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Effects of Infection with SARS-CoV-2 on the Male and Female Reproductive Systems: A Review

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Coronavirus Disease-2019 (COVID-19) is a rapidly spreading pandemic that began at the end of 2019. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Reproductive health has always been one of the most important healthcare problems, and the impacts of COVID-19 on the reproductive systems have become an emerging topic. The effects of infection with SARS-CoV-2 on males are more harmful than on females. The outcomes of pregnancy also can show the condition of male and female reproductive system health. The vertical transmission of SARS-CoV-2 significantly affects pregnancy healthy. SARS-CoV-2, antibody, and other factors, such as the decline of lymphocyte counts, and increased erythrocyte sedimentation rate, C-reactive protein, and D-dimer levels, are evidence of SARS-CoV-2 vertical transmission. Angiotensin-converting enzyme 2 (ACE2) is regarded as a virus receptor in the reproductive system. The expression and activity of ACE2 are influenced by sex hormones, especially the male sex hormones. The strength of immunity is crucial to fighting off viral infection. Antibodies against SARS-CoV-2 show different expression in male and female patients, and the antibodies have been regarded as having potential applications in COVID-19 prevention and treatment.

This review aims to present the current status of what is known about the involvement of the male and female reproductive systems, as well as the effects on pregnancy health, during infection with SARS-CoV-2, and discusses the implications for future fertility.

Keywords: **Female • Male • Genitalia, Male • Severe Acute Respiratory Syndrome Coronavirus 2 • Genitalia, Female**

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3022 — — 88

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Background

In December 2019, a novel and contagious pneumonia skyrocketed in China and quickly and alarmingly spread worldwide. On January 30, 2020, the World Health Organization (WHO) declared the Coronavirus Disease 2019 (COVID-19) a Public Health Emergency of International Concern (PHEIC) due to its high contagiousness and mortality [1]. More than 94 million people have been infected and more than 2.0 million people have died of COVID-19 as of January 16, 2021 all around the world, with the numbers still climbing. Furthermore, COVID-19 is considered the deadliest pandemic in over 100 years [2].

The presentations of COVID-19 are classified into mild/general, or severe symptoms. Usually, the patients with mild/general symptoms are either asymptomatic or have fever, cough, fatigue, shortness of breath, and respiratory illness, but this can then develop into severe symptoms like severe acute respiratory syndrome, bronchitis, pneumonia, organ dysfunction, and septic shock if no effective measures are applied [3]. The number of cases with mild and general symptoms is 4 times more than the number of cases of critical disease [4]. In addition, data from the National Health Commission of China showed that mild and general patients accounted for 80% of all COVID-19 cases, among which most had a good prognosis, and the fatality rate was approximately 5.6% [5]. However, the mortality rate for critically ill patients is up to 49% [6].

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a single-stranded RNA virus, is the cause of COVID-19, a respiratory illness. The genetic sequence of SARS-CoV-2, which is ~80% similar to that of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle-East Respiratory Syndrome Coronavirus (MERS-CoV) [7,8], is 26-32 kb in length [9]. The mortality rate of COVID-19 is 10- to 15-fold higher compared to other coronaviruses [4,10,11]. The numerous routes of infection, including direct contact, fomites, aerosol, delivery, and breastfeeding, were thought to be one of the reasons for the higher contagiousness of SARS-CoV-2 [4,12,13]. Multiple systems and organs were reported to be affected by SARS-CoV-2 (eg, respiratory, digestive, cardiovascular, liver, urinary, gastrointestinal, and reproductive systems) [4,10,14,15].

To ensure the health of newborns, it is necessary to discover the impacts of COVID-19 on human reproduction based on the symptoms and mechanisms in the reproductive system.

Due to the sex-specific biological susceptibility and genetics, COVID-19 may differ between males and females in behavioral risk factors, hormonal factors, environment, contagiousness, and mortality. For example, in females, the follicular membrane and granular cells of the ovary can be attacked by SARS-CoV-2, which can affect the quality of oocytes and even lead to female infertility [16]. However, there is no SARS-CoV-2 detected in the female reproductive system [17,18].

