

# Clinical Guidelines on the Use of Assisted Reproductive Technology During Covid-19 Pandemic: A Minireview of the Current Literature

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#### Abstract

**Background:** The coronavirus disease-2019 (COVID-19), caused by a the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is now spread worldwide. Therefore, informative and reliable data related to the exact effects of COVID-19 on fertility and pregnancy is still of great interest until the pandemic is declared over. General guidelines regarding the protection and management of COVID-19 have been published and new information will continue to be updated daily.

**Methods:** In this review, we summarized clinical health guidelines for reproductive and infertility centers to improve quality management in assisted reproductive technology and minimize the potentially harmful consequences of COVID-19 on pregnancy and fertility.

**Results:** As specified in the literature, protocols consist of five categories, including protocols for couples, protocols for women, protocols for men, labor and delivery, and postpartum and breastfeeding.

**Conclusion:** General protocols for patients and staff may vary depending on specific conditions. However, this review provides some rules to ensure their safety against the disease during the pandemic.

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**Keywords:** Assisted, Assisted reproductive technology, COVID-19, Infertility, Pandemic, Reproductive Techniques

## Introduction

The coronavirus disease-2019 (COVID-19), caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is now spread worldwide.<sup>1,2</sup> The disease is characterized by a broad range of clinical characteristics, leading to acute respiratory syndrome.<sup>3,4</sup> As there are not yet authorized selective antiviral drugs for the treatment of COVID-19, the World Health Organization (WHO) recommended reducing the contact between individuals, to prevent virus transmission. Furthermore, COVID-19 has also had many implications on assisted reproductive technology (ART) due to the implementation of rigorous social distancing procedures and the interruption of 'non-essential' medical treatments.

SARS-CoV-2 pandemic became a global threat, as WHO confirmed the outbreak of COVID-19 in more than 200 countries. As a result, on August 20, 2021, 209,876,613 COVID-19 infected cases with 4,400,284 deaths were reported all over the world.<sup>5</sup>

SARS-CoV-2 pandemic is a global health concern that will have devastating impacts on couples' family planning. On December 7th, 2020, 44,183 pregnant people with COVID-19 were reported in the United States, with 57 total deaths.<sup>6</sup> Although pregnant women do not have a significant risk of getting infected with SARS-CoV-2 compared to non-pregnant women, they have to be monitored for the development of symptoms. In addition, they should follow the recommended protocols to reduce the risk

of virus exposure.

American Academy of Paediatrics reported that children represented only 10,6% of all cases in 49 states. In addition, a systematic review on 936 neonates born from COVID-19 positive women revealed that only 27 neonates had SARS-CoV-2 positive test. In conclusion, the study suggested that possibility of COVID-19 vertical transmission is very low.<sup>7</sup>

However, hospitals and clinics' services, especially fertility centers, raise concerns about the SARS-CoV-2.<sup>8</sup> In many countries, health authorities have limited most non-urgent infertility procedures and have put them on hold to avoid possible complications such as vertical transmissions and virus contaminations. In addition, there are currently limited published scientific reports about the effects of COVID-19 infection on fertility.<sup>9</sup>

General ART protocols for patients and staff may vary depending on specific conditions. This review tried to provide some rules to ensure their safety against the disease during the pandemic. Furthermore, we focused on the effects of COVID-19 on infertile couples and the guidelines that they should follow to reduce the risk of virus exposure.

## Methods

In this review, we summarized clinical health guidelines for reproductive and infertility centers to improve quality management in assisted reproductive technology and minimize the potentially harmful consequences of COVID-19 on pregnancy and fertility.

### *Search Plan*

The authors Searched in PubMed, Scopus, and Web of Science, using the keywords "COVID-19", "2019-nCoV", "2019 novel coronavirus", "SARS-CoV-2", ART or "assisted reproductive technology", or "infertility" without language or date restrictions. The title and abstract of all articles identified and those describing the use of assisted reproductive technology during the Covid-19 pandemic were finally selected.

