ISFP – Newsletter

Impact of COVID- 19 on Fertility Preservation

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Since March 2020 the world has been in the grip of a highly transmissible and lethal respiratory virus SARS-CoV-2 (COVID-19). Routine medical services including fertility treatments were curtailed since the nature of the virus, optimal management of disease and its effect on reproduction were not well defined. Fertility preservation for cancer patients fell into the realm of 'emergency services' because of its time sensitive nature and procedures continued albeit under stressful conditions, given the high mortality rate with COVID-19. Unfortunately women with low ovarian reserve or advanced age for whom too, early intervention is important, were not included(1) Cryopreservation of gametes or gonadal tissue is integral to Fertility Preservation (FP). The impact of COVID-19 on reproductive tissue, the risk of cross contamination in storage and possibility of vertical transmission to the foetus remain a major concern.

Viral entry into host: The angiotensin-converting enzyme 2 (ACE2) receptor and the Trans-membrane protease serine 2 (TMPRSS2) aid viral entry into the cells, (2) their co-expression being essential for tissue involvement. ACE2 is expressed in spermatogonia, oocytes and granulosa cells of antral and pre-ovulatory follicles. Co-expression of ACE2 and TMPRSS2 receptors occurs in trophectoderm of the late blastocyst which is therefore susceptible to infection. Though trophectoderm contributes to the formation of placental tissue, foetal development may also be impacted. (3)

Effect of COVID-19 in Males: The testes are highly susceptible to the virus as high levels of ACE2 receptors are found on Spermatogonia, Leydig and Sertoli cells including a high co-expression of ACE2 and TMPRSS2.(4). Levels of ACE 2 receptor appear to be higher in the young. SARS -Co V induced orchitis with extensive destruction of testicular tissue has been reported (5), though the virus could not be demonstrated in the tissue. Literature suggests that semen parameters are affected by COVID-19, a result of infection of the testes and epididymis and/or changes in the cytokine profile and immune response.(6,7,8) Several mechanisms for this impairment have been suggested: 1. Genes involved in spermatogenesis are impaired in ACE2-positive spermatogonia. This leads to altered spermatogenesis in infected patients.(9) 2. Increased production of inflammatory cytokines with a subsequent immune response and antisperm antibody production.(8) 3. Impairment of the blood–testis barrier due to Sertoli cell involvement that allows for transfer of cytokines. 4. Excessive production of ROS which leads to sperm DNA damage. Hormonal alterations include an increase in serum LH levels but no significant change in testosterone and FSH levels in the acute phase. (8)

Presence of the virus in semen remains a major concern due to the potential risk of cross-contamination in storage and transmission at fertilization. Li et al (2020) (10) detected SARS-CoV-2 in semen during both acute (26.7%) and recovery phase (8%) of the disease, while several other authors were unable to do so. (11) It can be surmised that cryopreservation of semen is safe though extra precautions must be taken during cryopreservation. No reports are available for testicular tissue freezing, it can be considered after appropriate screening.

Effect of COVID-19 in Females : A medium to high level expression of ACE2 is found in oocytes and ovarian tissue. Age and level of ovarian reserve do not alter the co-expression of ACE-2 and TMPRSS2. A review of literature (12) suggests that COVID -19 infection does not appear to impact ovarian reserve. In patients undergoing IVF, SARS- CoV- 2 RNA has not been detected in follicular fluid or oocytes in infected

patients, though antibodies to the virus have been detected in follicular fluid. This did not affect the number of mature oocytes retrieved or fertilization rate but a reduced blastulation and euploidy rate were reported in most studies.(12) Ovarian tissue cryopreservation is advocated as a FP technique for pre-pubertal girls and post-pubertal women who cannot delay gonadotoxic treatment. Transplantation of infected tissue could potentially lead to reintroduction of the virus. Analysis of ovarian tissue in an asymptomatic patient with SARS CoV-2 infection did not detect virus in the tissue.(13) SARS CoV -2 has also not been detected in embryo culture media and vitrification solution.(14) ACE2 receptor is also expressed in the uterus and vagina leading to concerns about sexual transmission and changes in menstruation. Reversible alterations in the menstrual cycle have been observed while there has been no evidence of sexual transmission till date.(12)

Cryopreservation and risk of cross-contamination: The risk of cross-contamination through cryogenic medium needs to be kept in mind since viruses may retain their infectivity during cryostorage. Risk mitigation strategies include sperm washing, use of closed cryopreservation systems ,liquid nitrogen vapor and use of a quarantine cryostorage tank. Sperm washing and preparation techniques remove seminal fluid, dead sperms and infectious cells thereby reducing the volume of sperm preserved, and the viral load. Closed systems and nitrogen vapour prevent migration of virus during cryostorage. Semen from infected patients can be put in a quarantine cryostorage tank till complete assessment of the sample.(11) Good Laboratory Practices (GLP) recommend that gametes and embryos from infected patients be stored in separate containers and this must be strictly adhered to.

