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Impact of COVID-19 Disease on Male Infertility Patients: Literature Review

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ABSTRACT

COVID-19, the virus behind the COVID-19 pandemic, affects multiple organs, including the respiratory tract, liver, kidneys, heart, gastrointestinal tract, and the male reproductive system. The male reproductive tract expresses the angiotensin-converting enzyme II (ACE-2), the primary viral entry receptor, in spermatogonia, Leydig, and Sertoli cells. While viral infections can damage male fertility via cytokine storms, the effects of COVID-19 on male fertility are still unclear. Therapeutic methods to prevent and treat COVID-19 patients must consider the possibility of multiorgan dysfunction. While male patients may have infertility, there is little information available about how to treat them. Various microbes, including bacteria and viruses, can harm the male reproductive function. This review aims to investigate the possibility of infertility or diminished fertility in COVID-19 patients and the pathogenic mechanisms that may be causing infertility during and after recovery from COVID-19. This review produced the impact of COVID-19 on male reproductive health involving multiple mechanisms, including viral entry via ACE2 receptors, testicular inflammation, hormonal changes, and disruptions in RAS signaling. However, long COVID-19 does not include long-term detrimental consequences on male fertility potential since the observed alterations were reversible after 1-2 spermatogenesis cycles.

Keywords: ACE2, COVID-19, Leydig and Sertoli cells, sex hormone, Seminal fluid, TMPRSS2.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19), which has symptoms ranging from mild to severe, is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-COV-2). Coronaviruses are most common in humans, accounting for 15%–30% of respiratory tract infections per year, as designated by the World Health Organization (WHO). It was first discovered in Wuhan, China, in December 2019. The COVID-19 pandemic significantly impacted healthcare systems worldwide, affecting not only infected individuals with the virus but also the delivery of care for all patients. Many non-COVID medical services have been delayed or reduced, leading to delays in treatment for chronic conditions, elective surgeries, and preventive care (Silvia *et al*., 2023). Around 71 million people were infected globally, with over 1.5 million dead and more than 15 million people infected, with 300,000 in the United States alone infected. Many deaths have been confirmed due to complications arising from the disease. COVID-19 has a bat-origin CoV as a genetic trait. It has 79.5% identical sequences to SARS-CoV. Patients with COVID-19 have symptoms including fever, dyspnea, asthenia, anosmia, fatigue, and dry cough. Studies on complications from coronavirus infection have shown that it is a multisystemic disease (Kumar *et al*., 2023).

In the past, SARS-CoV, the H1N1 influenza virus, and Middle East respiratory syndrome CoV (MERS-CoV) have all been responsible for global viral epidemics (Matoba *et al*. 2015). Human Coronaviridae virus with a single-stranded RNA genome that is not segmented and has a large positive-sense genome (Li *et al*. 2020a). Unlike

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SARS-CoV and MERS-CoV, COVID-19 is more virulent (Naicker *et al*. 2020). Direct contact, drips, or excrement are all ways for this virus to spread from person to person. Because of immunocompromised patients and/or incubation periods of 1–14 days (about 3–7 days) in infected individuals, the risk of silent spread is higher than in other viruses (Adhikari *et al*., 2020; McMichael, 2020). Within a week of the start of the illness, dyspnea, hypoxemia, and acute respiratory distress syndrome (ARDS) develop (Chen *et al*. 2020b). COVID-19 mortality is thought to be related to ARDS and multi-organ failure, like liver, kidney, heart, and intestinal problems and death, as well as cancer progression and advanced age (more than 50 years), which are major risk factors for a dismal prognosis (El Zowalaty and Järhult, 2020; Zhou *et al*., 2020; Zsichla and Muller, 2023). The other concern is that infection can affect the reproductive system, increasing the chance of infertility in infected people (Ma *et al*., 2020; Dutta & Sengupta, 2021). Multiple and complex causes and pathological agents are involved in infertility; viruses might play a vital role in this process, interfering with male reproductive functions (Hezavehei *et al*., 2021). COVID-19 affects both males and females, although it can affect males with more severity and a higher mortality rate (Cui *et al*., 2020; Araújo *et al*., 2024). The male reproductive system and semen parameters are not well understood and still challenge the medical scientific community. This review aims to investigate the effects of COVID-19 infection on sperm quality, sex hormone levels, and the male reproductive system during and after recovery from COVID-19.

