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Review of the impact of COVID-19 on male reproduction, and its implications on assisted reproductive technology services

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Review Article

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Summary

The announcement in 2019 of a new coronavirus disease that quickly became a major pandemic, is an exceptional challenge to healthcare systems never seen before. Such a public health emergency can largely influence various aspects of people's health as well as reproductive outcome. IVF specialists should be vigilant, monitoring the situation whilst contributing by sharing novel evidence to counsel patients, both pregnant women and would-be mothers. Coronavirus infection might adversely affect pregnant women and their offspring. Consequently, this review paper aims to analyse its potential risks for reproductive health, as well as potential effects of the virus on gamete function and embryo development. In addition, reopening fertility clinics poses several concerns that need immediate addressing, such as the effect of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) on reproductive cells and also the potential risk of cross-contamination and viral transmission. Therefore, this manuscript summarizes what is currently known about the effect of the SARS-CoV-2 infection on medically assisted reproductive treatments and its effect on reproductive health and pregnancy.

Introduction

The rapid increase in severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) has led to a worldwide increase in coronavirus disease 2019 (COVID-19). It was declared to be a pandemic by the World Health Organization (WHO) on 11 March 2020. As of May 2021, there are more than 165 million cases worldwide and 3.4 million deaths associated with this new virus. On this basis, governments across the world have issued preventive measures such as social distancing to control community spread and to protect the vulnerable from infection, especially elderly people. Medically assisted reproductive (MAR) professional societies and regulatory authorities have issued guidelines and regulations based on expert opinion and new scientific knowledge.

To reallocate necessary resources to cope with the expected challenge posed to healthcare systems and to avoid major peaks of patients to manage the limited number of hospital beds demands, restrictions to non-emergency medical care, including fertility were advised or imposed by notional legislations (ASRM, 2020; Bedford *et al*., 2020; European Society for Human Reproduction and Embryology, 2020). Despite these efforts, the spread of COVID-19 is ongoing, creating a worldwide public health crisis.

Few studies have reported the detection of this virus on male and female reproductive cells (Holtmann *et al*., 2020; Esteves *et al*., 2021). Coronaviruses (CoVs) belong to the family of Coronaviridae, named based on the presence of antigens in their membrane that give them the characteristic 'crown-like' structure. Several CoVs have been identified in animals and humans (Szczepanski *et al*., 2019; Helmy *et al*., 2020). In humans, all identified coronaviruses have originated from animal reservoirs including bats and mice. Although most human CoVs can cause only minor flu-like symptoms, others, such as the severe acute respiratory syndrome (SARS)-CoV-1 and Middle Eastern Respiratory syndrome (MERS)-CoV, have received significant attention due to their severe lower respiratory tract infections. Symptoms of SARS-CoV-2 contamination include cough, fever, fatigue, shortness of breath, headache, and gastrointestinal symptoms may also be reported. The viral infection ranges from asymptomatic carriers to critical illness with acute respiratory distress syndrome, and death (Ye ZW *et al*., 2020).

The novel SARS-CoV-2 virus spreads rapidly; its genome sequence is 82% identical to that of SARS-CoV, and this could help in understanding the pathophysiology of the new virus for reproductive organs (Chan *et al*., 2020). The incubation period ranges from 2 to 14 days, and transmission is primarily through droplets generated by infected individuals during coughing, sneezing or speaking (Allam *et al*., 2020; Wu and McGoogan, 2020). Ong and colleagues

reported the presence of coronavirus in a hospital room of COVID-19 patients (Ong *et al.*, 2020). Environmental surfaces were positive for the virus, whilst room air samples collected after cleaning were negative (Faridi *et al.*, 2020; Ye G *et al.*, 2020). Due to the potential of the virus to survive in the environment for several days, it is critical to clean areas using products containing antimicrobial agents known to be effective against coronaviruses (Oliveira *et al.*, 2016). In addition, SARS-CoV-2 RNA also has been detected in blood and faeces and it is not clear whether the infection can be acquired through exposure to non-respiratory fluids (Li Q *et al.*, 2020). In a recent study, van Doremalen and colleagues detected viable viruses in aerosols for up to 3 h, and on plastics and stainless steel up to 72 h (van Doremalen *et al.*, 2020). According to the World Health Organization (2020), nearly 80% of infected patients have mild infections, between 15% and 20% are severe, and *c.* 5% are critical and require mechanical ventilation.

