



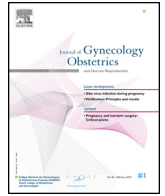
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en



Commentary

Fertility preservation in cancer patients at the time of COVID-19 pandemic



Erica Silvestris^{a,*}, Miriam Dellino^a, Raffaella Depalo^b

^a Gynecologic Oncology Unit, IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy

^b Institutional BioBank, Experimental Oncology and Biobank Management Unit, IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy

ARTICLE INFO

Article history:

Received 8 June 2020

Received in revised form 31 August 2020

Accepted 7 September 2020

Available online 9 September 2020

Keywords:

COVID-19

Cancer patients

Oncofertility

The SARS-CoV-2 pandemic, namely Coronavirus Disease 19 (COVID-19), has rapidly become an emergency world-wide, and cancer patients are considered at high risk and morbidity. To prevent the infertility risk induced by anti-cancer chemotherapy or other gonadotoxic treatments as well as pelvic surgery, these patients have access to fertility preservation (FP) procedures which include oocytes cryopreservation after hormone stimulation or ovarian cortex cryostorage in females, and sperm freezing in males [1,2]. Thus, before their gamete recruitment and storage to be performed prior of relative cancer treatments, these patients are currently investigated by blood screening for human immunodeficiency, as well as for B and C hepatitis viruses, and syphilis in some countries [3]. During the SARS-CoV-2 pandemic, however, while symptomatic COVID-19⁺ cancer patients candidate to FP are addressed to specific programs for the infection healing, asymptomatic patients considered virus-free through negative serological test may still have access to FP programs in Italy since only major procedures of ART (Assisted Reproduction Technology) have been restricted [4], whereas no structured recommendations have been issued for managing these patients [5]. Therefore, a prophylactic nasopharyngeal swab for COVID-19 RNA detection should be routinely adopted for all cancer patients undergoing FP which can be pursued when the molecular testing is negative. Nevertheless, for infected patients some questions would worry

the embryologists such as 'Is COVID-19 transmissible to gametes?', 'Is the FP procedure practicable or not?', and overall 'Are there additional risks for embryos?'

In females, putatively virus-infected components enabling the COVID-19 transmission include both cellular and acellular constituents of the ovarian follicle. Besides the oocyte itself in which it is essential to exclude the virus presence, the follicular fluid (FF) also needs proper definition. Indeed, FF is essential for the egg health and includes steroid hormones, metabolites, proteins, polysaccharides, ROS, and antioxidants, that physiologically undergo quantitative variations during the follicle maturation. It is conceivable that such biochemistry alterations might exert negative effects on the oocyte competence in presence of COVID-19 thus requiring full attention to investigate at least the FF protein content before deciding to address the FP procedure [6]. To this, it is unclear whether or not the virus is capable to cross the ovarian follicle and diffuse in FF, in which at least the structural spike protein (SP) expressed on COVID-19 membrane should be checked before addressing the FP procedure.

In prepuberal and adult patients affected by hormone-sensitive cancers and urgently requiring gonadotoxic protocols, the ovarian cortex cryopreservation for future reimplantation is considered a procedure free from oncogenic risk related to the estrogen stimulation adopted in the controlled ovary stimulation [7]. However, once the infected cortex fragment has been implanted, the virus would equally diffuse in host. Thus, once again it is critical for this FP technique to explore by genomic assessment the occurrence of COVID-19 within the samples to be cryopreserved to avoid possible reinfection.

* Corresponding author at: Gynecologic Oncology Unit, Oncofertility program, National Cancer Center, IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy.

E-mail address: ericasilvestris85@gmail.com (E. Silvestris).

Concerning the possible virus transmission through sperm by male cancer patients, it is also crucial to assess the liquid components of the seminal plasma. In fact, proteins at low molecular mass occurring within the vesicular fraction are capable not only to prepare the milieu during the capacitation and the sperm-egg interaction [8], but can also hypothetically play a role in supporting the COVID-19 entry and replication in host cells [9]. However, a single report in literature appears to exclude the virus presence in seminal plasma although the research for specific viral proteins as SP which allows the virus access in cells, was not assessed [10]. Thus, evaluation of the COVID-19 proteome in seminal plasma of cancer male patients undergoing FP should be suggested prior the sperm freezing and for avoiding possible biologic cross-contaminations of other stored samples.