1. Viruses' Impact on Infertility

Many viruses can cause the retrodictive system testis and orchitis and, in rare cases, cause male infertility. The inflammation of the testis and epididymis caused by the Zika virus (ZIKV) was discovered in the sperm of symptomatic males, and it is sexually transmitted in a mouse model that produces testicular dysfunction and male infertility (Yang *et al*., 2020). Orchitis is a common side effect of the mumps virus (MuV), which has a high testicular tropism. Human immunodeficiency virus (HIV) was found in sperm shortly after infection and throughout the infection, resulting in severe orchitis and male infertility. Both the hepatitis B virus (HBV) and the hepatitis C virus (HCV) can infect the human male germline. The transcription of the HBV gene in human sperm cells was regulated by host genes (Zhang *et al*., 2020), and HCV infection has mutagenic effects on sperm chromosome abnormality and has serious hereditary consequences owing to genetic alterations. Human papillomavirus (HPV) was found in the testis, epididymis, ductus deferens, and semen. Finally, cytomegalovirus (CMV) and herpes simplex virus (HSV) were discovered in human sperm in the ejaculate and were associated with sperm motility and morphology but did not influence male reproductive health (Lippold *et al*., 2019).

Understanding the short- and long-term effects of COVID-19 on male reproductive function requires a fundamental understanding of viral infection physiology. Mumps, HIV, and Zika virus influence male reproductive health and were used to frame the conversation about SARS-CoV-2's impact on male reproduction. Post-pubertal males with mumps have unilateral epididymitis-orchitis in about 20%–30% of cases. In 15% of instances, bilateral orchitis develops, resulting in testicular shrinkage, lower sperm concentration and motility, and potentially azoospermia and accompanying complications and subsequent impact on Leydig and Sertoli cell function. After infection, HIV may be found in the sperm, and sexual transmission is the most common way for it to spread (Martinez et al., 2023). Circumcision appears to prevent HIV transmission in heterosexual couples, according to large randomized studies. In sperm, HIV is transmitted mostly via leukocytes (Walls *et al*., 2020). Opportunistic infections and elevated cancer risk are hallmarks of the progression to acquired immunodeficiency syndrome (AIDS). Chronic orchitis and hypogonadism are common in male AIDS patients. HIV has been discovered in testicular germ cells. Inflammation,

reduced testosterone generation by Leydig cells, and HIV infection of testicular germ cells are all factors that can influence male reproductive and endocrine function. Zika virus has been found in sperm and can be transferred sexually. In males infected with Zika, viral levels in the sperm are frequently significantly greater than in the serum and can last up to 188 days in the sperm, whereas the virus is eliminated from the serum after the first symptoms fade (Lu *et al*., 2020). Given the Zika virus's recent introduction, information on the virus's long-term effects on human male reproductive and endocrine function is scarce. Mumps, HIV, and the Zika virus are among the viruses that can cause orchitis and have been found in the sperm (OurWorldinData, 2023).

Male fertility is harmed by Zika (ZIKV), mumps (MuV), and SARS-CoV-1 virus infections, while the picture of COVID-19 is less apparent (Chen *et al*., 2020; Huang *et al*., 2020). Long-term observation and study will be required to have a better knowledge of infection and pathogenesis mechanisms. COVID-19 might infect the seminal vesicles and prostate gland, which provide seminal fluid to the sperm. COVID-19 might infect the male reproductive organs and endanger male fertility, which contributes seminal fluid to the semen (Fan *et al*. 2020). COVID-19 patients have been observed to have decreased spermatogenesis and lower sperm quality parameters (Li *et al*. 2020; Ruan *et al*. 2021). According to Hajizadeh and Tartibian (2021), these abnormalities occurred over time and were correlated with significant impairments in sperm parameters like morphology, concentration, semen volume, progressive motility, and spermatozoa quantity.