Currently, the available evidence suggests that the gravity of the disease is lower in younger people and in women, but no reasonable evidence has been furnished (Verity *et al.*, 2020). Risk factors for severe illness include age and other medical conditions such as obesity and cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer (Zheng *et al.*, 2020). Although the mortality rate is reported at 2% or 3%, and is more common in individuals older than 60 years of age, SARS-CoV-2 is expected to result in many more deaths due to its extensive and rapid infections (Guarner, 2020; World Health Organization, 2020).

Objective

The novel COVID-19 virus has been detected on human reproductive cells; male and female patients of reproductive age might also be at risk for development of the disease (Esteves *et al.*, 2021), even though viral transmission during sexual contact and assisted reproductive techniques has not been demonstrated (Holtmann *et al.*, 2020). Reproduction is an essential human right that goes beyond race, gender and sexual orientation, and is fundamental to the continuation of all species. Infertility is the impairment of reproductive capacity that affect *c.* 10% of couples of reproductive age (ASRM, 2020; European Society for Human Reproduction and Embryology, 2020). It is time sensitive, and the female age is recognized to be extremely important to obtain a successful pregnancy. In addition, as stated by the American Society for Reproductive Medicine (ASRM), the window of opportunity for infertile couples is finite. Postponing treatment for too long due to the SARS-CoV-2 infection, could reduce the chances of pregnancy. On this basis, the aim of this review was to summarize what is currently known about the effect of the SARS-CoV-2 infection on MAR treatments and its effect on reproductive health and pregnancy.

Physiology of coronavirus

Coronaviruses are single-stranded, enveloped RNA viruses that are kept inside a nucleocapsid (Ortega *et al.*, 2020). The envelope consists of three proteins: a membrane protein, an envelope protein, and the spike protein, which is responsible for the entry into host cells, and gives the crown-like structure to the virus (Li F, 2016). The spike proteins, which are made of S1 and S2 domains, help to initiate the critical process of human infection, as well as determining host tissue specificity and inducing the host immune response (Kirchdoerfer *et al.*, 2016). The S1 domain is critical for viral binding and attachment to the host cell membrane (Hulswit *et al.*, 2019). Receptors on the human cell membrane that are involved in S1 subunit binding have been illustrated, including (ACE2) angiotensin-converting enzyme-2. The S2 domain is involved in the fusion process of the virus and the host cell membranes, enabling this COVID-19 RNA to penetrate the host cell (Song *et al.*, 2018).

Coronavirus and reproductive system

Much research on this new virus is carried out to reveal its pathology. Notably, men are reportedly more vulnerable to COVID-19, even with a higher fatality rate compared with women. It is imperative to determine whether SARS-CoV-2 might affect male and female fertility as an immediate or long-term consequence of the disease (Song *et al.*, 2018).

Male

There is enough evidence to suggest that COVID-19 infection may have an effect on the male reproductive system. Among the data available, an important finding is that ACE2 receptor is deeply expressed on Leydig cells in the testis (Douglas *et al.*, 2004). In addition, Fan and collaborators found that ACE2 was highly expressed in renal tubular cells, Leydig cells and cells in the seminiferous ducts of the testis (Fan *et al.*, 2021a), as well as on human oocytes and blastocysts (Essahib *et al.*, 2020). There have been several studies on male reproductive damage after SARS-CoV infection. In a 2005 study of eight post-mortem SARS-CoV patients, testicular tissue revealed atrophy despite lacking identifiable SARS viral RNA (Gu *et al.*, 2005). Accordingly, Xu and colleagues noted that orchitis was a complication of SARS, inducing germ cell destruction and widespread testicular leukocyte infiltration. The authors suggested that the reproductive function should be followed and deeply evaluated in recovered male SARS patients (Xu *et al.*, 2006).

