

COVID-19 and ART

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COVID-19 Transmission

COVID-19 Transmission

- SARS-CoV-2 enters host cells by binding to membrane **angiotensin-converting enzyme II (ACE2) receptors**. Therefore, organs containing a large number of cells with ACE2 receptors are susceptible to the infection caused by SARS-CoV-2.
- ACE2 receptor expression in reproductive organs and the contribution of these receptors to sperm function and fertilization have been reported previously. Indeed, there are reports of enriched ACE2 receptor expression in **testicular cells, including spermatogonia, Sertoli and Leydig cells and prostate cells**.
- Although the shedding of some viruses through the seminal fluid has been reported previously, whether SARS-CoV-2 is shed through the seminal fluid remains unclear.

COVID-19 Transmission

- In one recent study involving the semen of 38 positive COVID-19 males, 23 (60.5%) were clinically recovering, and 15 (39.5%) with acute infection, were tested for COVID-19 in their semen; 6 (15.8%) were positive for COVID-19; 4 in the acute stage, and 2 in the recovering group.
- In a systematic review, **only 1 out of 7 studies** found positive SARS-CoV-2 RNA tests in seminal fluid (6 out of 143 total men).
- From this study, it is evident that **the transmission of COVID-19 through the semen is possible**, meaning that extra care needs to be taken while dealing with semen in the lab.

COVID-19 Transmission

- **ACE2 is highly expressed in the ovaries. Human oocytes** from the in vitro fertilization program **expressed the ACE2** at both gene and protein. This means that human oocytes possess the molecular 'machinery' to facilitate SARS-CoV-2 entrance and infection.
- According to various studies, especially in animal models, **different viruses can infect oocytes**, so infection of the oocyte with SARS-Cov-2 cannot be completely ruled out.
- There are two hypothetical ways for a virus (including SARS-CoV-2) to be delivered to human oocyte: **blood-borne transmission or sexual transmission.**

COVID-19 Transmission

- Current evidence **does not support sexual transmission of SARS-CoV-2**. Even though SARS-CoV-2 RNA has been found in semen, infectious **virus has not been isolated** and vaginal fluid has been negative except in a single case that reported RNA with a low viral level.
- According to a recent review on transmission of SARS-CoV-2, similar conclusions are also valid for blood-borne transmission with a little bit more uncertainties. **Findings on the proportion of persons with viral RNA detectable in blood are rather heterogeneous.**

COVID-19 Transmission

- Ataei et al. describe 32 patients who were candidates for IVF, with approved positive COVID-19 PCR tests to evaluate whether the virus is present in the follicular and endocervical fluid or not? In this study, **virus particles were not detected in the follicular and endocervical fluid of the women with positive PCR tests.**
- Rajput et al. analysed follicular fluid from 300 patients. **All samples were negative for SARS-CoV-2 viral RNA.**
- A very recent article **failed to detect viral RNA of SARSCoV-2 in oocytes from women who were positive by PCR.** In this report, viral RNA was undetectable in all 16 oocytes tested from two asymptomatic positive women in a donation program.

COVID-19 Transmission

- **There are no reports of vertical disease transmission** from parents to children concerning the previous SARS outbreak, in 2002-2003, which also uses ACE2 as the main point of entry into cells.
- There is much controversy concerning the vertical transmissions of COVID-19 to infants before birth from an infected mother. In a study involving 9 infants, the authors reported no transmission from mother to child