## Results

As specified in the literature, protocols consist of five categories, including protocols for couples, protocols for women, protocols for men, labor and delivery, and postpartum and breastfeeding.

## Discussion

### *Protocols for Couples*

Most non-urgent surgeries, diagnostic procedures, and embryo transfers have been suspended in many fertility centers during the COVID-19 pandemic. However, there are two main exceptions. The first

exception is patients with cancer who need to freeze their gametes and the second one is women who have already initiated ovulation-stimulating therapies. The patients in these two groups will be referred to COVID-19 testing centers if they have symptoms of COVID-19 infection.<sup>10</sup>

Based on the American Society for Reproductive Medicine (ASRM) protocols, both fresh and frozen embryo transfers should be postponed for infertile couples who plan a new in vitro fertilization (IVF) transfer. Furthermore, new treatment cycles of intrauterine inseminations (IUIs) and ovulation induction should be suspended. For couples who are currently in-cycle, it is suggested that clinics continue their treatment procedures. Furthermore, all non-urgent surgeries should be suspended for couples with an upcoming scheduled IVF procedure. Except for urgent problems, most in-person appointments for couples should be done remotely through telehealth platforms. Nevertheless, these guidelines can be altered for women in their early 40's as well as couples who are about to start urgent cancer treatments.<sup>11,12</sup>

Based on the European Society of Human Reproduction and Embryology (ESHRE) declarations, once the outbreak of the COVID-19 is decreasing, appropriate steps can be taken to resume all treatments at the infertility centers. It is also recommended that couples who have already initiated their treatments, freeze their embryo or oocyte for later transfer. For urgent cases, including cancer patients, the cryopreservation of sperms, oocytes, embryos, or tissue should be performed. Moreover, as repeated washing steps may lead to an increased risk of viral contamination, the culture and freezing protocols should be minimized. Due to many conflictions regarding the effects of the COVID-19 infection on infertility treatment cycles and reproduction, any procedure currently considered as "very high risk" by ESHRE can be postponed. Patients do not require specific regulatory restrictions for homologous fertility treatments, except for couples with ongoing respiratory symptoms.<sup>13</sup>

According to the Italian health authorities, all donors should be screened for respiratory symptoms and travel history to high-risk places. Any procedure for donors with these criteria should be paused for two weeks. However, the Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) proposed 28 days for these cases. Moreover, couples are advised not to follow fertility tourism at present.<sup>14</sup>

Equipment for personal protection should be available for both patients and healthcare personnel. It is recommended that all patients always wear surgical-grade masks and clothes in clinics, except when under anesthesia. In addition, all staff should use medical masks, face shields, gloves, and gowns

during the reproductive care procedures and activities, including phlebotomy, saline infusion sonogram, hysterosalpingogram, office hysteroscopy, endometrial biopsy, specimen handling (blood, semen, follicular fluid), IV line insertion, airway management, oocyte retrieval, operative hysteroscopy, operative laparoscopy, open reproductive surgery, and post-anesthesia care. Besides, a documented risk mitigation plan must be in place for each protocol.

It is essential to inform couples regarding the unknown effects of COVID-19 on pregnancy, including maternal or fetal risks. Furthermore, patients should receive explanation about the exposure risk at the clinic during treatment. Patients with a known or suspected infection should not enter the clinic. In all steps, frequent hand washing for at least 20 seconds with water and soap or using a sanitizing gel is required.<sup>15</sup>

