

# A review of severe acute respiratory syndrome coronavirus 2 infection in the reproductive system

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**Abstract:** An outbreak of pneumonia associated with coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred in Wuhan, China, in December 2019, and has been spread worldwide rapidly now. Over 5.3-million confirmed cases and 340,000 disease-associated deaths have been found till May 25, 2020. The potential pathophysiology for SARS-CoV-2 to affect the target is via the receptor, angiotensin-converting enzyme 2 (ACE2). ACE2 can be found in the respiratory, cardiovascular, gastrointestinal tract, urinary tract, and reproductive organs such as human ovaries and Leydig cells in the testis. This receptor plays a dominant role in the fertility function. Considering the crucial roles of testicular cells of the male reproductive system, increasing numbers of studies focus on the effects of SARS-CoV-2 on the testis. In this literature, we reviewed several studies to evaluate the relevance between SARS-CoV-2, ACE receptor, and female and male reproductive system and found that the risk of being attacked by SARS-CoV-2 is higher in males than in females. Since men infected with SARS-CoV-2 virus may have the risk of impaired reproductive performance, such as the orchitis and an elevated of luteinizing hormone (LH), and additionally, SARS-CoV-2 virus may be found in semen, although the latter is still debated, all suggest that we should pay much attention to sexual transmitted disease and male fertility after recovering from COVID-19.

**Keywords:** Female; Fertility; Reproductive health

## 1. INTRODUCTION

The 2019 novel coronavirus (2019-nCoV, also known as severe acute respiratory syndrome (SARS) coronavirus 2 [SARS-CoV-2]) is the virus that causes the pandemic coronavirus disease 2019 (COVID-19, named by the World Health Organization [WHO]).<sup>1</sup> The first virus is identified in Wuhan, Hubei Province, China, in December 2019, and that has spread worldwide now. According to WHO statistics, there have been 7,039,918 confirmed cases and 404,396 deaths globally till June 09, 2020. Confronting the tricky disease, new developments in molecular virology of SARS-CoV-2 help us to understand more about prevention, management, and even further vaccine development. SARS-CoV-2 is an enveloped single-strand RNA virus, and the transmission occurs mainly through the respiratory tract. There are four clinical classifications of severity, including mild (mild

symptoms, and imaging shows no pneumonia), moderate (with fever, respiratory tract symptoms, and imaging shows pneumonia), severe (imaging shows any of the following signs: (1) respiratory distress or (2) the level of arterial partial pressure of oxygen/fractional inspired O<sub>2</sub> concentration lower than 300 mmHg), and critical (imaging shows any of following signs: (1) respiratory failure, (2) shock, or (3) ICU admission due to organ failure).<sup>2</sup> Symptoms of most patients with COVID-19 were cough, fever, and even respiratory failure. People worldwide experienced physical stress, including virus infection, related complications, and mental stress, including panic caused by the public health emergency. All these stresses affected reproductive health. We reviewed literature related to reproductive health and SARS-CoV-2 infection to provide health care.

## 2. HOW CORONAVIRUS ATTACKS THE HUMAN CELLS

The outbreak of pneumonia associated with COVID-19 arouses the public's concern to health. The COVID-19 is caused by SARS-CoV-2. The homology of the amino acid sequence is 76% between SARS-CoV-2 and SARS-CoV, responsible for the global outbreak of SARS in November 2002. This virus affects host cell via the cellular receptor, angiotensin-converting enzyme 2 (ACE2).<sup>3-5</sup> ACE2 was first identified by Li et al<sup>6</sup> as a metallopeptidase from SARS-CoV-permissive Vero-E6 cells in the year 2000, which converts angiotensin I to angiotensin 1-9, angiotensin II to angiotensin 1-7, and provides the binding site for the Spike protein

