SARS-CoV-2 and human reproduction: An open question

Frida Entezami, Marise Samama, Nathalie Dejucq-Rainsford, Louis Bujan

EClinicalMedicine 25 (2020) 100473

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Commentary

SARS-CoV-2 and human reproduction: An open question

Frida Entezami[a,b,*], Marise Samama[c,d], Nathalie Dejucq-Rainsford[e,1], Louis Bujan[f,1]

[a] American Hospital of Paris, IVF Department, 63 boulevard Victor Hugo, 92200 Neuilly sur Seine, France
[b] Inserm U1203, Human Early Embryonic Development and Pluripotency, Montpellier, France
[c] Department of Gynecology, Federal University of São Paulo, Brazil
[d] GERA Institute of Reproductive Medicine, São Paulo, Brazil
[e] Inserm, EHESP, Irset - UMR_S1085, University Rennes, France
[f] Research Group on Human Fertility EA 3694, University Paul Sabatier Toulouse III and CECOS, Hôpital Paule de Viguier CHU de Toulouse, Toulouse, France

ARTICLE INFO

Article History:
Received 27 June 2020
Revised 8 July 2020
Accepted 9 July 2020
Available online 24 July 2020

In late 2019, a new coronavirus, SARS-CoV-2, started spreading in China and resulted in the Covid-19 pandemic. SARS-CoV-2 is a respiratory virus with a broad organ tropism gradually unveiled. Over 30 viruses infect male genital organs and semen, including viruses whose tropism for the male genital tract and sexual transmission was unexpected [1]. Several viruses also target the female genital tract [2]. Infection of the genital tract is particularly problematic since (i) male genital organs can act as viral reservoirs with persistent excretion in semen, leading to sexual transmission by cured men (e.g. Zika and Ebola viruses) [1,4], and (ii) the gametes and/or progenitor cells may be infected [1,3]. This could pose an issue for both assisted reproduction technologies (ART) and natural procreation.

The use of ART is growing, with millions of treatment cycles being performed annually in the world to care for infertility, a disease, which is a public health concern. During the acute phase of Covid-19 pandemic, fertility care has been postponed almost worldwide but is currently resuming.

Data on SARS-CoV-2 in male and female genital tracts are very scarce. It is crucial to assess the risk of viral transmission by genital fluids and gametes in order to prevent transmission to the embryo and to ensure laboratory safety during ART. Beyond ART, it is important to evaluate the risk of sexual transmission of SARS-CoV-2 in real life.

SARS-CoV-2 was detected in the semen of patients in the acute phase of Covid-19 (4 of 15) and in the recovery phase (2 of 23) in a single study [5], whereas other reports did not detect viral RNA in semen [6]. The cumulative number of patients tested is currently not sufficient (n = 103) to estimate the frequency of SARS-CoV-2 in semen. Moreover, the viral load, duration of excretion and infectivity of the viral material detected in semen are unknown. Importantly also, it remains to be determined whether the cellular components of semen (leukocytes, epithelial cells, and spermatozoa) are infected.

Based on known mechanisms of SARS-CoV-2 entry into cells (i.e. requirement for dual expression of the ACE2 receptor and protease TMPRSS2), transcriptomic and protein databases were screened for relevant gene expression in genital organs. Overall, it appears that while *ACE2* is highly expressed in the testis, its co-expression with *TMPRSS2* transcripts is rare among the cell types tested (less than 0.1%) [7]. Nevertheless, alternative cell targets for SARS-CoV-2 (i.e. basigin receptor, BSG, and the lysosomal cysteine protease cathepsin L, CTSL), appear to be widely expressed in testicular cells [7]. However, these data need to be taken with caution without proper validation *in situ* at both RNA and protein levels. Furthermore, conclusions on SARS-CoV-2 tropism cannot be drawn from the sole analysis of putative receptor expression. *In vivo* and/or *ex vivo* studies are required to determine whether SARS-CoV-2 can infect the genital tract.

Interestingly, Yang and colleagues lately reported SARS-CoV-2 detection by RT-PCR in the testes from one out of 12 patients deceased from Covid-19 [8]. Sertoli and Leydig cells, which expressed ACE2, were altered in these patients. In a previous report, testicular tissue from only one deceased patient was RT-PCR negative [8]. Here again, the cumulative number of patients tested is not sufficient (n = 13) to estimate the frequency of SARS-CoV-2 in testicular tissue, with only 2 studies performed on 13 patients [8]. Whether testicular alterations result from a direct or indirect effect of SARS-CoV-2 remains to be determined.