2. Coronaviruses: Structure and Pathogenic Mechanism

Coronaviruses are the most prominent positive-stranded RNA virus family, with 30 members now (Zhao *et al*., 2020). Coronavirus (CoV) is an enveloped positive-sense RNA virus with unique glycoprotein spikes that give it a crown-like appearance when seen under an electron microscope (Pal *et al*., 2020). It's divided into four major genera: Alphacoronavirus (αCoV), Betacoronavirus (β-CoV), Gammacoronavirus (γ-CoV), and Deltacoronavirus (δCoV) based on its genes. These four genera are the primary groupings of viruses that cause respiratory and gastrointestinal diseases. The αCoV and β-CoV may both infect mammals; however, γ-CoV and δCoV mostly infect birds (Madabhavi *et al*., 2020). This genome includes spike (S) glycoprotein, matrix (M), envelope (E), and nucleocapsid (N) proteins (Guo *et al*., 2020). COVID-19 has a bat origin of CoV as a genetic trait. It has 79.5% identical sequences to SARS-CoV. Angiotensin-converting enzyme II (ACE2) is bound by the virus and enters host cells using its surface spike (S) protein (Fan *et al*. 2020). It also uses cellular serine protease. Transmembrane protease, serine 2 (TMPRSS2), allowing the initiation of viral protein S. The COVID-19 virus enters the body via binding to ACE2 expressed on target host cells and attaches to this receptor, similarly to SARS-CoV-1, to facilitate endocytosis and cellular infection (Akhigbe *et al*., 2020). The angiotensin II (Ang II) and Ang (1-7) hormones have opposing effects. Whereas Ang II is pro-inflammatory, profibrotic, and proapoptotic with tissue remodeling properties, Ang-(1-7) is anti-inflammatory and anti-fibrotic.

In other words, ACE1 and ACE2 counteract each other, and their roles are essential in balancing the renin-angiotensin system (RAS). Infection with COVID-19 causes reduced ACE2 activity and downregulation (Gkogkou *et al*. 2020, Zhou *et al*. 2020b). Both ACE2 and TMPRSS2 have appeared to be strongly expressed not only in the lungs, kidneys, intestines, and heart tissues, but also in the spermatogonia, Leydig, and Sertoli cells in the human testes, as well as other male reproductive organs such as the prostate gland (Maya & Carvajal 2020, Raouf *et al*., 2020).

SARS-CoV-2 uses MAS receptors that are present in the lung, in the testicles, and in Leydig and Sertoli cells. The first hypothesis is that the virus could enter the testicle and lead to alterations in testicular functionality. A second

hypothesis is that the binding of the virus to the ACE2 receptor could cause an excess of ACE2 and give rise to a typical inflammatory response. The inflammatory cells could interfere with the function of Leydig and Sertoli cells. Both hypotheses should be evaluated and confirmed to possibly monitor fertility in patients with COVID-19 (Illiano *et al*., 2020). COVID-19 employs the angiotensin-converting enzyme 2 (ACE2) receptors in the RAS for viral entry. The ACE2 receptor is present in the reproductive system, and reports of multi-organ involvement have led to uncertainty regarding COVID-19's effects on the reproductive system and fertility (Younis *et al*., 2020).

The renin-angiotensin-aldosterone system (RAAS) relies on ACE2 (Klein *et al*., 2020). Renin breaks down angiotensinogen (Ang) I, which ACE then converts to Ang II. Ang II causes smooth muscle contraction in the bronchi, pulmonary fibroblast growth, alveolar epithelial cell apoptosis, and pulmonary vascular permeability. ACE2, on the other hand, is an angiotensin II-degrading enzyme that produces angiotensin (Guan *et al*., 2019; Mo *et al*., 2020), which has hypotension, hypertension, and renal effects (La Vignera *et al*., 2020; Ardestani and Arab, 2021). Furthermore, in the intestines, ACE2 assists in the digestion of neutral amino acids.

