Possible impact of COVID-19 on fertility and assisted reproductive technologies

More than 4.5 million people have been infected, almost 1.5 million in the USA alone, by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic, and 300,000 have had coronavirus disease 2019 (COVID-19) at the time of death (1).

Many investigators have embarked on the global endeavor to study the pathophysiology of SARS-CoV-2 in an attempt to generate and supply guidance on its disease transmission, susceptibility, and treatment.

In a contrast from influenza virus infection, 118 pregnant women in Wuhan, China, with Covid-19 infection did not exhibit an increased risk of complications or severe disease versus nonpregnant women with similar age and infection (2). Neonatal throat swabs testing of eight newborns for SARS-CoV-2 was negative, as were breast milk samples from three parturients (2).

Nevertheless, living with uncertainty has led most countries to outright cancel all assisted reproductive technology (ART)/in vitro fertilization (IVF) interventions and even all fertility treatments, except for fertility preservation in patients exposed to gonadotoxic chemotherapy or radiotherapy. However, because of the declining success rates of ART/IVF in late-reproductive-age women, several countries have reintroduced, and many more are considering resuming, these treatments, initially in women older that 39 years, and later even to younger patients. It is imperative, therefore, to know whether SARS-CoV-2 may infect gametes and embryos, considering the possible consequences on natural conceptions and on ART/IVF–generated pregnancies.

Most recently, in a report from a Wuhan university hospital in China, none of the serum or throat swabs of the newborns of six parturients with confirmed COVID-19 displayed SARS-CoV-19 according to reverse-transcription polymerase chain reaction testing (1). However, their neonatal umbilical blood did display virus-specific antibodies (1). Five infants had elevated IgG concentrations and two newborns had IgM antibodies (1). Unlike IgG, the larger macromolecular IgM does not usually pass through the placenta from the maternal compartment to the fetus (1). In another study, of mothers with SARS, abnormal weights and pathology were observed in the placentas of two patients infected with SARS-CoV in the third trimester (1). It has been speculated that the IgM detected in the neonates could have evolved from the abnormal or damaged placentae or, on the other hand, possibly could have been generated by the neonates in response to transplacental viral infection (1).

These observations raise the question of possible transplacental viral infection vertical transmission of the SARS-CoV infection from mother to fetus. Therefore, the study by Stanley et al. (3), in the current issue of *Fertility and Sterility* is of utmost importance. Those authors assessed the gene and protein expression patterns of SARS-Cov-2 host entry proteins in several reproductive tissues. The authors are lauded for their elegant study despite the limited number of samples. Using single-cell RNA sequencing data, the authors did not detect coexpression of angiotensin-converting enzyme (ACE) 2 and transmembrane protease, serine 2 (TMPRSS2) in the sperm or other testicular cells. However, they detected expression of ACE2 and TMPRSS2 in a subpopulation of oocytes in nonhuman primate ovarian tissue, but the coexpression was not observed in ovarian somatic cells. The authors also evaluated the expression of the receptor basigin (BSG/CD147), which may possibly modulate viral entry, and the cysteine protease cathepsin L (CTSL), which potentially cleaves the viral S protein. They found that BSG was more broadly expressed across testicular cell types than ACE2 and was coexpressed with CSTL in early and late primary spermatocytes (78.7% and 90.8% of cells with mRNA transcripts, respectively). Similarly, BSG and CTSL transcripts were detectable in all of the 18 tested human cumulus cell samples. However, there was no, or low, expression of TMPRSS2 in the human cumulus cell samples.

Based on their results, the authors concluded that SARS-CoV-2 infection is unlikely to have long-term effects on male and female reproductive function, suggesting that the risks of ART/IVF are not altered by the COVID-19 pandemic (3). They may be right. Although reassuring, we still need to be on the alert and live with uncertainty. This is because SARS-CoV-2 has been detected in various secretions, such as saliva, stool, urine, and the gastrointestinal tract (4). Therefore, the inevitable question whether the virus is transmitted through semen needs to be answered. Whereas the blood-testicular barrier is not perfect, SARS-CoV-2 may inoculate the male reproductive tract, especially in the presence of inflammation (4). To date, 27 viruses have been detected in human semen in association with viremia (4). It has been speculated that the presence of viruses in semen may be more common than appreciated, and that traditional non–sexually transmitted viruses may be present in the genital secretions (4). Indeed, Li et al. recently identified SARS-CoV-2 in six out of 38 positive patients (15.8%), including four of 15 patients (26.7%) in the acute stage of infection (4). Furthermore, two of the 23 recovering patients (8.7%) also tested positive for SARS-CoV-2 in their semen, with no difference in days since clinical recovery, suggesting that semen may be contagious for the virus not only in the acute stage of illness but even later on. Because there was no difference between the positive and negative results, it is unknown yet for how long the semen may be contagious, which is definitely alarming.

Assuming that most patients positive for SARS-CoV-2 may abstain from intercourse in the acute phase of the disease, owing to weakness, erectile dysfunction, fear of transferring the virus to their partners, or other causes, this may not be true for recovering patients. Several additional questions need urgent answers for the general public: For how long should they abstain from intercourse? Are condoms protective enough? Are the medical laboratory workers and personnel in contact with infertile patients' semen, for intrauterine insemination or ART/IVF, at risk of acquiring the viral infection? If the semen may be infectious, would the

generated embryos and the female partners be at risk of acquiring SARS-CoV-2? What are the possible remote consequences on the future infants? Many alarming questions and few reliable answers.

Recently, it was suggested that one out of many monoclonal antibodies targeting SARS-CoV-2 S protein identified from memory B cells of an individual who was infected with SARS-CoV in 2003, could neutralize SARS-CoV-2 (5). This antibody, named S309, engaged with the S receptor-binding domain and recognized a glycan-containing epitope without competing with receptor attachment. The authors suggested that this antibody and S309-containing antibody cocktails could be used either prophylactically in high-risk individuals or as a postexposure therapy to ameliorate disease severity. Similarly, almost a hundred potential COVID-19 vaccines are being investigated, and a few of them are under human clinical trials for efficacy and safety. Most recently, a Massachusetts-based pharmaceutical laboratory has developed a coronavirus vaccine called mRNA-1273, which has been tested on human volunteers and was apparently effective. It is hoped that these preliminary encouraging reports are validated and prove to be reliable. It is, therefore, suggested to consider immunizing infertile couples with these vaccines before ART/IVF, after safety and efficacy are proven, before turning to global immunization of the public.

COVID-19 challenges all of the medical specialties, including reproductive medicine. Because many clinical questions remain unanswered yet, all health care providers need to be alert, amending and adjusting treatment modalities according to the daily changing information and published experience on the behavior of this new and unknown disease.

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