Males age 30 to 60 are more susceptible than those who are younger and older. More than 55% of male COVID-19 patients are reproductive-aged (15-49 years old) [19]. Therefore, researchers hypothesized that COVID-19 may have a huge impact on reproductive health. While some obvious clinical symptoms caused by SARS-CoV-2 had been reported, such as scrotal discomfort and orchitis [20], penile pain [21], Leydig cell reduction, inflammation, and hormonal abnormalities [22], no abnormal semen parameters have been found and no SARS-CoV-2 has been detected in the testes of male COVID-19 patients [23].

Like many viruses, SARS-CoV-2 can be transmitted from mother to fetus and then impair the newborns' health. Pregnant women are more likely to have complications and are more susceptible to most viruses because of their increased oxygen consumption, immunologic changes, and physiological adaptations of pregnancy, and the possibility of vertical transmission [24,25]. The transmission of SARS-CoV-2 in pregnant women was found in research on SARS-CoV-2-specific antibody production, infants' inflammation, liver injury, and some abnormal laboratory test results [26-28], but no virus transmission was found in both pregnant women and infants [29]. The vertical transmission of SARS-CoV-2 needs to be investigated further because of the limited information currently available.

Angiotensin-converting enzyme 2 (ACE2) is a trans-membrane zinc metallopeptidase containing a single catalytic domain encoded by a gene located on chromosome X [30]. ACE2 is an entry point for the SARS-CoV-2 envelope [31], as well as SARS-CoV, to infect cells through the binding of viruses to the extracellular domain of ACE2. ACE2 is highly expressed in the ovaries, vagina, placenta, uterus, and endometrial epithelial cells in the secretory phase in women [32,33], and in the testes, Leydig cells, Sertoli cells, and spermatogonia in men [34]. Theoretically, SARS-CoV-2 could be transmitted by sexual and vertical transmission [35,36]. Practically, many studies proved that SARS-CoV-2 indeed could be transmitted through the reproductive system, as shown by evidence of antibody, laboratory tests, inflammation, and liver injury in infants [27,28].

The immunological system is certainly important in COVID-19. Studies showed that SARS-CoV-2-specific antibody develops within 2 to 4 weeks, and that ACE2 occurs at high levels in some cells where IgG is also highly expressed [19,35]. Furthermore, the SARS-CoV-2-specific antibody has been used in the diagnosis and treatment of COVID-19. It is reasonable to believe that immunoreaction if of great significance in COVID-19.Therefore, this review presents the current status of what is known about the involvement of the male and female reproductive systems

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and pregnancy health during infection with SARS-CoV-2 and discusses the implications for future fertility.

SARS-CoV-2 Infection in Females

More than 70% of healthcare and social care workers around the world are women, and these populations are exposed to SARS-CoV-2 and are more susceptible to infection [37]. SARS-CoV-2 can attack the follicular membrane and granular cells of the ovaries and reduce the quality of oocytes, leading to female infertility [16]. However, previous studies indicated no SARS-CoV existed in vaginal fluids, ovaries, or the uterus [38]. SARS-CoV-2 cannot be detected due to the high similarity of the sequence to that of SARS-CoV, but SARS-CoV-2 can be detected in the lower genital tract [39]. Although whether SARS-CoV-2 can be detected in the female reproductive system is unclear, there is no doubt that the chronic inflammation caused by SARS-CoV-2 can pose high risks in the ovaries directly and the hypothalamic-pituitary-ovarian axis, impairing female reproductive structure and function [17,18]. For example, SARS-CoV-2 infection is also related to the menstrual cycle phase [40]. Few studies have reported the influence of COVID-19 on females. Therefore, more and deeper research is needed.