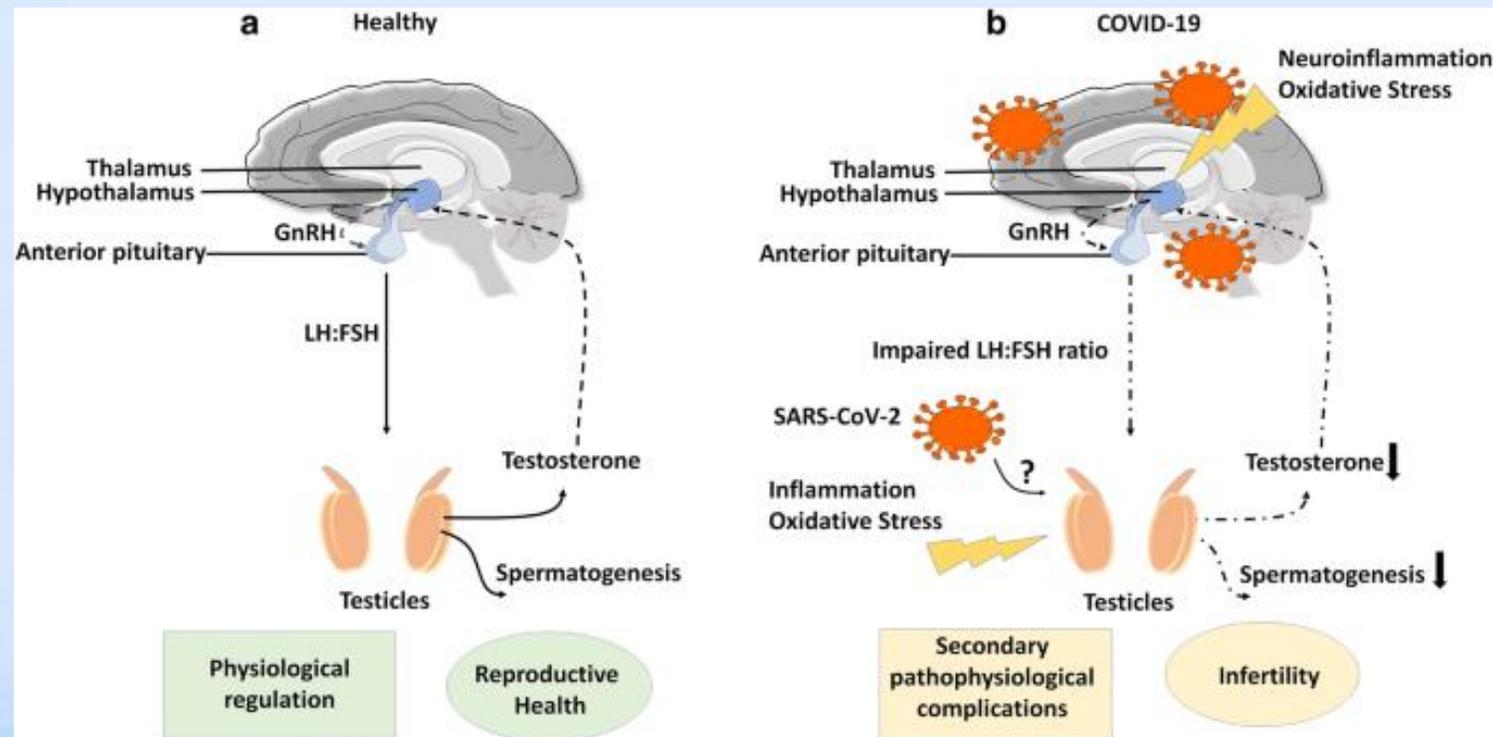
COVID-19 and Fertility

COVID-19 and Male Fertility

- It is unclear whether SARS-CoV-2 has the ability to affect testis tissue, the male urogenital tract and/or accessory glands.
- An association between SARS-CoV-1, another severe acute respiratory syndrome (SARS)-related coronavirus (SARSr-CoV), and **orchitis** was shown in a previous study
- In addition, there is a report of **testicular pathological changes**, including germ cell damage, thickening of the basement membrane of the seminiferous tubules, infiltration of leucocytes and a reduction in the number of spermatozoa in the tubules, in the testes of patients who died because of SARS

COVID-19 and Male Fertility

- Aspects of the viral illness, such as **fever, inflammation, and dysregulation of HPG axis**, may also impair testosterone secretion and sperm production. **Increased oxidative stress**, as may be caused by COVID-19, could reduce sperm motility and **increase sperm DNA fragmentation**.



