de Almeida AB, et al., J Reprod Med Gynecol Obstet 2022, 7: 118
DOI: 10.24966/RMGO-2574/100118

HSOA Journal of Reproductive Medicine, Gynecology & Obstetrics

Short review

Reviewing the Impact of SARS-Cov-2 Infection on Human Fertility

Ana Beatriz de Almeida[1,2*] and Márcia Barreiro[1,2,3]

[1]*Department of Women's and Reproductive Health, Centro Materno-Infantil do Norte Dr. Albino Aroso (CMIN), Centro Hospitalar Universitário do Porto (CHUP), Porto, Portugal*

[2]*Institute of Biomedical Sciences Abel Salazar (ICBAS), University of Porto, Porto, Portugal*

[3]*Centre of Assisted Medical Procriation (CPMA), Centro Materno-Infantil do Norte Dr. Albino Aroso (CMIN), Centro Hospitalar Universitário do Porto (CHUP), Porto, Portugal*

Abstract

The Coronavirus Disease 2019 (COVID-19) pandemic brought a significant impact on medically assisted reproduction services. Besides its negative impact relative to non-urgent cycle cancelations, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is thought to affect the human reproductive system through Angiotensin-Converting Enzyme 2 (ACE2) receptor and consequently lead to infertility. In this short review we tried to summarize the information regarding the main mechanisms through SARS-CoV-2 could impact male (sperm quality, orchitis, hypogonadism) and female (endometrial receptivity, oocyte quality, menstrual cycle changes) fertility and what it is known about vertical transmission. We also assessed the importance of fertility preservation during the pandemic to urgent subgroups of patients and the implications of SARS-CoV-2 effects as well as of its vaccination on Assisted Reproductive Technology (ART) outcomes.

Introduction

The COVID-19, which is mainly characterized by the SARS-CoV-2 acute respiratory syndrome, was first described in the city of Wuhan by the end of 2019 and it was recognized as a global pandemic on 11th March 2020 [1,2]. The unknown effects of SARS-CoV-2 infection in human fertility and pregnancy limited Assisted Reproduction Techniques (ART) to couples with treatments in progress and to those with conditions requiring urgent gamete cryopreservation [3]. For the remaining infertile couples, the cessation of ART and the uncertainty surrounding its resumption impacted overall health as well as induced psychological distress regarding infertility [4]. Around 5,546,290 cases were confirmed in Portugal and more than 646 million people were affected worldwide, bringing a significant socioeconomic burden [5]. COVID-19 vaccination provided new perspectives on prevention and control of the disease, nonetheless, its effect on ART remains undetermined [6].

This short review aims to summarize our last publication entitled "Impact of SARS-CoV-2 infection on fertility: concerns in Reproductive Medicine", which presents the available information about the impact of SARS-CoV-2 infection on human fertility as well as on ART [7].

Influence of SARS-CoV-2 on the Reproductive System

Mechanisms involved in impairment of female and male fertility in case of COVID-19 infection have been proposed but are still not well-established. Both Angiotensin-Converting Enzyme 2 (ACE2) protein and protease like transmembrane serine protease 2 (TMPRSS2) are needed for coronavirus hosting, and besides the pulmonary tract, those proteins were found in the reproductive system [2]. In the male, they are selectively expressed by Leydig, Sertoli and peritubular myoid cells as well as by spermatogonial stem cells of adult testes, playing a role in spermatogenesis and steroidogenesis [8]. Despite of the immunological protection provided by the blood-testis barrier, SARS-CoV-2 can reach the testes causing scrotal discomfort as well as imagiological findings of epididymitis or orchitis, which have been reported up to 22,5% of acute COVID-19 infection cases [9]. Postmortem studies also shown signs of seminiferous tubules injury, presence of T-lymphocytic inflammation in interstitial tissue and a reduction in the number of Leydig cells, explaining the disruption of spermatogenesis and a low ratio of testosterone to Luteinizing Hormone (LH) [8,10]. Cases of moderate infection presented a significant impairment of sperm quality (reduction of total spermatozoa per ejaculate as well as a decrease in their motility) when compared to men with mild or no infection, which probably results from inflammatory responses induced by SARS-CoV-2 oxidative stress [2,9]. On the other hand, SARS-CoV-2 detection in semen samples is still controversial, rising a concern about semen cryopreservation [10,11]. Consequently, international guidelines state that semen freezing of COVID-19 positive cases should only be recommended in specific situations and it should be submitted to a two-step preparation technique for intra-uterine insemination or *In Vitro* Fertilization (IVF) [8].