3. COVID-19 and Male Infertility

COVID-19 may cause inflammation in approximately 5%–10% of men of reproductive age and, rarely, even infection of the testes. Such orchitis is highly correlated with the severity of the disease and age. Several studies have indicated that COVID-19 may impair the testes and quality of sperm and sex hormones (Patel and Hsieh, 2022). Infertility is a reproductive system disorder affecting up to 15% of reproductive-age couples worldwide. Male-related dysfunctions account for 40 to 50% of all cases of infertility. Viruses cause infections of the male reproductive system. Infectious and inflammatory illnesses of the reproductive system can induce male infertility. Viral infections that directly affect spermatozoa can harm male fertility by causing sperm mortality, lowering sperm count, and decreasing motility by releasing inflammatory cytokines. Infections can also affect sperm production and genital organ function indirectly (Aitken, 2021).

Studies also showed that coronavirus infection results in orchitis and epididymitis inflammation, causing male sexual dysfunction and infertility. Infection can lead to morphological and functional changes in semen parameters and impaired fertility. Testicle injuries caused by the virus could cause circulatory changes, a decrease in sperm-producing cells, and hormonal changes (Tian & Zhou, 2021). It is important to consider that sperm quality in semen is crucial to successful reproduction. Males may experience reduced sperm viability, sperm counts, and sperm motility because of direct testicular infection, primarily due to effects on the testicles (Pal *et al*., 2020). Viruses usually enter the testes via hematogenous dissemination. The testicular immune privilege protects testicular germ cells from the host's inflammatory reaction to systemic infection in normal conditions. Certain viruses, on the other hand, can pass the blood-testis barrier and even infect testicular cells, triggering an immune response in the testis (Li *et al*., 2020).

The SARS virus causes orchitis, testis damage, and spermatogenesis issues, and high temperatures might be one cause of testis damage in SARS patients. Temperatures below 37°C are essential for germ cell growth. Long-term fever may be harmful to spermatogenesis and increase oxidative stress (Tur-Kaspa *et al*., 2021; Dutta and Sengupta, 2021).

1. Testis Orchitis

The presence of COVID-19 spike protein and viral nucleic acid in testicular samples from COVID-19 patients suggests that the virus may have an impact on spermatogenesis. Heat-induced testicular cell degeneration has been linked to apoptosis, which has been hypothesized as a plausible mechanism. Although high fever is known to have a role in viral orchitis, SARS likely

has an influence on testicular function in ways other than temperature. Demonstrated fibrosis and congestion in the testes of non-SARS-infected people who had a long-term high fever but no signs of germ cell loss or leukocyte infiltration (Giugliano *et al*., 2023).

Many viruses, like the mumps virus, human immunodeficiency virus (HIV), and SARS-CoV, have previously been discovered to infect testes (Zadeh and Arab, 2021). It is possible that the new SARS-CoV-2, which has 76% amino acid sequence similarity with the original SARS-CoV, can infect the testes, presenting a case of orchid-epididymitis associated with SARS-CoV-2 infection (Lu *et al*., 2020). SARS-CoV patients also demonstrated orchitis and testicular injury, including lower germ cell counts and apoptotic death with interstitial leukocyte infiltration, as well as decreased germ cell counts and apoptotic death. Histopathologically, inflammatory infiltrates and immunoglobulin G (IgG) accumulation were seen mostly in the seminiferous epithelium, interstitium, degenerated germ cells, and Sertoli cells (Li *et al*., 2020). Males who recovered from SARS-CoV-2 infection had scrotal discomfort (Pan *et al*. 2020). Furthermore, fibrin microthrombi orchitis was found in two of the testes tested in a study of severe COVID-19 cases in Brazil (Walls *et al*., 2020). Significant seminiferous cellular damage reduced Leydig cell counts, and moderate lymphocytic inflammation was found in the postmortem examinations of 12 COVID-19 male patients in China. Given the association between COVID-19 and coagulation disorders, one study proposed that orchitis was caused by vasculitis and that segmental vascularization of the testes might create an orchitis-like syndrome. According to the findings, SARS-CoV-2 infection can cause testicular ultrastructural lesions and orchitis in severely infected males (Bani *et al*., 2023).