COVID-19 and Male Hormone

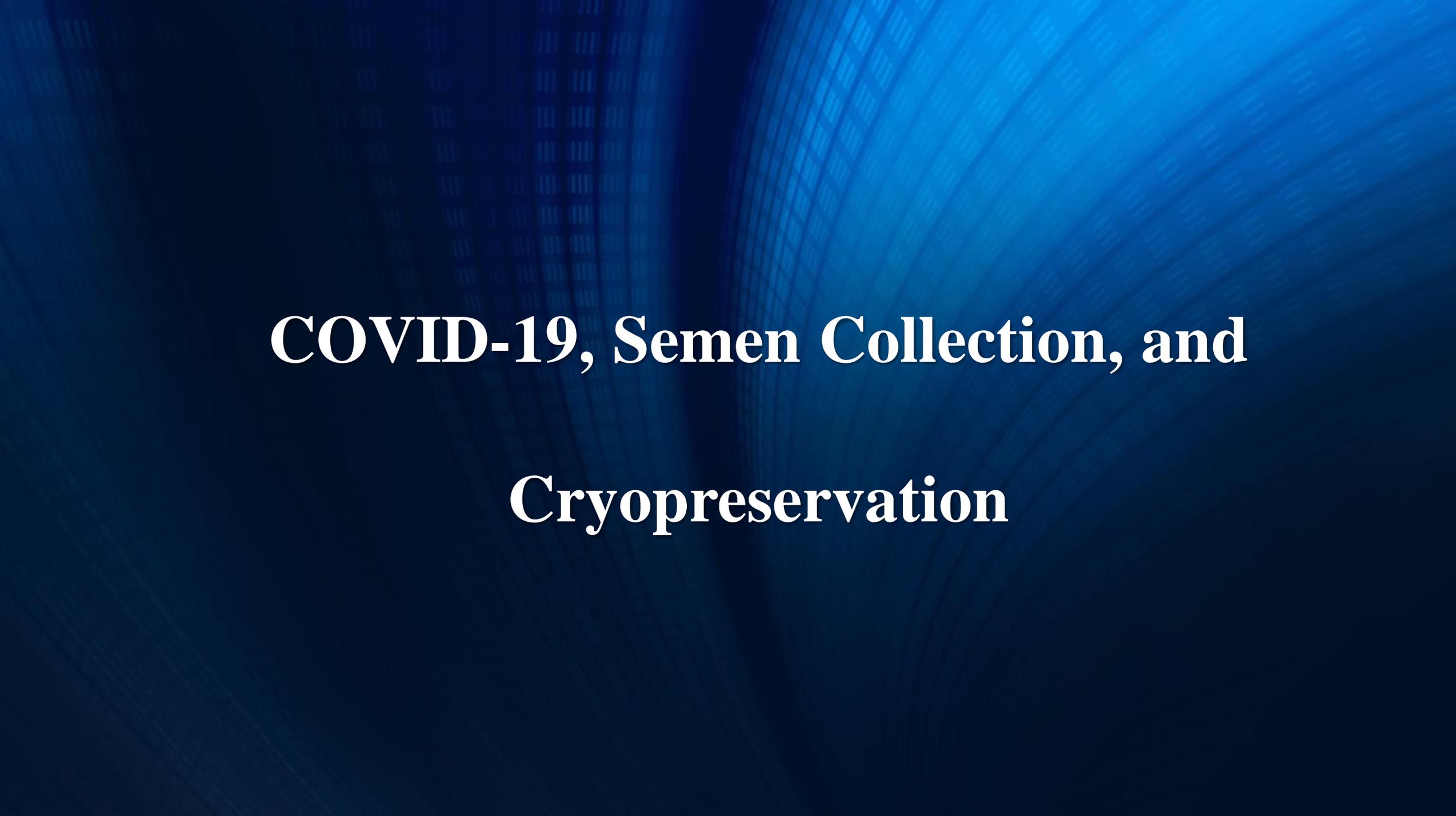
- Ma et al. compared **sex-related hormone levels** between 119 reproductive-aged men with SARS-CoV-2 infection and 273 age-matched controls. Most patients had moderately severe disease. **A higher LH and a lower ratio of T to LH were observed in the COVID-19 group.**
- Rastrelli et al. investigated hormone levels in male patients admitted to the respiratory intensive care unit (ICU) with SARS-CoV-2. Worsening of clinical status was coupled with a progressive **reduction in T levels and increase in LH levels.**
- However, these results should be interpreted with caution, since the **sex hormone baseline** in these patients before infection was not available. Furthermore, **hypogonadism is a common finding in systemic illnesses.**