#### *Protocols for Women*

Pregnant women may be more susceptible to COVID-19 infection due to physiological and immunological changes. However, WHO declared that pregnant and non-pregnant women did not show differences in the clinical outcomes of SARS-CoV-2 infection. Indeed, unlike pregnant women with SARS and MERS, COVID-19 infection in pregnant women does not result in deaths. Furthermore, there is no evidence of vertical transmission to the fetus. According to ESHRE, it is better not to initiate any assisted reproduction treatments for women at the time of COVID-19 pandemic; however, the cryopreservation of tissue, embryos or oocytes should be performed for urgent cases such as oncologic women. In cases of women using IVF and receiving ovarian stimulation, a mild stimulant, Gonadotropin-releasing hormone (GnRH) antagonist control of the LH surge, GnRH agonist triggering, and single embryo transfer or freeze-all are recommended. Since SARS-CoV-2 is not present at the oocytes surface, it is assumed that these cells are unlikely to be infected. However, ESHRE considers any risk too high at present, particularly for new donors.<sup>16</sup>

Pregnant women should be monitored, preferably by telephone or online platforms, regarding symptoms of the COVID-19 infection, especially if they have had recent contact with a COVID-19 positive case. Based on the American College of Obstetricians and Gynecologists (ACOG), pregnant women suspected of having COVID-19 should be prioritized for molecular testing such as PCR by a nasopharyngeal swab. COVID-19 negative pregnant women who have a high risk for placental complications can take aspirin in low doses.<sup>17</sup> Indeed, the current studies demonstrated that the benefits of administration of low-dose aspirin for the prevention of placental problems are more than the potential side effects in COVID-19 positive patients.

For women who are suspected of having positive SARS-CoV-2 test, nifedipine is recommended. Several studies reported that nifedipine commonly used in pregnancy to reduce high blood pressure, may also act as a COVID-19 treatment.<sup>18</sup>

Women without should stay home. However, if they are waiting for results, telecommunications are suggested. Each woman should be contacted the day before admission for cesarean section or labor induction to prevent any unnecessary commute to the hospital before hospitalization.

#### *Protocols for Men*

COVID-19 is more frequent in men. The primary cell receptor of SARS-CoV-2, angiotensin-converting enzyme 2 (ACE2), shows high expression in testicular cells.<sup>19</sup> ACE2 is one of the receptors that plays a crucial role in transmitting the SARS-CoV-2 into the host cells.<sup>20, 21</sup> However, there is little evidence of the existence of the SARS-CoV-2 in the semen of COVID-19 positive men.<sup>22</sup> Currently, it is assumed that the impact of the COVID-19 on male fertility is temporary and like common seasonal flu. A high fever with any reason may temporarily decrease spermiogenesis and fertility. As there are no receptors for the SARS-CoV-2 virus on the sperms, these cells are unlikely to be infected. A study revealed a low risk of sperms infection with SARS-CoV-2 and subsequent transmission to embryos.<sup>23</sup>

However, ESHRE declared that all male donors should be screened for COVID-19 symptoms through phone calls, particularly new donors. Donors from high-risk areas need to be quarantined for two weeks although the JPAC recommends 28 days. The declaration is required only for new donors and not those who had sperm cryopreservation before the COVID-19 pandemic. Furthermore, it is suggested to postpone new treatment cycles, sperm freezing, and non-urgent diagnostic procedures. In emergency cases, patients should utilize telehealth. According to Canadian Fertility and Andrology Society (CFAS), minimizing the number of in-person interactions can reduce virus transmission.<sup>14</sup> For urgent cases such as oncologic patients, the cryopreservation of sperms may be required. So, sterilizing each sperm collection room for every patient is recommended. However, the risk of exposure at the clinic should be considered during treatment.