2. Disruption and Hormonal Imbalance

In postmortem samples collected from SARS patients, changes in various pituitary cell types were discovered, showing endocrine dysfunction in these individuals, which might be connected to spermatogenesis issues (Borges *et al*., 2021). COVID-19 infection has been associated with alterations in hormonal profiles, including decreased testosterone levels and impaired spermatogenesis. Severe COVID-19 cases exhibit a dysregulated immune response characterized by cytokine storms, which may lead to testicular damage via inflammatory pathways. These disruptions can lead to temporary or permanent hormonal imbalances, potentially impacting fertility in male COVID-19 patients. Healthcare providers need to consider these potential reproductive implications when managing and treating individuals with COVID-19 infection.

The association between SARS and testicular damage in other types of viral orchitis may be due to endocrine disruption. The viruses themselves may have an impact on pituitary function. Hypogonadism has been attributed to low LH and FSH levels rather than intrinsic testicular failure in HIV-positive people because of hypothalamic-pituitary-gonadal axis dysfunction (Tur-Kaspa *et al*., 2021). HIV has been found in pituitary cells, which might explain the harm to the hypothalamus and pituitary gland. Hypogonadism has been discovered in HCV-infected men. Systemic inflammation associated with hypothalamic-pituitary-gonadal axis suppression cannot be ruled out as a cause (Brown, 2019). Hemorrhagic fever virus (HFV) and herpes simplex virus (HSV) are both known to influence the pituitary-gonadal axis. Serum luteinizing hormone (LH) levels have recently been revealed to be higher. The ratios of testosterone/LH and follicle-stimulating hormone (FSH)/LH were dramatically reduced in many male COVID-19 patients with moderate-to-severe COVID-19.

3. Immune Dysregulation and Testicular Damage

Severe COVID-19 cases exhibit a dysregulated immune response characterized by cytokine storms, which may lead to testicular damage via inflammatory pathways. Elevated levels of pro-inflammatory cytokines have been detected in the semen of COVID-19 patients, indicating systemic inflammation with potential repercussions for

male reproductive function (Rastrelli *et al*., 2021). Testicular immune privilege provides a degree of immune protection unique to the testis, and the blood-testis barrier, special immunomodulatory molecules, and lack of MHC expression by germ cells facilitate it. The immune response in the lungs and other infected tissues is characterized by an uncontrolled cytokine release, leading to a cytokine storm, and an overall increase in anti-inflammatory cytokines. Like the lung, severe cases of COVID-19 may elicit a cytokine storm in the testis. This event is speculated to be a mechanism of tissue injury and damage to germ cells, potentially the cause of subsequent subfertility among survivors of severe disease.

According to the results of another molecular and morphological investigation, an autopsy of six males with COVID-19 demonstrated significant spermatogenesis damage in these patients when compared to controls. In addition to the identification of viral RNA and particles, TMPRSS2 and ACE2 were assessed. Furthermore, histological examinations indicated the existence of many leukocytes (CD68 macrophages, CD3 T-cells, CD20 B-cells, CD38 plasma cells, and HLA-DR myeloid cells) (Marthasari *et al*. 2023).

4. Medications and Treatments:

The presence of COVID-19 in semen is controversial, but impaired semen quality has been found in males with moderate coronavirus disease 2019 infection)Lee *et al*., 2021). The increased evidence of orchitis and hormonal changes seen in male coronavirus disease 2019 infection may lead to infertility. Male reproductive system cells, such as spermatogonia and testicular Leydig and Sertoli cells, express ACE2. It has been speculated that COVID-19 might impair testicular histology, causing morphological and functional changes in these cells. While conflicting evidence exists regarding ACE2 expression in the testes, viral particles have been detected in testicular biopsies of COVID-19 patients, suggesting possible testicular tropism. Sperm and oocytes are unlikely to be susceptible to infection by COVID-19. Some medications used to manage COVID-19 symptoms may have implications for male fertility.