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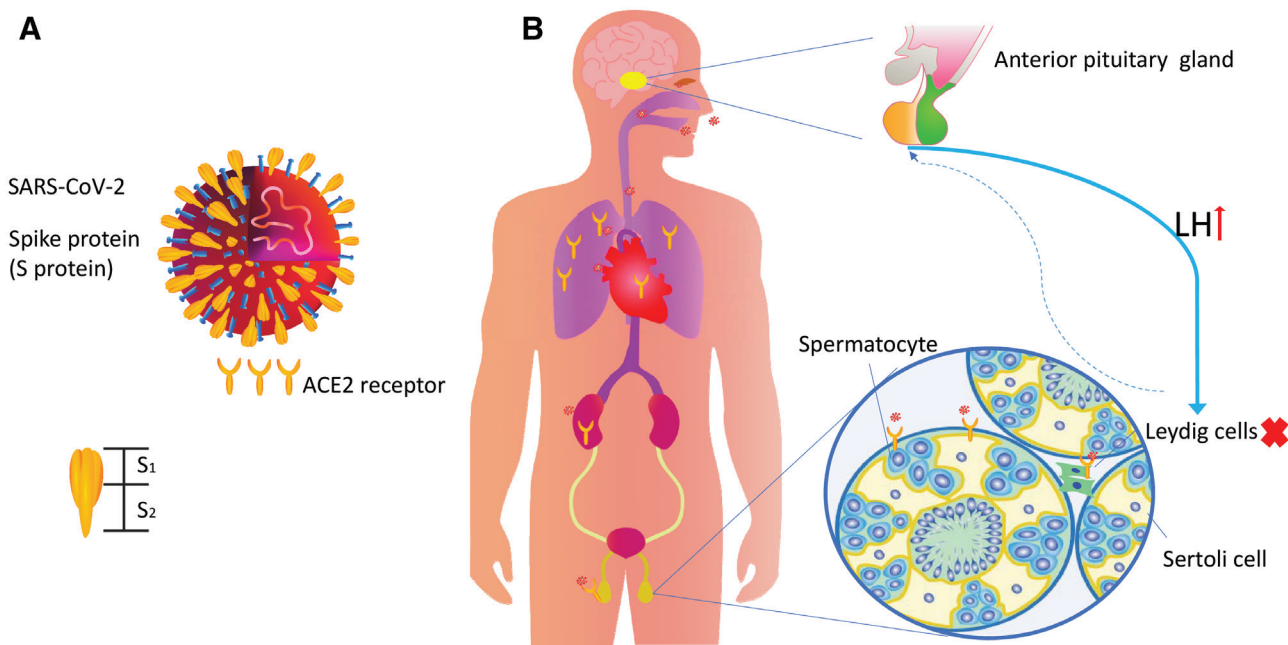
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**Fig. 1** A, The illustration of SARS-CoV-2 and ACE2 receptor. SARS-CoV-2 S protein bind to ACE2 receptor, S1 subunit binds to host cell, and S2 subunit triggers fusion of the viral envelope and target cell. B, The transmission pathway of SARS-CoV-2 and impact of male genital organ infection. Several organs (lung, heart, kidney, ovaries, and testis) and male genital cells (Sertoli cells, Leydig cells, and spermatocytes) with ACE2 receptor could be infected by SARS-CoV-2. Virus attacks cause dysfunction of these organs, such as lung injury, heart failure, kidney injury, and male infertility. The damage of Leydig cells caused by virus infection may result in the increased level of LH from the pituitary gland (dotted line), which could stimulate Leydig cell consequently (solid line). ACE2 = angiotensin-converting enzyme 2; LH = luteinizing hormone; S protein = Spike protein; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

(S protein) of coronavirus. Theoretically, human cells with ACE2 expression are believed to be the target of SARS-CoV-2 infection, which including lung, gastrointestinal tract, kidney, heart, ovaries, and testis.<sup>7,8</sup> ACE also plays a dominant role in fertility, especially ACE2 is related to oocyte maturation, ovulation, and spermatogenesis.<sup>9</sup>

### 3. ACE AND THE FEMALE REPRODUCTIVE SYSTEM

Ovulation abnormality accounts for a major reason for female infertility.<sup>10</sup> Among these anovulation patients, polycystic ovary syndrome is the most common endocrinopathy. The connection between polycystic ovarian syndrome (PCO) and renin-angiotensin system (RAS) was revealed by enhanced RAS activity in PCO.<sup>11,12</sup> Angiotensin 1–7, functions through the G protein-coupled receptor Mas, and ACE2 are present in human ovaries and related to ovarian functions such as steroidogenesis, follicular development, granulosa-lutein cell apoptosis, oocyte maturation, and ovulation.<sup>13–16</sup> In addition, ACE2 can be found in the epithelial cell of the endometrium.<sup>17</sup> Although these studies suggested, there are imaginative ways for SARS-CoV-2 to attack female fertility, no known damage to the reproductive system to the female COVID-19 patient reported. The potential risk of COVID-19 infection in female fertility should be assured further.