Although expression of ACE2 receptors is more important on male reproductive system than on the female, its presence has also been reported in human ovaries and endometrial cells [6]. ACE2 and Angiotensin-(1-7) are found in all follicular stages, either in granulosa and theca-interstitial cells, regulating its development and atresia,

***Corresponding author:** Ana Beatriz de Almeida, Department of Women's and Reproductive Health, Centro Materno-Infantil do Norte Dr. Albino Aroso (CMIN), Centro Hospitalar Universitário do Porto (CHUP), Porto, Portugal, Tel: +351 967311366; E-mail: anabeatriz29@gmail.com

Citation: de Almeida AB, Barreiro M (2022) Reviewing the Impact of SARS-Cov-2 Infection on Human Fertility. J Reprod Med Gynecol Obstet 7: 118.

Received: December 12, 2022; **Accepted:** December 23, 2022; **Published:** December 30, 2022

as well as ovulation and steroidogenesis [2]. Increased serum levels of LH and prolactin have been reported in COVID-19 patients, as a result from central nervous system injuries or anxiety disorders, causing Hypothalamus-Pituitary-Ovary (HPO) axis dysfunction [11,12]. Despite of not being clearly demonstrated, a downregulation of ACE2 induced by SARS-CoV-2 could disrupt the oocyte quality and possibly lower the ovarian reserve, which was shown by some authors through lower Anti-Mullerian (AMH) levels in COVID-19 recovered patients [8]. An immune/inflammatory response against viral infection, with Angiotensin II-mediated synthesis of Reactive Oxygen Species (ROS), is also reported as a possible indirect cause of ovarian injury [2]. On the other hand, ACE2 cleaves Angiotensin II in endometrial cells, promoting spiral artery vasoconstriction and endometrial proliferation [8]. Changes in menstrual pattern were also reported, with an incidence of dysmenorrhea and irregular menses, including decreased or prolonged menstrual flow, in 32% and 15% respectively [8]. The viral gene expression seems to increase with age, suggesting that older women undergoing ART present a higher risk of endometrial viral infection [8]. In this manner, SARS-CoV-2 is suspected of affecting the early embryo implantation [2].

The components of RAAS system are also expressed in the placental cells, posing the possibility of vertical transmission of SARS-CoV-2 through the placenta. Their expression is involved in the regulation trophoblast invasion and establishment of fetoplacental circulation, explaining the higher rates of hypertensive disorders of pregnancy and fetal growth restriction in pregnant patients with COVID-19 infection [13]. However, placental co-expression of ACE2 and TMPRSS2 has not been yet identified, which suggests more research is needed to confirm the possibility of transplacental COVID-19 infection and its potential impact on pregnancy outcomes [13].

Impact of COVID-19 for Patients Undergoing ART and Practical Considerations

Since May of 2020, the gradual re-establishment of Reproductive Medicine encouraged to initially prioritize access to fertility treatments [8]. The stratification of women with low-prognosis of conceiving (Poseidon - Patient-Oriented Strategies Encompassing Individualize D Oocyte Number) allowed the establishment of groups of patients whose fertility preservation or ART should not be delayed [14]. At the beginning of pandemics, Poseidon group 4 (≥35 years with low ovarian reserve) were considered either to embryo freezing or fresh embryo transfer while Poseidon group 2 (≥35 year with normal ovarian reserve) and group 3 (<35 years with low ovarian reserve) were only proposed to freeze-all cycles [14]. Other group of patients considered to preserve fertility were those with oncological and other medical conditions [e.g., Systemic Autoimmune Diseases (SAD)], which have their fertility potential reduced by exposure to gonadotoxic treatments. SAD patients also present a chronic inflammation status that might disrupt the ovarian tissue and the HPO axis, impairing the ovarian reserve [14]. Time is crucial for these patients as they need to discontinue their treatments and achieve remission of the disease at least six months before fertility preservation [2,14]. The "remission window" was coincident with the beginning of pandemics for some couples, raising the question of whether to restart their treatment and postpone ART or to stop it for extended periods, with the risk of a disease flare [2].