COVID-19 and Sperm Parameters

- Most studies demonstrated that **sperm concentration and motility decreased significantly** in patients who had recovered from moderate type of COVID-19 infection compared with control subjects.
- In the study of Guo et al. sperm **parameters were reportedly normal in all samples** (n=23), regardless of the severity of the infection in the patients from whom the samples were collected.
- **One possible explanation for the heterogeneous results reported** by these studies could be the differences in when semen samples were collected after the COVID-19 diagnosis. In addition, these studies compared results from COVID-19-patients with those of non-infected men as a control group, and this type of comparison may not be suitable because of the large variability in sperm parameters among individuals.

COVID-19 and Female Fertility

- SARS-CoV-2 may interrupt female fertility by attacking **ovarian tissue and granulosa cells or damaging endometrial epithelial cells.**
- COVID-19, impairing the **immune system might** alter the function of the **hypothalamic-pituitary-gonadal axis.** Sex steroids are potent immune modulators, thus different progesterone and androgen concentrations are likely to influence the immune response and inflammatory outcomes of COVID-19.



**COVID-19, Semen Collection, and
Cryopreservation**

Semen Handling

- On a practical note, in an andrology laboratory, semen collection and cryopreservation are very important and routine procedures. Apart from following good laboratory techniques, andrologists need to **be extra vigilant**.
- Since reports of COVID-19 transmission through the semen, it is necessary to **take proper measures in semen collection. All males should be tested for COVID-19** and only those patients with negative tests should be allowed to continue their fertility treatment.
- One should **avoid freezing raw semen samples**, and high-security cryo-vials should be used for sperm cryopreservation, preferably using the **density gradient wash method**.

Semen Handling

- The **transportation of cryopreserved** samples between centers should be discouraged during this epidemic.
- A possible threat to all cryopreserved samples is the **liquid nitrogen contaminated with COVID-19**, which should be taken care at the time of thawing. Wherever possible, safety **cabinet class II** should be used, as they protect the operator in the handling of the samples.
- Sperm cryopreservation should be considered in a special **vulnerable group of patients**, due to loss of valuable time for their fertility preservation.

Semen Handling

- In the case of semen cryopreservation, a **separate tank should be assigned** for all COVID-19 positive males. If possible, dedicated areas and equipment should be assigned for patients with COVID-19, followed by thorough disinfection after the procedure.
- **Air quality requires special attention**, with proper filtration systems in the Andrology laboratory as well. **Mobile towers** can be used for additional filtration of the air inside the Andrology laboratory.
- **All andrologists should have proper understanding** on how to handle semen samples, and it is the duty of scientific directors/senior staff to properly train all staff members on a different procedure, where possible risks concerning viral transmission are high.

Embryology Laboratory

Embryology Laboratory

- We know that it is routine to discuss different embryological procedures between couples and embryologist; however, one should **avoid in-person counseling for now**; physicians should talk to patients using **tele calling**. It is wise to keep adequate time in-between cases for thorough cleaning.
- **Mini embryologist teams** (one senior and one junior) can be assigned to work in the embryology laboratory in cases of heavy workloads. **One should take extra-care when working with follicular fluids, and avoid spillage**. Embryologists should make sure of **proper lid closing of the follicular fluid** container after oocyte screening, for immediate disposal.

Embryology Laboratory

- **Frozen Embryo Transfer (FET)** can be postponed for women who can postpone their ovarian stimulation.
- Any risk of viral contamination to gametes or embryos in the IVF laboratory is likely to be minimal when **following protocols** of repeated washing, which will result in high dilution of any possible contaminants (if at all).

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Thank You