The likelihood of sexual transmission is presently unknown. This is a question of extreme importance that needs elucidation. In addition, the risk of using (potentially contaminated) sperm for ART, in samples from asymptomatic carriers of SARS-CoV-2, needs to be determined. Other airborne viruses have been detected in human and animal semen including an alphacoronavirus that persisted at a high level in the sperm-enriched fraction of boar semen [1]. In view of all these elements, the presence of SARS-CoV-2 in human semen should not be ruled out before in-depth analysis of well-designed studies.

The female gamete, the oocyte, is out of reach by natural means. During oocyte retrieval for ART, fluids from mature follicles are aspirated to harvest cumulus oocyte complexes where the oocytes are individually surrounded by cumulus cells.

E-mail address: Frida.ENTEZAMI@ahparis.org (F. Entezami).
[1] Drs Nathalie Dejucq-Rainsford and Louis Bujan contributed equally to this work.

https://doi.org/10.1016/j.eclinm.2020.100473

The expression of *ACE2* mRNA has been found in human ovarian tissue based again on RNAseq databases. Stanley and colleagues reported on the wide expression of *ACE2* and absence or very low expression of *TMPRSS2* transcripts in human cumulus cells [7]. Conversely, *BSG* and *CTSL* were both expressed at high levels, and as they are possible targets for SARS-CoV-2 entry into the cells, cumulus cells display some potential to be infected [7]. Therefore human cumulus cells may not act as a barrier to entry of the virus in the oocyte, as has been suggested. The same study reported on the co-expression of *ACE2* and *TMPRSS2* in the oocyte and found an increase in expression levels with oocyte maturity [7]. The mature oocyte may thus present a risk of infection and viral transmission that needs to be confirmed. An alternative pathway of oocyte infection may potentially occur through the oocyte retrieval process. Transvaginal oocyte retrieval is an invasive procedure and blood or vaginal contamination of follicular fluid samples is difficult to avoid. The presence of the virus has been shown in the blood of infected patients. Moreover, Scorzolini and colleagues [9], in contrast with reassuring data on vaginal status regarding SARS-CoV-2 [10], reported the case of a woman who tested positive in vaginal fluid on the 7th and 20th days after infection subsequent to a previous negative testing at symptoms onset.

SARS-CoV-2 is believed to become a long-term problem. This being so, fertility and ART treatments are resuming in a climate of uncertainty and without crystal clear information about the safety of male and female gametes. We have too little information to be completely sure that there are no risks of infection of gametes and semen components by SARS-CoV-2. Thorough studies are therefore required, with reliable data on the safety of human gametes for ART at the time of Covid-19, and on the risk of sexual virus transmission during infection and after recovery.

Funding

None.

Declaration of Competing Interest

We declare no competing interest.

References

[1] Le Tortorec A, Matusali G, Mahé D, et al. From ancient to emerging infections: the odyssey of viruses in the male genital tract. Physiol Rev 2020;100(3):1349–414.
[2] Prisant N, Breurec S, Moriniere C, Bujan L, Joguet G. Zika virus genital tract shedding in infected women of childbearing age. Clin Infect Dis 2017;64(1):107–9.
[3] Matusali G, Houzet L, Satie AP, et al. Zika virus infects human testicular tissue and germ cells. J Clin Investig 2018;128(10):4697–710.
[4] Bujan L, Mansuy JM, Hamdi S, Pasquier C, Joguet G. 1 year after acute Zika virus infection in men. Lancet Infect Dis 2020;20(1):25–6.
[5] Li D, Jin M, Bao P, Zhao W, Zhang S. Clinical characteristics and results of semen tests among men with coronavirus disease 2019. JAMA Netw Open 2020;3(5):e208292.
[6] Holtmann N, Edimiris P, Andree M, et al. Assessment of SARS-CoV-2 in human semen – a cohort study. Fertil Steril 2020 preprint. Date accessed: June 12 2020. doi: 10.1016/j.fertnstert.2020.05.028.
[7] 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(1):33–43.
[8] Yang M, et al. Pathological findings in the testes of COVID-19 patients: clinical implications. Eur Urol Focus 2020 Preprint. Date accessed: June 24 2020. doi: 10.1016/j.euf.2020.05.009.
[9] Scorzolini L, Corpolongo A, Castilletti C, Lalle E, Mariano A, Nicastri E. Comment of the potential risks of sexual and vertical transmission of Covid-19 infection [advanced online publication, 2020 Apr 16] Clin Infect Dis 2020 pii: ciaa445.. doi: 10.1093/cid/ciaa445.
[10] Cui P, Chen Z, Wang T, et al. Severe acute respiratory syndrome coronavirus 2 detection in the female lower genital tract. Am J Obstet Gynecol 2020;223(1):131–4.