Currently, Reproductive Medicine centers have resumed their activity for all infertile couples, according to local protocols and international guidelines elaborated to face some issues of the pandemic era [3]. The emergence of SARS-CoV-2 vaccination brought a new hope to these couples waiting for ART resumption, while doubts were raised about the safety profile of vaccines in regarding the risk of infertility [15]. To date, there is a lack of information about the possible effects of COVID-19 vaccination, however the studies performed in vaccinated people have demonstrated no influence either on sperm parameters nor on follicular steroidogenesis and oocyte quality [7,16]. In addition, IVF treatment parameters, such as number of oocytes and fertilization rate, did not differ between vaccinated groups, indicating that the COVID vaccines may not have deleterious effects on the human reproductive system [17]. The ESHRE COVID-19 Working Group currently recommends that all people should have access to fertility treatments despite its vaccination status and if people become vaccinated, the treatment may be postponed for at least a few days to allow the immunological response to be established.

Despite of fearing long-term repercussions, there are some short-term issues regarding ART outcomes that must be discussed. Fever is a common sign of SARS-CoV-2 infection, being thought to impact male and female fertility [2]. In male patients, fever can transiently impair spermatogenesis and the sperm quality for a mean period of 70 days and lead to a cytokine storm syndrome, which will have a negative impact on the testicular function. On the other hand, it negatively affects follicular development and estradiol production in female patients undergoing ovarian stimulation for IVF [7,16]. Despite of the inherent complications of SARS-CoV-2 infection, the risk of developing pulmonary and renal injuries, as well as the thromboembolic risk, increases if a COVID-19 patient presents an Ovarian Hyperstimulation Syndrome (OHS) [2,7]. In order to reduce the risk of OHS and coagulopathy, specific gonadotropin protocols have been adopted, as well as the administration of prophylactic low-molecular weight heparin and segmentation of IVF technique [2,9,16]. Similarly to ART patients, pregnant women are also at higher risk of adverse obstetrical outcomes, explaining why ESHRE advised to defer embryo transfer during or right after a COVID-19 infection [2,16]. Not withstanding the immunosuppressive status of pregnancy, the risk of SARS-CoV-2 infection in pregnant women is similar to non-pregnant [2].

Conclusion

SARS-CoV-2 infection seems to influence the human fertility, and the establishment of individualized ART treatments seem to be a crucial key to improve chances of conceive and deliver safely. Not least, the psychological support of infertile couple is also of great important in order to reduce the negative impact of the uncertainty period we are living. Further research about COVID-19 impact on the reproductive system as well as on fetomaternal outcomes is still needed in order to constantly improve the healthcare policies in Reproductive Medicine.

References

1. Sharma I, Kumari P, Sharma A, Saha SC (2021) SARS-CoV-2 and the reproductive system: Known and the unknown..!! Middle East Fertil Soc J 26: 1.

2. Lee WY, Mok A, Chung JPW (2021) Potential effects of COVID-19 on reproductive systems and fertility; assisted reproductive technology guidelines and considerations: a review. Hong Kong Med J 27: 118-126.

3. ESHRE COVID-19 Working Group, Vermeulen N, Ata B, Gianaroli L, Lundin K, et al. (2020) A picture of medically assisted reproduction activities during the COVID-19 pandemic in Europe. Hum Reprod Open 2020: hoaa035.

4. Veiga A, Gianaroli L, Ory S, Horton M, Feinberg E, et al. (2020) Assisted reproduction and COVID-19: A joint statement of ASRM, ESHRE, and IFFS. Hum Reprod Open 2020: hoaa033.