In a recent study, Pan and associates were not able to detected any viral genome in the semen of males recovering from SARS-CoV-2 (Pan *et al.*, 2020). In another study, Guo and co-workers recruited 23 male patients with a recent infection or recovering from SARS-CoV-2, and no viral RNA was detected in their semen samples, which indicated the unlikely possibility of sexual transmission through semen (Guo *et al.*, 2021). However, these studies cannot definitively exclude the presence of the virus in the seminal fluid of men during an acute infection of SARS-CoV-2 (Pan *et al.*, 2020; Guo *et al.*, 2021). Finally, there is evidence that high temperature and fever can affect spermatogenesis, therefore male fertility may be diminished for up to 3 months following COVID-19 infection due to decreased sperm concentration and motility (Carlsen *et al.*, 2003). Further studies on the reproductive involvement of coronavirus infections are required, particularly within recovered patients. Therefore, MAR specialists should be very cautious when assessing male infertile patients, including sperm assessment and follow-up of reproductive function for the few months following the infection.

Female

At the moment of writing, available data suggest that the female reproductive system may be saved from COVID-19 infection. Indeed, there are no studies to date that have shown virus in the female reproductive system, including vaginal secretions, the

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amniotic and peritoneal fluids (Ding *et al.*, 2004). Immunohistochemical studies on tissues collected from a small cohort of deceased women that were affected by SARS-CoV failed to identify viral RNA within the female reproductive system, including the uterine compartment and the ovarian tissue (Ding *et al.*, 2004). However, Reis and collaborators found the existence of ACE2 markers in the human ovary, in particular these were localized to primordial, primary, secondary, and antral follicles, stroma, and corpora lutea of reproductive-age ovaries (Reis *et al.*, 2011). ACE2 was also expressed on the surface of oocytes (Essahib *et al.*, 2020) and in the endometrium, where it has been shown that its expression changed according to the menstrual cycle, being more abundant in the secretory phase than the proliferative phase (Reis *et al.*, 2011). Moreover, animal investigations have reported that ACE2 is expressed in bovine and rat ovarian granulosa cells, and is involved in follicular development (Pereira *et al.*, 2009).

Based on previous animal studies, it is therefore plausible to propose ways in which SARS-CoV-2 might affect female fertility: (i) the virus might harm ovarian tissue and granulosa cells, and decrease ovarian function and oocyte quality, leading to female infertility; and (ii) COVID-19 might damage endometrial epithelial cells and affect early embryo implantation and miscarriage. However, there is still a lack of evidence to support those theories and further studies are mandatory to clarify those concerns.

SARS-CoV-2 emergency and effect on pregnancy

The new COVID-19 virus has generated the first major pandemic of the new millennium (Bedford *et al.*, 2020; World Health Organization, 2020; Wu and McGoogan, 2020). The fast financial progress in southern China has led to a rising request for animal proteins including those from exotic animals. Large numbers and varieties of these wild mammals enclosed in overcrowded cages and the lack of biosecurity measures in those markets permitted the jump of this virus from animals to humans (Webster, 2004). Its capacity for human-to-human transmission, the lack of awareness in hospital infection control, and international air travel promoted the fast global circulation of the virus.

A few years ago, Cheng and collaborators in a review paper announced that the risk of emerging infections in Asia and China could be very high. Moreover, the authors noted that horseshoe bats are the natural reservoir for SARS-CoV-like virus and that civets are the amplification host, featuring the importance of wildlife and biosecurity in farms and wet markets, which can serve as the source and amplification centres for developing infections, with the risk of pandemics (Cheng *et al.*, 2007). Consequently, at the beginning of January 2020, China reported a new major presence of coronavirus disease 2019 (COVID-19), which is at the time of writing rapidly expanding worldwide. Its natural development has been demonstrated by Andersen and colleagues (Andersen *et al.*, 2020). Confirmation of infection at present is based on nasopharyngeal swab and PCR for acute illness and, although many serological tests to identify antibodies are being developed, they still require validation before being considered reliable.

Coronavirus epidemics have occurred three times in the past decades: in 2003, SARS; in 2012, MERS-CoV; and in 2020, SARS-CoV-2. Perhaps more lethal than COVID-19, both SARS and MERS had more limited spread and, although they all cause respiratory disease, they might have effects on pregnancy and on gestation. Fan and colleagues reported no vertical transmission of SARS-CoV-2 (Fan *et al.*, 2021b). In another study from China, COVID-19 infection did not lead to maternal deaths and there were no confirmed cases of vertical transmission (Schwartz, 2020). A case series of nine COVID-19 positive women who delivered via caesarean section showed no viral RNA in the amniotic fluid, cord blood, or breastmilk (Chen *et al.*, 2020). However, a recent case suggested that vertical transmission may be possible (Dong *et al.*, 2020). Overall, evidence of vertical transmission is, at the present time, inconclusive, and further observation is necessary as more data are gathered during the course of this pandemic. According to Dong and colleagues, the effect of SARS-CoV-2 infection on babies is low. However, newborns might be asymptomatic carriers of the infection, which might go undetected whilst being spread to the population (Dong *et al.*, 2020). Several studies have also investigated cases of pregnant COVID-19 patients and their infants (Li N *et al.*, 2020; Yu *et al.*, 2020; Zeng *et al.*, 2020; Zhang *et al.*, 2020).