SARS-CoV-2 Infection in Males

Women are more susceptible to SARS-CoV-2 because of their wide exposure to the virus and the high expression of ACE2 in their reproductive system. Surprisingly, many studies have found much higher contagiousness and mortality rates in males than in females (1.5: 1) in the COVID-19 pandemic [3,4,6,41]. The clinic outcomes of SARS and MERS displayed similar results in previous epidemics of coronaviruses [45]. In the SARS pandemic, male patients had various damages in the testes, including abnormal germ cells, decreased spermatozoon, and thickened basement membrane of the testes [43]. The testes are the organ for spermatogenesis and steroidogenesis. Therefore, excellent testicular function is essential for good reproductive outcome. It is important to explore whether SARS-CoV-2 can infect the testes. Similar to SARS-CoV [44], no evidence has been reported that SARS-CoV-2 is found in testicular tissues [45,46]. However, just as orchitis can be presented in SARS patients [43], testicular tissue damages and obvious clinical symptoms have been reported in male COVID-19 patients [47]. The men infected by SARS-CoV-2 exhibited male genitourinary (GU) trauma involving scrotal discomfort and orchitis, chemic priapism, testicular rupture, penile fracture, and penile pain [21], and Leydig cell reduction, inflammation, and edema in the interstitium [46].

Besides the direct damage to the testes, abnormal hormone levels, such as testosterone (T), were detected in COVID-19 patients [22]. The infected male patients expressed hypergonadotropic hypogonadism and low levels of serum testosterone in Italy. Additionally, the disorders of the hypothalamo-hypophyseal axis can also affect the reproductive functions in COVID-19 patients [48]. The impacts of SARS-CoV-2 on hormones are complex and also controversial. Ma showed no significant difference between a COVID-19 group and the controls in the ratio of follicle-stimulating hormone (FSH), estradiol (E_2), and T-E_2. Some studies reported that COVID-19 patients' semen had lower levels of T, higher serum luteinizing hormone (LH), and decreased T-to-LH ratio [22]. The association between the male hormones and COVID-19 may be the next important topic in COVID-19 research. The contagiousness and mortality rate of COVID-19 was higher in males than in females [49]. These differences between males and females in SARS-CoV-2 infection may be explained by hormone changes.

Sperm is the carrier of male genetic material and is one of the important gametes for human reproduction. Thus, it is crucial to understand whether SARS-CoV-2 can be transmitted through the semen. However, the question is still controversial. Only one case reported SARS-CoV-2 was found in semen samples until now [50]. Other researchers did not detect SARS-CoV-2 in semen samples [20,54-56], but seminiferous tubule injury was observed [46,51]. Additionally, abnormal sperm parameters of the total sperm count, total number motile sperm, and sperm concentration were not observed in male COVID-19 patients [23].

Some clinical manifestations such as inflammation, fever, and hypoxia may also influence the male hypothalamic-pituitary-gonadal axis, testis function, and spermatogenesis. Fever is one of the most common presentations in COVID-19 patients, and elevated body temperature is harmful to the testis and then hinders spermatogenesis via multiple mechanisms [53].

SARS-CoV-2 Infection in Pregnancy

In this review, we focus on the effects of infection with SARS-CoV-2 on the male and female reproductive systems, but the outcomes of pregnancy also could show the health condition of male and female reproductive systems and the vertical transmission of SARS-CoV-2 is meaningful for COVID-19 research. Therefore, it is important to understand the effects of COVID-19 on pregnancy and the vertical transmission of SARS-CoV-2.

The incidence of infertility is nearly 20% worldwide [54]. Assisted reproductive technology (ART) has played a crucial role in helping infertile people to conceive successfully. Approximately 0.3% of newborns every year are conceived by ART globally [55]. Pregnancy is achieved through fertilization of the sperm and egg in vitro, and then the fertilized egg is

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transplanted into the mother's uterus. The possible risks of COVID-19 for a pregnant woman should be considered in both natural and ART pregnancy.