5. Yüce M, Filiztekin E, Özkaya KG (2021) COVID-19 diagnosis -A review of current methods. Biosens Bioelectron 172: 112752.

6. ESHRE (2022) COVID-19 vaccination and assisted reproduction. ESHRE, Belgium.

7. de Almeida AB, Meneses TA, Macedo RZ, Barreiro M (2022) Impact of SARS-CoV-2 infection on fertility: Concerns in Reproductive Medicine. REVNEC 31: 212-219.

8. Alviggi C, Esteves SC, Orvieto R, Conforti A, La Marca A, et al. (2020) COVID-19 and assisted reproductive technology services: repercussions for patients and proposal for individualized clinical management. Reprod Biol Endocrinol 18: 45.

9. Seymen CM (2021) The other side of COVID-19 pandemic: Effects on male fertility. J Med Virol 93: 1396-1402.

10. Ma L, Xie W, Li D, Shi L, Ye G, et al. (2021) Evaluation of sex-related hormones and semen characteristics in reproductive-aged male COVID-19 patients. J Med Virol 93: 456-462.

11. Ding T, Wang T, Zhang J, Cui P, Chen Z, et al. (2021) Analysis of ovarian injury associated with COVID-19 disease in reproductive-aged women in Wuhan, China: An observational study. Front Med (Lausanne) 8: 635255.

12. Singh B, Gornet M, Sims H, Kisanga E, Knight Z, et al. (2020) Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and its effect on gametogenesis and early pregnancy. Am J Reprod Immunol 84: 13351.

13. Li R, Yin T, Fang F, Li Q, Chen J, et al. (2020) Potential risks of SARS-CoV-2 infection on reproductive health. Reprod Biomed Online 41: 89-95.

14. Chen L, Huang X, Yi Z, Deng Q, Jiang N, et al. (2021) Ultrasound Imaging Findings of Acute Testicular Infection in Patients With Coronavirus Disease 2019: A Single-Center-Based Study in Wuhan, China. J Ultrasound Med 40: 1787-1794.

15. La J, Katz DJ (2022) Linking COVID-19 vaccine and male infertility - not on fertile ground. BJU Int 130: 20-21.

16. Cirillo M, Rizzello F, Badolato L, De Angelis D, Evangelisti P, et al. (2021) The effects of COVID-19 lockdown on lifestyle and emotional state in women undergoing assisted reproductive technology: Results of an Italian survey. J Gynecol Obstet Hum Reprod 50: 102079.

17. Chen F, Zhu S, Dai Z, Hao L, Luan C, et al. (2021) Effects of COVID-19 and mRNA vaccines on human fertility. Hum Reprod 37: 5-13.