The COVID-19 transmission to newborns from infected parents is also a disturbing issue in Coronavirus pandemic, but no additional risk should be theoretically envisaged in cancer patients. News from mass-media of the last weeks, indeed, reported the birth of at least two COVID-19 negative newborns from positive mothers in Lombardy, whereas 20 asymptomatic virus-positive newborns have been registered at the National Health Ministry [11]. However, COVID-19 placental transmission has not been yet demonstrated [12].

In conclusion, due to lack of information on COVID-19 transmission through gametes and relative components, it appears essential that, in addition to the government policy to extend the serological test for SP immunization to the full Italian population, cancer patients candidate to FP procedures can be mandatorily screened by nasopharyngeal pad and that both seminal plasma and FFs are explored in their proteomic content before cryopreserving the relative gametes in males and females respectively.

Authors' contribution

E.S. reviewed the literature and wrote the manuscript. M.D. reviewed the literature and wrote the manuscript. R.DP. contributed critically reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding source

Not applicable.

Declaration of Competing Interest

The authors report no declarations of interest.

References

- [1] Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, et al. Fertility preservation for patients with cancer: American society of clinical oncology clinical practice guideline update. *J Clin Oncol* 2013;31(19):2500–10.
- [2] Peccatori FA, Azim [23_TD\$DIFF][20_TD\$DIFF]r: HA, Orecchia R, Hoekstra HJ, Pavlidis N, Kesic V, et al. Cancer, pregnancy and fertility: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;(24 Suppl 6):vi160–70.
- [3] Associazione Italiana di Oncologia Medica - Linee guida. Preservazione della fertilità nei pazienti oncologici. 2018.
- [4] Istituto Superiore di Sanità, Centro Nazionale trapianti. Misure di prevenzione della trasmissione dell'infezione da nuovo Coronavirus (SARS-CoV-2) in Italia per le cellule riproduttive e i trattamenti di PMA (procreazione medicalmente assistita). Prot. 605/CNT2020, Roma 17/03/2020. 2020.
- [5] Day M. Covid-19: identifying and isolating asymptomatic people helped eliminate virus in Italian village. *BMJ* 2020;23(368):m1165.
- [6] Da Broi MG, Giorgi VSI, Wang F, Keefe DL, Albertini D, Navarro PA. Influence of follicular fluid and cumulus cells on oocyte quality: clinical implications. *J Assis Reprod Genet* 2018;35:735–51. doi:http://dx.doi.org/10.1007/s10815-018-1143-3.
- [7] Hoekman EJ, Louwe LA, Rooijers M, van der Westerlaken LAJ, Klijn NF, Pilgram GSK, et al. Ovarian tissue cryopreservation: low usage rates and high live-birth rate after transplantation. *Acta Obstet Gynecol Scand* 2020;99(2):213–21. doi: http://dx.doi.org/10.1111/aogs.13735 Epub 2019 Oct 8, 2020.
- [8] Szczykutowicz J, Kałuża A, Kaźmierowska-Niemczuk M, Ferens-Sieczkowska M. The potential role of seminal plasma in the fertilization outcomes. *Biomed Res Int* 2019;5397804. doi:http://dx.doi.org/10.1155/2019/5397804 eCollection 2019. Review.
- [9] Shanmugaraj B, Siriattananon K, Wangkanont K, Phoolcharoen W. Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID-19). *Asian Pac J Allergy Immunol* 2020;38(1):10–8. doi:http://dx.doi.org/10.12932/AP-200220-0773.
- [10] Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr* 2020;9(1):51–60. doi:http://dx.doi.org/10.21037/tp.2020.02.06.
- [11] Ministero della salute. Covid-19, in Italia circa 20 i neonati positivi al virus ma nessuno grave. *Bollettino protezione civile* 2020;22(April).
- [12] Lv Y, Gu B, Chen Y, Hu S, Ruan T, Xu G, et al. No intrauterine vertical transmission in pregnancy with COVID-19: a case report. *J Infect Chemother* 2020(August). doi:http://dx.doi.org/10.1016/j.jiac.2020.07.015 S1341-321X (20)30266-X.