These studies taken together reported the experience of 162 COVID-19-positive pregnant patients and their 184 babies. The majority of these patients achieved labour or near term, with 12 cases before 36 weeks of gestation, and only one case of miscarriage was seen. Currently, no investigations have yet directly investigated SARS-CoV-2 patients at earlier stages of pregnancy. The evidence from the two case–control studies, including 46 patients and 287 controls, reported similar patterns of symptomatology, disease severity, and outcome. The authors concluded that COVID-19 during early pregnancy is not more severe than among non-pregnant women (Zhang *et al.*, 2020). Moreover, some infected pregnant women displayed severe disease, five needed mechanical ventilation, and two patients have died. Full-term babies born from mothers affected by active COVID-19 infections have been well, overall positively. Most are of normal weight and although the majority were delivered electively using caesarean section to reduce the risk of maternal transmission, 18 cases of fetal distress have been reported. Among the 184 fetuses reported, 13 were delivered prematurely, 12 were small for gestational age, and one was large for gestational age. One stillbirth and one neonatal death were recorded (Li N *et al.*, 2020; Zhang *et al.*, 2020).

Risk of infection for patients attending ART services

Currently, it is still not clear if the SARS-CoV-2 virus uses ACE2 receptors in the reproductive system and if this would have any effect on oocyte quality, embryo development, or potential cross-contamination (Essahib *et al.*, 2020; Fan *et al.*, 2021a). Surely, gametes obtained from patients with other viral infections, such as human immunodeficiency virus or hepatitis, must be treated with special precautions designed at reducing exposure of the noninfected partner and cross-contamination of reproductive tissue within the laboratory (Practice Committee of American Society for Reproductive Medicine, 2013).

Currently, these precautions are not suggested for COVID-19 infection, given the lack of evidence for transmission through blood (Chan *et al.*, 2020; World Health Organization, 2020). European Society for Human Reproduction and Embryology (ESHRE) guidelines now recommend molecular testing in all patients undergoing MAR treatment, and increased counselling and information to patients planning a pregnancy with the use of telemedicine and virtual consultation. Embryo transfer should be avoided and a freeze-all strategy advised to all patients, particularly in cities with high COVID-19 incidence (European Society for Human Reproduction and Embryology, 2020). Mandatory

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SARS-CoV-2 testing for all patients undergoing fertility preservation (FP) would be optimal to ensure that their gametes are not infected by SARS-CoV-2 and can therefore be safely cryopreserved (Dellino *et al.*, 2020). Indeed, we do suppose that further studies are needed to ensure the safety of stored gametes and the safety of patients undergoing assisted reproduction.

During the pandemic it is prudent to propose the closure of non-emergency health services, including fertility and elective MAR treatments. However, during the pandemic, there has been a sharp raise in the prevalence of stress and depression in the infertile population (Ben-Kimhy *et al.*, 2020). It is important to mention the huge need for many adult male cancer patients to cryostore their spermatozoa and testicular tissue, as well as ovarian tissue and oocytes for women, to preserve their fertile future. Currently, a reliable method of FP in reproductive-aged men and women is sperm/oocyte banking, which must be ideally completed before the start of gonadotoxic therapy (Adiga *et al.*, 2020). Those drugs have been reported to induce sexual dysfunction and impaired reproductive activities, with possible irreversible effects (Wallace *et al.*, 2005; Sciorio, 2020; Sciorio and Anderson, 2020). Along with cancer patients, loss of time is extremely important for male patients under medical treatment aimed at improving sperm features, as well as men with non-obstructive azoospermia or cryptozoospermic patients being medically treated to restore or improve spermatogenesis. On this basis, the fertility time for those patients may be transient, therefore FP for cancer treatment and provision of andrological services should not be delayed, even during the pandemic.