HERALD

Advances In Industrial Biotechnology | ISSN: 2639-5665

Advances In Microbiology Research | ISSN: 2689-694X

Archives Of Surgery And Surgical Education | ISSN: 2689-3126

Archives Of Urology

Archives Of Zoological Studies | ISSN: 2640-7779

Current Trends Medical And Biological Engineering

International Journal Of Case Reports And Therapeutic Studies | ISSN: 2689-310X

Journal Of Addiction & Addictive Disorders | ISSN: 2578-7276

Journal Of Agronomy & Agricultural Science | ISSN: 2689-8292

Journal Of AIDS Clinical Research & STDs | ISSN: 2572-7370

Journal Of Alcoholism Drug Abuse & Substance Dependence | ISSN: 2572-9594

Journal Of Allergy Disorders & Therapy | ISSN: 2470-749X

Journal Of Alternative Complementary & Integrative Medicine | ISSN: 2470-7562

Journal Of Alzheimers & Neurodegenerative Diseases | ISSN: 2572-9608

Journal Of Anesthesia & Clinical Care | ISSN: 2378-8879

Journal Of Angiology & Vascular Surgery | ISSN: 2572-7397

Journal Of Animal Research & Veterinary Science | ISSN: 2639-3751

Journal Of Aquaculture & Fisheries | ISSN: 2576-5523

Journal Of Atmospheric & Earth Sciences | ISSN: 2689-8780

Journal Of Biotech Research & Biochemistry

Journal Of Brain & Neuroscience Research

Journal Of Cancer Biology & Treatment | ISSN: 2470-7546

Journal Of Cardiology Study & Research | ISSN: 2640-768X

Journal Of Cell Biology & Cell Metabolism | ISSN: 2381-1943

Journal Of Clinical Dermatology & Therapy | ISSN: 2378-8771

Journal Of Clinical Immunology & Immunotherapy | ISSN: 2378-8844

Journal Of Clinical Studies & Medical Case Reports | ISSN: 2378-8801

Journal Of Community Medicine & Public Health Care | ISSN: 2381-1978

Journal Of Cytology & Tissue Biology | ISSN: 2378-9107

Journal Of Dairy Research & Technology | ISSN: 2688-9315

Journal Of Dentistry Oral Health & Cosmesis | ISSN: 2473-6783

Journal Of Diabetes & Metabolic Disorders | ISSN: 2381-201X

Journal Of Emergency Medicine Trauma & Surgical Care | ISSN: 2378-8798

Journal Of Environmental Science Current Research | ISSN: 2643-5020

Journal Of Food Science & Nutrition | ISSN: 2470-1076

Journal Of Forensic Legal & Investigative Sciences | ISSN: 2473-733X

Journal Of Gastroenterology & Hepatology Research | ISSN: 2574-2566

Journal Of Genetics & Genomic Sciences | ISSN: 2574-2485

Journal Of Gerontology & Geriatric Medicine | ISSN: 2381-8662

Journal Of Hematology Blood Transfusion & Disorders | ISSN: 2572-2999

Journal Of Hospice & Palliative Medical Care

Journal Of Human Endocrinology | ISSN: 2572-9640

Journal Of Infectious & Non Infectious Diseases | ISSN: 2381-8654

Journal Of Internal Medicine & Primary Healthcare | ISSN: 2574-2493

Journal Of Light & Laser Current Trends

Journal Of Medicine Study & Research | ISSN: 2639-5657

Journal Of Modern Chemical Sciences

Journal Of Nanotechnology Nanomedicine & Nanobiotechnology | ISSN: 2381-2044

Journal Of Neonatology & Clinical Pediatrics | ISSN: 2378-878X

Journal Of Nephrology & Renal Therapy | ISSN: 2473-7313

Journal Of Non Invasive Vascular Investigation | ISSN: 2572-7400

Journal Of Nuclear Medicine Radiology & Radiation Therapy | ISSN: 2572-7419

Journal Of Obesity & Weight Loss | ISSN: 2473-7372

Journal Of Ophthalmology & Clinical Research | ISSN: 2378-8887

Journal Of Orthopedic Research & Physiotherapy | ISSN: 2381-2052

Journal Of Otolaryngology Head & Neck Surgery | ISSN: 2573-010X

Journal Of Pathology Clinical & Medical Research

Journal Of Pharmacology Pharmaceutics & Pharmacovigilance | ISSN: 2639-5649

Journal Of Physical Medicine Rehabilitation & Disabilities | ISSN: 2381-8670

Journal Of Plant Science Current Research | ISSN: 2639-3743

Journal Of Practical & Professional Nursing | ISSN: 2639-5681

Journal Of Protein Research & Bioinformatics

Journal Of Psychiatry Depression & Anxiety | ISSN: 2573-0150

Journal Of Pulmonary Medicine & Respiratory Research | ISSN: 2573-0177

Journal Of Reproductive Medicine Gynaecology & Obstetrics | ISSN: 2574-2574

Journal Of Stem Cells Research Development & Therapy | ISSN: 2381-2060

Journal Of Surgery Current Trends & Innovations | ISSN: 2578-7284

Journal Of Toxicology Current Research | ISSN: 2639-3735

Journal Of Translational Science And Research

Journal Of Vaccines Research & Vaccination | ISSN: 2573-0193

Journal Of Virology & Antivirals

Sports Medicine And Injury Care Journal | ISSN: 2689-8829

Trends In Anatomy & Physiology | ISSN: 2640-7752