Previous data showed that the mortality rates of SARS and H1N1 in pregnant women (25%) were much higher than in non-pregnant women (10%) [56,57].The mortality rate of newborns was approximately 27% in MERS-infected pregnant women [58,59]. The health of fetuses and mothers is the biggest concern for all families. It has not been clear whether COVID-19 is more deleterious to pregnant women than non-pregnant women until now. On the one hand, data are not available showing that SARS-CoV-2 is harmful to pregnant women. There is no difference between the pregnant women with COVID-19 in the third trimester and non-pregnant women with COVID-19 [24,60]. On the other hand, SARS-CoV-2 infection increases maternal and neonatal risk of mortality and morbidity, including the phases of pregnancy, childbirth, breastfeeding [59]. The phases may be critical to the impact of SARS-CoV2 on pregnant women. SARS-CoV2 infection in the first trimester is more severe than at 20 weeks of pregnancy [61]. Apart from the COVID-19 patients with symptoms, many infected pregnant women are asymptomatic, and many asymptomatic carriers ultimately develop symptoms, which increases the threat to both infants and mothers [62].

Many viruses can be transmitted from mothers to infants. In studies, virus existence, antibody production, and some other risk factors were employed to demonstrate whether SARS-CoV-2 can be vertically transmitted.

Vertical Transmission of SARS-CoV-2

Virus as the Evidence of SARS-CoV-2 Vertical Transmission

No sufficient evidence has confirmed the vertical transmission of SARS-CoV and MERS-CoV [56,63,64]. Whether SARS-CoV-2 can be transmitted from mother to child is important for giving birth to a healthy infant through both natural conception and ART, and the conclusion is still unclear [61]. The vertical transmission of SARS-CoV-2 was suggested because SARS-CoV-2 can be detected in blood of infants delivered by infected mothers [29]. In Zeng's research, 3 neonates were found to have intrauterine vertical transmission among 33 patients [65]. Therefore, it is necessary to segregate the newborns from their virus-positive mothers and to avoid breastfeeding, reducing the risk of neonatal infections.

In contrast, other studies failed to provide solid evidence to confirm the vertical transmission of SARS-CoV-2. SARS-CoV-2 was not detected in the amniotic fluid of pregnant women in the early stage of pregnancy [66], or in the newborn's serum and pharyngeal swabs [29]. No evidence is available to show the viruses' existence in the placenta and cord blood of the infected newborn who was observed 36 h after birth [67], suggesting no vertical transmission of COVID-19 [24]. Similar to SARS, SARS-CoV-2 has not been found in breast milk either [68]. The data are in line with some previous reports about SARS-CoV and MERS-CoV [69].

The conflicting conclusions may result from the blood-testes barrier, the time of infection, and the semen samples collection, small size of samples, short period of follow-up, and drug intervention in different studies [70,71]. Further investigations will be helpful to confirm whether SARS-CoV-2 can be vertically transmitted by expanding the sample size and extending follow-up times.

Antibody as the Evidence of SARS-CoV-2 Vertical Transmission

The vertical transmission of SARS-CoV-2 could be identified by testing the antibodies against SARS-CoV-2 in a newborn. IgG can be transmitted via the placenta and be detected in both infants and mothers. Therefore, the detection of IgG alone in infants cannot confirm the possibility of vertical transmission of SARS-CoV-2. The best candidate is IgM, which is produced in utero and cannot be transmitted through the placenta. Many studies reported that IgM antibody was found in newborns born to women with COVID-19 [26-28]. One publication demonstrated that both the SARS-CoV-2 virus and IgG antibody were negative in infected pregnant women's amniotic fluid, but IgM was observed in one of the patient's serum [66]. We must understand that the specificity and sensitivity of IgM testing are much poorer compared to virus testing, and false-positive or false-negative results of IgM may occur [62]. Therefore, the conclusion of virus transmission from mothers to infants based on antibody expression should be made carefully.

