semen, spermatogenesis

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

All authors help to write this manuscript.

DATA AVAILABILITY STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT


Not applicable.

Marion Bendayan^{1,2,3}

Geoffroy Robin^{4,5,6}

Safouane Hamdi^{7,8}

Roger Mieusset^{7,8}

Florence Boitrelle^{1,2,3} 

¹Service de Biologie de la Reproduction-Préservation de la fertilité- Andrologie, Hôpital de Poissy Saint Germain en Laye, Poissy, France

²Université Paris-Saclay, UVSQ, INRAE, BREED, Jouy-en-Josas, France

³École Nationale Vétérinaire d'Alfort, BREED, Maisons-Alfort, France

⁴Service d'AMP et Préservation de la Fertilité, Hôpital Jeanne de Flandre, CHU de Lille, Lille cedex, France

⁵Service d'Andrologie, Hôpital Claude Huriez, CHU de Lille, Lille cedex, France

⁶Lille University, EA4308 "Gametogenesis and gamete quality", Loos, France

⁷Université de Toulouse, UPS, Groupe de Recherche en Fertilité Humaine (EA, Human Fertility Research Group), Toulouse, France

⁸Unité d'Andrologie, Groupe d'activité de Médecine de la Reproduction, Hôpital Paule de Viguier, CHU Toulouse, Toulouse, France

Correspondence

Florence Boitrelle, Service de Biologie de la Reproduction-Préservation de la fertilité- Andrologie, Hôpital de Poissy Saint Germain en Laye, Poissy 78300, France.

Email: florenceboitrelle@yahoo.fr

ORCID

Florence Boitrelle  <https://orcid.org/0000-0002-5322-0141>

REFERENCES

- Carlsen, E., Andersson, A.M., Petersen, J.H., & Skakkebaek, N.E. (2003). History of febrile illness and variation in semen quality. *Human Reproduction (Oxford, England)*, 18(10), 2089-2092. <https://doi.org/10.1093/humrep/deg412>

- Guo, L., Zhao, S., Li, W., Wang, Y., Li, L., Jiang, S., Ren, W., Yuan, Q., Zhang, F., Kong, F., Lei, J., & Yuan, M. (2020). Absence of SARS-CoV-2 in Semen of a COVID-19 Patient Cohort. *Andrology, in Press.*, <https://doi.org/10.1111/andr.12848>
- Hamdi, S., Bendayan, M., Huyghe, E., Soufir, J.C., Amar, E., El Osta, R., Plotton, I., Delalande, C., Perrin, J., Leroy, C., Bouker, A., Pons, H., Lejeune, H., Robin, G., & Boitrelle, F. (2020). COVID-19 and andrology: Recommendations of the French-speaking society of andrology (Société d'Andrologie de langue Française SALF). *Basic and Clinical Andrology*, 30, 10. <https://doi.org/10.1186/s12610-020-00106-4>
- Holtmann, N., Edimiris, P., Andree, M., Doehmen, C., Baston-Buest, D., Adams, O., Kruessel, J.S., & Bielfeld, A.P. (2020). Assessment of SARS-CoV-2 in human semen-a cohort study. *Fertility and Sterility*, 114(2), 233-238. <https://doi.org/10.1016/j.fertnstert.2020.05.028>
- Lazarus, B.A., & Zorgniotti, A.W. (1975). Thermoregulation of the human testis. *Fertility and Sterility*, 26(8), 757-759.
- Li, D., Jin, M., Bao, P., Zhao, W., & Zhang, S. (2020). Clinical characteristics and results of semen tests among men with coronavirus disease 2019. *JAMA Network Open*, 3(5), e208292. <https://doi.org/10.1001/jamanetworkopen.2020.8292>
- Pan, F., Xiao, X., Guo, J., Song, Y., Li, H., Patel, D.P., Spivak, A.M., Alukal, J.P., Zhang, X., Xiong, C., Li, P.S., & Hotaling, J.M. (2020). No evidence of severe acute respiratory syndrome-coronavirus 2 in semen of males recovering from coronavirus disease 2019. *Fertility and Sterility*, 113(6), 1135-1139. <https://doi.org/10.1016/j.fertnstert.2020.04.024>
- Paoli, D., Pallotti, F., Colangelo, S., Basilico, F., Mazzuti, L., Turriziani, O., Antonelli, G., Lenzi, A., & Lombardo, F. (2020). Study of SARS-CoV-2 in semen and urine samples of a volunteer with positive nasopharyngeal swab. *Journal of Endocrinological Investigation*, 1-4, <https://doi.org/10.1007/s40618-020-01261-1>
- Pozzilli, P., & Lenzi, A. (2020). Commentary: Testosterone, a key hormone in the context of COVID-19 pandemic. *Metabolism: Clinical and Experimental*, 108, 154252. <https://doi.org/10.1016/j.metabol.2020.154252>
- Rastrelli, G., Di Stasi, V., Inglese, F., Beccaria, M., Garuti, M., Di Costanzo, D., Spreafico, F., Greco, G.F., Cervi, G., Pecoriello, A., Magini, A., Todisco, T., Cipriani, S., Maseroli, E., Corona, G., Salonia, A., Lenzi, A., Maggi, M., De Donno, G., & Vignozzi, L. (2020). Low testosterone levels predict clinical adverse outcomes in SARS-CoV-2 pneumonia patients. *Andrology, in Press.* <https://doi.org/10.1111/andr.12821>
- Schrader, C., Schielke, A., Ellerbroek, L., & John, R. (2012). PCR inhibitors - occurrence, properties and removal. *Journal of Applied Microbiology*, 113(5), 1014-1026. <https://doi.org/10.1111/j.1365-2672.2012.05384.x>
- Sergerie, M., Mieuisset, R., Croute, F., Daudin, M., & Bujan, L. (2007). High risk of temporary alteration of semen parameters after recent acute febrile illness. *Fertility and Sterility*, 88(4), 970. <https://doi.org/10.1016/j.fertnstert.2006.12.045>
- Shen, Q., Xiao, X., Aierken, A., Yue, W., Wu, X., & Liao, M. (2020). The ACE2 expression in Sertoli cells and germ cells may cause male reproductive disorder after SARS-CoV-2 infection. *Journal of Cellular and Molecular Medicine*, 24, 9472-9477. <https://doi.org/10.1111/jcmm.15541>
- Song, C., Wang, Y., Li, W., Hu, B., Chen, G., Xia, P., Wang, W., Li, C., Diao, F., Hu, Z., Yang, X., Yao, B., & Liu, Y. (2020). Absence of 2019 novel coronavirus in semen and testes of COVID-19 patients†. *Biology of Reproduction*, 103(1), 4-6. <https://doi.org/10.1093/biolre/ioaa050>
- Verma, S., Saksena, S., & Sadri-Ardekani, H. (2020). ACE2 receptor expression in testes: Implications in COVID-19 pathogenesis. *Biology of Reproduction*, 103(3), 449-451. <https://doi.org/10.1093/biolre/ioaa080>
- Vishvkarma, R., & Rajender, S. (2020). Could SARS-CoV-2 affect male fertility? *Andrologia*, 52(9), e13712. <https://doi.org/10.1111/and.13712>