### 4. ACE AND MALE REPRODUCTIVE SYSTEM

Like the female reproductive system, we can detect angiotensin 1–7, Mas, and ACE2 in the testis. Reis et al<sup>18</sup> found that the lower level of ACE2 is related to severe spermatogenesis impairment. Wang and Xu<sup>19</sup> investigated the ACE2 expression via a single-cell RNA sequence and found that ACE2 is abundant in spermatogonia, Leydig, and Sertoli cells. Shen et al<sup>20</sup> found a similar result, they detect mRNA expression of ACE2,

and the result showed that both germ and somatic are enriched with ACE2 expression. The aforementioned findings are especially important in Sertoli cells, because these interstitial cells are responsible for androgen biosynthesis and play an essential role in the testicular microenvironment. Age is related to the ACE2 expression in the testicular cells. The highest expression of ACE2 occurs at the age of the 30-year-old group (2.84%) and the lowest rate recorded in patients aged 60-year-old group.<sup>20</sup>

Furthermore, another study showed that orchitis was defined as a complication of SARS patients by examination of autopsy specimens of the testis from six patients who died of SARS.<sup>21</sup> Figure 1 demonstrates the interaction between SARS-CoV-2 and ACE2 receptor in men who have been infected by SARS-CoV-2 virus. These findings imply that the male reproductive system could be affected by SARS-CoV-2 infection. The pathological mechanism of SARS-CoV-2 is considered as direct cell infection, thus cause cell damage. As mentioned before, ACE2 receptors provide the virus to enter host cells and complete its replication cycle. These cells with a higher rate of ACE2 mRNA expression stand the higher risk of being infected by the SARS-CoV-2 and concern of male infertility, including spermatogenesis, which worsens the male gamete to survive.

Furthermore, SARS-CoV-2 may cause severe damage to the testicular of a young male in their reproductive age than older patients. Since body temperature is crucial to germ cell development; therefore, testicular temperature changes, along with persistent high fever may cause germ cell degeneration and destruction. Xu et al<sup>22</sup> reported that meiotic germ cell apoptosis is related to high temperature. Fever is one of the common symptoms in SARS-CoV-2 and might have an indirect effect on testicular malfunction.

Whether the SARS-CoV-2 can be transmitted by semen or not is not clearly defined. Pan et al<sup>23</sup> analyzed 34 semen samples from male patients diagnosed and recovering from COVID-19. No SARS-CoV-2 were detected in the study samples.<sup>23</sup>

However, this study did not perform semen analyses; only three semen samples (8.82%) provided during the acute stage of SARS-CoV-2 infection. Also, the severity of men recruited in this study was categorized in the mild group. Thus, the study result cannot rule out the virus exists in the seminal fluid, especially during the acute infection or with severe symptoms.<sup>23</sup> Li and coworkers detected SARS-CoV-2 for 38 patients, including acute stages of infection, 23 recovering stages.<sup>6</sup> The positive detection rate was 26.7% (4 of 15) and 8.7% (2 of 23). However, the results of these two studies are the opposite, and both studies were limited by sample size. Thus, we cannot obtain the conclusion that SARS-CoV-2 can be transmitted sexually.

Further research is needed to learn about SARS-CoV-2 and male fertility. Indeed, the people who have a active SARS-CoV-2 infection may impair their daily activities, including sexual and social activities. Moreover, this may be the difficulty of collecting related specimens for analysis.

One study showed the significantly increased serum luteinizing hormone (LH), dramatically decreased in the ratio of testosterone to LH and follicle-stimulating hormone (FSH) to LH in males with COVID-19,<sup>24</sup> which raised the question that "Is COVID-19 is associated with negative impact on male fertility?".<sup>25</sup> One of the Leydig cell's significant products is the sex hormone (testosterone, androstenedione, and dehydroepiandrosterone); also, LH from the pituitary gland is responsible for the stimulation of Leydig cell. It is suggested that Leydig cell, which is enriched with ACE2 expression, may cause malfunction caused by SARS-CoV-2 infection.

In conclusion, the pandemic of COVID-19 is spreading all over the world. Based on the limited data, the possibility of testicular damage and possibly subsequent impairment of daily activities in human beings still have an uncertain influence on the male and female fertility, including the performance and pregnancy status after SARS-CoV-2 infection.<sup>26,27</sup> We should pay attention to reproductive health, especially in male patients, under the potential risk of SARS-CoV-2 infection. The relevance between SARS-CoV-2 infection and fertility function needs further warranted.

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