The potential risk of semen handling is splash and droplet. Hence, patients and staff should wear surgical masks and gloves during sperm retrieval and semen handling. For suspected patients, droplet precautions should be considered. Patients with respiratory symptoms such as cough and sneeze should be isolated during sperm retrieval. Patients movement and transportation outside of the room should be minimized. Patients, who need transportation, should

**Table 1:** Guidelines from Professional Societies for couples, women, men, and breastfeeding.

Protocols for couples, women, and men	
Professional Society	Guidelines
ASRM, ESHRE	Postpone: - Fresh and frozen embryo transfers for in vitro fertilization (IVF) - New treatment cycles of intrauterine inseminations (IUIs) and ovulation induction - Sperm freezing To be continued or under consideration: - Couples who are currently in-cycle of IUIs - Women who are in their early 40's or cancer patients - Homology fertility treatments Recommended: - Appointments using telemedicine platforms
Italian health authorities	- A quarantine period of 14 days (travel from high-risk states)
JPAC	- A quarantine period of 28 days (travel from high-risk states)
ACOG	Recommended: - Diagnostic test with a nasopharyngeal swab for pregnant women
Breastfeeding	
CDC	- Wear a medical mask when near your infant - Wash your hands and breast before and after pumping

wear a surgical mask and gloves. All equipment should be disposable. When shared use of equipment for different patients is inevitable, it should be cleaned or disinfected before use by another patient.<sup>24</sup>

#### *Labor and Delivery*

Clinical protocols of Labor and Delivery (L&D) centers during the COVID-19 pandemic have been optimized to increase the safety of patients and medical staff.

Screening of pregnant women regarding COVID-19 symptoms at their arrival at the L&D centers is necessary. All women with respiratory symptoms, including chest pain, cough, or fever should receive medical masks and gloves. If screen results were positive or pregnant women have had a contact history with a suspected or confirmed case of COVID-19, they should be referred to specific medical care. A special room should be considered for triage and labor of COVID-19-positive women. All COVID-19 positive pregnant women should be in isolation rooms, and all emergency cesarean section (C/S) delivery equipment should be available at their bedside. Also, transferring pregnant women from one center to another and the total number of in-person visits should be limited if possible.<sup>21</sup> Potential patients with COVID-19 awaiting a swab result should be evaluated to determine if rescheduling the labor or cesarean delivery is required.

Regarding asymptomatic women, inductions of labor should not be postponed. All asymptomatic women who had vaginal deliveries should be discharged from the hospital on the first postpartum day or even the same day if possible. Besides, women with, or the first day if they had a low-risk cesarean delivery.

Patients with a maternal hypertensive disorder should be monitored at home. All follow-up visits for assessment of the site of cesarean section (C/S) surgery should be done remotely through telehealth

appointments.<sup>25</sup> The visitor policy of L&D centers has strict restrictions. Indeed, only one visitor is admitted as a support person for the entire period of hospitalization, including doulas.

#### *Postpartum and Breastfeeding*

There is no report of SARS-CoV-2 transmission to the infant through breast milk. However, temporary separation of the infant from the mother with suspected or confirmed COVID-19 should be recommended. Neonatology experts should be present at delivery time, and newborns should be isolated after delivery as soon as possible.<sup>26</sup>

Based on the Centers for Disease Control and Prevention (CDC), breastfeeding mothers who are temporarily separated from their infants should express their milk to maintain their milk production and supply. They must wash their hands and breast before pumping. It is advised that healthy caregivers practice hand hygiene and feed the infant with the expressed breast milk. If mothers are not separated from the newborns, they should wash their hands and put on a mask during each feeding.<sup>27</sup>

#### **Conclusion**

In this review, we discussed the effects of COVID-19 on ART procedures. Table 1 summarizes the primary professional society guidelines for couples, women, men, and breastfeeding.

Currently, few works are reporting the impact of COVID-19 in this field; therefore, the impacts of COVID-19 on reproduction should be further studied. The treatment of infertility can be resumed when infection rates are declining. It is unknown how long the SARS-CoV-2 pandemic will continue; however, hospitals and fertility clinics continue to be committed to a return to their routine patient care as soon as

possible. Therefore, the general recommendations may change depending on individual specific situations. However, both patients and staff should educate themselves regarding COVID-19 to ensure their safety against the disease during the pandemic.

**Conflicts of interest:** None declared.

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