Vertical Transmission: Though there is a potential risk of vertical transmission most studies have not been able to demonstrate infection in the newborns of COVID-19 positive mothers, suggesting that placental barrier is effective in preventing transmission. Literature indicates that the chance of transmission of SARS-CoV-2 from gamete to offspring is very low and it is safe to practice fertility preservation. Co-expression of ACE2 and TMPRSS2 occurs only in the late blastocyst stage it would therefore be appropriate to cryopreserve embryos at the 8 cell stage. (3)

Recommendations: ESHRE and ASRM recommend screening of patients before initiating FP procedure. A questionnaire based triage and an RT-PCR test should be carried out.(14,15)

Cancer and COVID-19: Protective measures to prevent infection of cancer patients with COVID-19 should be in place when FP procedures are carried out. A 2.2 fold increase in possibility of infection has been reported in cancer patients on treatment with chemotherapy or immunotherapy. (17)

Conclusion: The COVID-19 pandemic has created a challenge for providing both fertility and fertility preservation services. Since age and ovarian reserve are the two most important parameters for success in FP / ART, it is imperative to offer gamete/embryo/ tissue freezing not only to patients undergoing gonadotoxic treatments but also to other age related or medical conditions that may compromise their future fertility. Current literature suggests that It is safe to offer FP to patients if appropriate measures like screening, testing and GLP are in place.

References

1. Geber S, Prates N, Sampaio M, Valle M, Meseguer M. COVID-19 should be a novel indication for fertility preservation [published online ahead of print, 2020 Jul 14]. JBRA Assist Reprod. 2020;24(3):233-234.
2. Hoffmann, M. , Kleine-Weber, H. , Schroeder, S. , Krüger, N. , Herrler, T. , Erichsen, S. , Schiergens, T. S. , Herrler, G. , Wu, N.-H. , Nitsche, A. , Müller, M. A. , Drosten, C. , & Pöhlmann, S. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*, 181(2), 271–280.e278.

3. Cheng GP, Guo SM, Zhou LQ. Suggestions on cleavage embryo and blastocyst vitrification/transfer based on expression profile of ACE2 and TMPRSS2 in current COVID-19 pandemic. Mol Reprod Dev. 2021;88(3):211-216
4. Ren, X. , Wei, X. , Li, G. , Ren, S. , Chen, X. , Zhang, T. , Zhang, X. , Zhongwen, L. , You, Z. , Wang, S. , Qin, C. , & Song, N. & Wang, Z. (2020). Multiple expression assessments of ACE2 and TMPRSS2 SARS-CoV-2 entry molecules in the urinary tract and their associations with clinical manifestations of COVID-19. bioRxiv. 10.1101/2020.05.08.083618
5. Xu, J. , Qi, L. , Chi, X. , Yang, J. , Wei, X. , Gong, E. , Peh, S. & Gu, J. (2006). Orchitis: A complication of severe acute respiratory syndrome (SARS). *Biology of Reproduction*, 74(2), 410–416.
6. Navarra A, Albani E, Castellano S, Arruzzolo L, Levi-Setti PE. Coronavirus Disease-19 Infection: Implications on Male Fertility and Reproduction.Front Physiol. 2020; 11():574761
7. Holtmann N, Edimiris P, Andree M, Doehmen C, Baston-Buest D, Adams O, Kruessel JS, Bielfeld AP. Assessment of SARS-CoV-2 in human semen-a cohort study. Fertil Steril. 2020 Aug; 114(2):233-238
8. Haghpanah A, Masjedi F, Alborzi S, Hosseinpour A, Dehghani A, Malekmakan L, Roozbeh J. Potential mechanisms of SARS-CoV-2 action on male gonadal function and fertility: Current status and future prospects. Andrologia. 2021 Feb;53(1):e13883
9. Fan, C. , Li, K. , Ding, Y. , Lu, W. L. , & Wang, J. (2020). ACE2 expression in kidney and testis may cause kidney and testis damage after 2019-nCoV infection. medRxiv. 10.1101/2020.02.12.20022418
10. 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
11. Anifandis G, Taylor TH, Messini CI, Chatzimeletiou K, Daponte A, Ioannou D, Tempest HG. The Impact of SARS-CoV-2 on Sperm Cryostorage, Theoretical or Real Risk? Medicina (Kaunas). 2021 Sep 8;57(9):946.
12. Carp-Veliscu A, Mehedintu C, Frincu F, Bratila E, Rasu S, Iordache I, Bordea A, Braga M. The Effects of SARS-CoV-2 Infection on Female Fertility: A Review of the Literature. Int J Environ Res Public Health. 2022 Jan 16;19(2):984.
13. Seracchioli r, raimondo d, Salucci P, la Marca a, Vicenti r, Paradisi r, et al. No evidence for SarS- coV-2 presence in ovarian tissue and peritoneal cavity from a coVid-19-positive woman undergoing urgent fertility pres- ervation procedure. Minerva endocrinol 2021;46:365-7.
14. Rajput SK, Khan SA, Goheen BB, Engelhorn HJ, Logsdon DM, Grimm CK, Kile RA, West RC, Yuan Y, Schoolcraft WB, McCormick S, Krisher RL, Swain JE. Absence of SARS-CoV-2 (COVID-19 virus) within the IVF laboratory using strict patient screening and safety criteria. Reprod Biomed Online. 2021 Jun;42(6):1067-1074.
15. European Society of Human Reproduction and Embryology. News and Statements. Assisted reproduction and COVID 19: An updated statement from ESHRE 17th April 2020b.https://www.eshre.eu/Press-Room/ESHRENews#COVID19_April2.
16. American Society of Reproductive Medicine. Patient management and clinical recommendations during coronavirus (COVID-19) pandemic. Second update published 13th April 2020a.https://www.asrm.org/blobalassets/asrm/asrm-content/news-andpublications/COVIDtaskforce.pdf
17. Lee KA, Ma W, Sikavi DR, Drew DA, Nguyen LH, et al; COPE consortium. Cancer and Risk of COVID-19 Through a General Community Survey. Oncologist. 2021 Jan;26(1):e182–5. doi: 10.1634/theoncologist.2020-0572. Epub 2020 Sep 7.