Healthcare providers need to consider these factors when treating patients with COVID-19. It is crucial for individuals, especially those trying to conceive, to discuss any concerns about male fertility and COVID-19 with healthcare providers. Research is ongoing to better understand the potential impact of the virus on male reproductive health. In the meantime, following public health guidelines, maintaining overall health, and seeking medical advice when needed are essential steps in protecting both general health and fertility (Salonia *et al*., 2021; Wang *et al*., 2023; Yuanita et al, 2025).

Semen Quality and Reproductive Outcomes: Assessment of semen parameters in COVID-19 patients has revealed variable effects on sperm quality, including decreased sperm concentration, motility, and morphology. The implications of these changes for male fertility and reproductive outcomes require further investigation.

Long-term Implications and ART Considerations: Emerging evidence suggests potential long-term consequences of COVID-19 infection on male fertility, raising questions about the safety of ART procedures **(**Rastrelli *et al*., 2021; Mumtazet al., 2025).

Impact on Assisted Reproductive Technologies: The COVID-19 pandemic has significantly impacted assisted reproductive technologies (ART), including in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). Challenges related to patient management, laboratory protocols, and gamete and embryo storage safety have emerged. Strategies to mitigate the risks of COVID-19 transmission in ART settings while ensuring continuity of care are essential considerations for reproductive medicine specialists (Silvia *et al*., 2023; Khdair et al., 2025).

DISCUSSION

This review explores how COVID-19 could impact male reproductive health, including viral entry via ACE2

receptors, orchitis, hormonal changes, and sperm parameter deficiency. COVID-19 and ACE receptors in spermatogenesis demonstrated and established infection in host cells. The male reproductive tract may be directly vulnerable to coronavirus invasion via virus binding to the enzyme present in testicular cells, leading to reduced spermatogenesis and fertility problems and a better understanding of COVID-19-associated sequelae, fundamental for semen collection in assisted reproduction. The virus may indirectly affect gametes and embryos. Management strategies during COVID-19 illness and post-recovery monitoring are crucial.

The review indicates that COVID-19 can cause testicular inflammation, known as orchitis, leading to severe testicular damage due to inflammation and oxidative stress, as observed in mortality cases. This inflammation can contribute to a decrease in semen quality and fertility potential (**s**perm quality, motility, morphology, concentration, and volume were significantly affected by COVID-19, and the inflammatory response could explain the observed changes). COVID-19. The limitations of the practical study need to be understood to understand the long-term effects on male fertility. To fully understand the long-term effects on male fertility, more research is required. Studies that compare patients, controls, or pre- and post-COVID-19 use a variety of approaches. Further research is necessary to determine COVID-19's long-term effects on semen.

CONCLUSION

This review produced the impact of COVID-19 on male reproductive health involving multiple mechanisms, including viral entry via ACE2 receptors, testicular inflammation, hormonal changes, and disruptions in RAS signaling. Understanding these mechanisms is essential for developing management strategies and ensuring the reproductive health of affected individuals. The coronavirus pandemic is still a relevant public health concern, with many unknown aspects related to pathogenesis, including short- and long-term effects in different organs and systems and the male genital tract. The impact of COVID-19 on male fertility and its mechanisms are still in the early stages; further investigations on the evolution of sperm quality, reproduction, and male fertility are required to clarify and understand the many complex, challenging, and interesting phenomena involved in this subject. Despite the limited data, the evidence points to potential short-term effects on semen quality and fertility, with a likely reversible impact over time.