Other Risk Factors for SARS-CoV-2 Vertical Transmission

In addition to the direct damage caused by the virus itself, research on many viral epidemics has reported some adverse indicators and symptoms of mothers and babies [72]. The laboratory tests of COVID-19 in pregnant women showed the decline of lymphocyte counts, and the rise of erythrocyte sedimentation rate, C-reactive protein, and D-dimer, which varies from the results of non-pregnant women [67]. According to the WHO recommendation, a higher oxygenation goal is required for pregnant women to ensure the safety of the fetus in the uterus. In China, 8% of pregnant women had severe complications because of hypoxia in the COVID-19 pandemic [73]. Additionally, placental inflammation [74] and liver injury of an infant could be induced by SARS-CoV-2, which directly supports the conclusion that SARS-CoV-2 can be transmitted vertically [27].

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The poor prognosis of pregnancy is mainly attributed to the severe complications [75]. Taking careful and necessary measures to prevent pregnant women from being infected by the SARS-CoV-2 seems particularly important [76,77].

ACE2 is the Receptor by Which SARS-CoV-2 Enters Cells

Structural and functional studies showed that the full-length of ACE2 was required for SARS-CoV-2 to get into target cells [35,36]. ACE2 is enriched in testis, Leydig cell, Sertoli cell, and spermatogonia [35,36,78]. The binding of ACE2 to SARS-CoV-2 is necessary for virus infection, reproduction, and transmission [35], the cell replication cycle in spermatogenesis [78], and the regulation of steroidogenesis [79,80]. Therefore, researchers hypothesized the male reproductive system may be one of the important targets of SARS-CoV-2 [35,36]. Inversely, the expression and activity of ACE2 are influenced by sex hormones [81]. The severity of COVID-19 might be determined by the androgen level, since the androgen receptor plays a key role in innate and adaptive immunity [35,36] and male sex hormones affect the way of the virus enters host cells [81-83]. However, the interaction between SARS-CoV-2 and androgen level needs further investigation.

The Immunity of Male and Female Patients Infected by SARS-CoV-2

Abundant IgG precipitation had been found in the testes of SARS patients [38,43], indicating that the immunological system may play an important role in COVID-19 [43]. The SARS-CoV-2-specific antibody, including IgG and IgM, can be generated nearly 1 week after symptoms occur [84]. IgG peak is presented between 2 and 4 weeks. IgG is also highly expressed in COVID-19 patients' cells [19,35]. SARS-CoV-2 induced testicular damage that resulted from the immunological response rather than the direct influence [85]. Women generally have a stronger immune response, which may why the contagiousness and mortality of SARS-CoV-2 in men are higher than in women [86]. Zeng reported that the IgG antibody against SARS-CoV-2 in the serum is higher and stronger in female patients than in males. However, other studies did not find any difference in IgG expression between male and female COVID-19 patients with mild or with severe symptoms.

The detection of the SARS-CoV-2-specific antibody has been added to the New Coronavirus Pneumonia Prevention and Control Program (7th edition) and has been used in the diagnosis and treatment of SARS-CoV-2 infection in China [28,87,88]. The patients treated with IgG displayed an obvious decrease in virus loading and had alleviated symptoms. Patients lacking SARS-CoV-2 antibodies are more likely to develop severe disease and to die.

Women recovering from COVID-19 have less potential to develop pregnancy complications and risks with ART-assisted conception. Therefore, SARS-CoV-2-specific antibodies, in addition to ACE2, may be another key pathway to suppress SARS-CoV-2 infection.

Conclusions

This review has presented the current status of what is known about the involvement of the male and female reproductive systems as well as pregnancy health during infection with SARS-CoV-2. Although it is difficult to evaluate the effects of stress and anxiety during the ongoing COVID-19 pandemic on fertility, there is now evidence that the SARS-CoV-2 virus has direct effects on spermatogenesis, endometrial, ovarian function, and pregnancy health. At this time, the implications for SARS-CoV-2 infection on human fertility during the global pandemic and as the virus becomes endemic will require further study.

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Conflict of Interest

None.

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