In that regard, the introduction of 'vitrification' in the late 1990s has represented a massive breakthrough in oncofertility and FP. The new procedure was adopted as an alternative to the slow-freezing technique for human oocytes and embryos, aimed at providing superior success rates in terms of cryo-survival and pregnancy outcomes. The vitrification method has been extremely efficient for cryopreserving oocytes, which are difficult cells to freeze successfully (Paynter *et al.*, 1999). However, there are some concerns associated with the risk of cross-contamination during cryostorage, and eventually for the reintroduction of the virus when patients return to the clinic to use their gametes or embryos. Indeed, it has been reported that vitrification efficiency depends on both the choice of the carrier used to preserve gametes or embryos and whether or not liquid nitrogen comes in contact with the droplet containing the sample (open vitrification versus closed vitrification). The issue with open vitrification is that LN_2 itself can contain pathogens and direct contact with the vitrification sample might induce a potential contamination between the vitrification sample and LN_2.

In the published literature to date, an episode of pathogen infection and transmission in samples stored in fertility cryobanks has never been reported (Yakass and Woodward, 2020). Cobo and collaborators were not able to reveal the presence of viral RNA or DNA sequences in liquid nitrogen used for oocyte or embryo vitrification in patients seropositive for HIV, hepatitis C virus, and hepatitis B virus undergoing ART cycles (Cobo *et al.*, 2012). In contrast, cross-contamination events between cryopreserved samples in LN_2 have been reported by Tedder and co-authors, who described a report of human hepatitis virus transmission from bone marrow transplants stored in the same LN_2 tank (Tedder *et al.*, 1995). Therefore, the risk of contamination due to the direct contact of embryos with liquid nitrogen is not excluded (Bielanski *et al.*, 2000). In addition, there is some reason to believe that specific cryoprotectants used during the process of vitrification–warming, might also promote protection on the viral envelope, inducing virus cryoprotection and that could increase the transmission efficacy of the pathogen to the other stored materials (Tedder *et al.*, 1995; Bielanski *et al.*, 2000). Some authors have suggested alternatives to overcome the issue of cross-contamination in open vitrification, including the sterilization of liquid nitrogen (Parmegiani *et al.*, 2010), and the storage of embryos in vapour phase liquid nitrogen (Cobo *et al.*, 2010).

Conclusion

On January 2020, the SARS-CoV-2 virus was identified as a cause of severe cases of pneumonia in Wuhan, China. In the first 3 months of 2020, the new virus had infected more than 1.4 million people and caused more than 87,000 deaths. It was declared a pandemic by the WHO on March 2020, and, after 1 year in May 2021, the virus has infected over 165 million people with 3.4 million deaths worldwide. COVID-19 disease is an unprecedented global situation that is drastically changing our daily life and perspective. As ART specialists we should be precautious, carefully following the situation whilst contributing by sharing novel evidence to counsel couples coming to the fertility clinic. However, despite the magnitude of the disease and its worldwide prevalence, information regarding the effects of the new COVID-19 on human reproduction are currently restricted, and the lack of evidence should not be considered reassuring.

The SARS-CoV-2 spike protein binds to the ACE2 receptor, a protein found in many reproductive tissues, including the testis. Evidence suggests a relationship between coronaviruses and severe orchitis, as well as sperm counts than can be reduced by high temperature and fever. However, further studies are needed to clarify the question of the long-term effects on male and female gametes, and whether there might be shedding of virus in some patients that might affect the safety and storage of gametes or embryos. Emerging evidence has suggested that complications in pregnancy, especially after delivery, might be associated with the new COVID-19. However, additional studies are urgently needed to confirm this concern. With the restart of fertility clinics, it is crucial for the healthcare providers to be ready to deal with the effect of SARS-CoV-2 on male and female reproductive gametes and embryos, as well as the risk of contamination and transmission through cryobanking services. Finally, the huge effect of the COVID-19 pandemic on deaths, healthcare expenses, and the economic crisis around the globe is inestimable, considering that the pandemic at the time of writing is still growing, and probably the emergency is expected to last for several months, therefore new strategies need to be taken to cope with COVID-19 when offering MAR treatments.

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