REFERENCES

1. Adhikari SP, Meng S, Wu YJ, Mao YP, Ye RX, Wang QZ, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. *Infect Dis Poverty* 2020;9(1):1–12. https://doi.org/10.1186/s40249-020-00646-x
2. Aitken RJ. COVID-19 and human spermatozoa: potential risks for infertility and sexual transmission? *Andrology* 2021;9(1):48–52
3. Akhigbe RE, Hamed MA. Possible links between COVID-19 and male fertility. *Asian Pac J Reprod* 2020;9(5):211
4. Araújo ALM, Almeida VLL, Costa TML, Mendonça ACG, Penna MLF, Santos AD, et al. Evaluation of the effects of COVID-19 on semen parameters and male infertility. *JBRA Assist Reprod* 2024;28(1):90–95. https://doi.org/10.5935/1518-0557.20230067

5. Ardestani ZA, Arab D. COVID-19 and male reproductive system: pathogenic features and possible mechanisms. *J Mol Histol* 2021;52(5):869–878
6. Bani I, Zulkarnain, Dedy Syahrizal, Fauzul Husna, Winda Yulia, Mulkan Azhari. COVID-19 infection and male fertility problems. *Trends Infect Glob Health* 2023;2(2):86–93. https://doi.org/10.24815/tigh.v2i2.29426
7. Borges E Jr, Setti AS, Iaconelli A Jr, de Almeida Ferreira Braga DP. Current status of COVID-19 and male reproduction: a literature review. *Andrology* 2021
8. Brown TT. Hypogonadism in men with hepatitis C: what is a clinician to do? *Clin Infect Dis* 2019;69(4):577–579
9. Chen H, Guo J, Wang C, Luo F, Yu X. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* 2020;395(10226):809–815
10. Cui P, Chen Z, Wang T, Dai J, Zhang J, Ding T, et al. Clinical features and sexual transmission potential of COVID-19–infected female patients: a descriptive study in Wuhan, China. *medRxiv* 2020
11. Dutta S, Sengupta P. COVID-19 and male infertility: possible multifaceted pathology. *Reprod Sci* 2021;28:23–26. https://doi.org/10.1007/s43032-020-00261-z
12. El Zowalaty ME, Järhult JD. From SARS to COVID-19: a previously unknown SARS-related coronavirus of pandemic potential infecting humans – call for a One Health approach. *One Health* 2020;9:100124. https://doi.org/10.1016/j.onehlt.2020.100124
13. Fan C, Li K, Ding Y, Lu WL, Wang J. ACE2 expression in kidney and testis may cause kidney and testis infection in COVID-19 patients. *Front Med* 2020;7:563893
14. Giugliano S, Mozzarelli A, Navarra A, De Simone G, Rescigno M, Levi Setti PE, Albani E. Impact of COVID-19 on the male reproductive tract: insights from semen analysis and cryopreservation. 2023. https://doi.org/10.22541/au.169511612.24040116/v1
15. Gkogkou E, Barnasas G, Vougas K, Trougakos IP. Expression profiling meta-analysis of ACE2 and TMPRSS2 in human cells and identification of putative modulators. *Redox Biol* 2020;36:101615
16. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382(18):1708–1720. https://doi.org/10.1056/NEJMoa2002032
17. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak: an update on the status. *Mil Med Res* 2020;7(1):1–10. https://doi.org/10.1186/s40779-020-00240-0.
18. Hajizadeh M, Tartibian B. COVID-19 and male reproductive function: a prospective observational study. *Biol Reprod* 2021;105(3):588–597
19. Hezavehei M, Shokoohian B, Nasr-Esfahani MH, Shpichka A, Timashev P, Shahverdi AH, Vosough M. Possible male reproduction complications after coronavirus pandemic. *Cell J* 2021;23:382–388. https://doi.org/10.22074/cellj.2021.7982
20. Huang C, Wang Y, Li X, Ren L, Zhao J. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395(10223):497–506
21. Illiano E, Trama F, Costantini E. Could COVID-19 have an impact on male fertility? *Andrologia* 2020. PMID: 32436229; PMCID: PMC7267130
22. Klein SL, Morgan R. The impact of sex and gender on immunotherapy outcomes. *Biol Sex Differ* 2020;11:24. https://doi.org/10.1186/s13293-020-00301-y

23. Kumar T, Jha K, Zabihullah M, Neelu K, Kumar Y, Siddharth K. Effects of the COVID-19 pandemic on semen quality in male partners of infertile couples: a hospital-based observational study. *Asian J Androl* 2023;25(2):240. https://doi.org/10.4103/aja202278
24. La Vignera S, Cannarella R, Condorelli RA, Torre F, Aversa A, Calogero AE. Sex-specific COVID-19 mortality: among hormone-modulated ACE2 expression, risk of venous thromboembolism and hypovitaminosis D. *Int J Mol Sci* 2020;21(8):2948
25. Lee WY, Mok A, Chung JP. Potential effects of COVID-19 on reproductive systems and fertility; assisted reproductive technology guidelines and considerations: a review. *Hong Kong Med J* 2021;27(2):118–126
26. Li D, Jin M, Bao P, Zhao W, Zhang S. Clinical characteristics and results of semen tests among men with coronavirus disease 2019. *JAMA Netw Open* 2020;3(5):e208292
27. Lippold S, Braun B, Krüger F, Harms M, Müller JA, Groß R, et al. Natural inhibitor of human cytomegalovirus in human seminal plasma. *J Virol* 2019;93(6):e01855–18
28. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020;395:565–574. https://doi.org/10.1016/S0140-6736(20)30251-8
29. Ma L, Xie W, Li D, Shi L, Mao Y, Xiong Y, et al. Effect of COVID-19 infection upon male gonadal function: a single-centre study. *medRxiv* 2020. https://doi.org/10.1101/2020.03.21.20037267
30. Madabhavi I, Sarkar M, Kadakol N. COVID-19: a review. *Monaldi Arch Chest Dis* 2020;90(2). doi: 10.1016/j.sjbs.2020.04.033
31. Marthasari R, Yan I, Glamour S, Harijanto, Ronggani A. The effect of COVID-19 infection on sperm DNA fragmentation index and pregnancy outcome in Teratai IVF Clinic Jakarta. *Fertil Reprod* 2023;5(4):739. https://doi.org/10.1142/S2661318223744417
32. Martinez MS, Ferreyra FN, Paira DA, Rivero VE, Olmedo JJ, Tissera AD, et al. COVID-19 associates with semen inflammation and sperm quality impairment that reverses shortly after recovery. *Front Physiol* 2023;14:1220048. https://doi.org/10.3389/fphys.2023.1220048
33. Matoba Y, Abiko C, Ikeda T, Aoki Y, Suzuki Y, Yahagi K, et al. Detection of human coronavirus 229E, HKU1, NL63, and OC43 between 2010 and 2013 in Yamagata, Japan. *Jpn J Infect Dis* 2015;68(2):138–141. https://doi.org/10.7883/yoken.JJID.2014.266
34. Maya WDC, Du Plessis SS, Velilla PA. COVID-19 and the testis: similarity with other viruses and routes of infection. *Reprod Biomed Online* 2020;40(6):763–764.
35. McMichael TM, Clark S, Pogosjans S, Kay M, Lewis J, Baer A, et al. COVID-19 in a long-term care facility—King County, Washington, February 27–March 9, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69(12):339–342
36. Mo P, Xing Y, Xiao YU, Deng L, Zhao Q, Wang H, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin Infect Dis* 2020. doi:10.1093/cid/ciaa270
37. Naicker S, Yang CW, Hwang SJ, Liu BC, Chen JH, Jha V. The novel coronavirus 2019 epidemic and kidneys. *Kidney Int* 2020;97(5):824–828
38. Our World in Data. Coronavirus pandemic (COVID-19). Available from: https://ourworldindata.org/coronavirus#explore-the-global-situation (accessed May 5, 2023)

39. Pal M, Berhanu G, Desalegn C, Kandi V. Severe acute respiratory syndrome coronavirus-2 (COVID-19): an update. *Cureus* 2020;12(3):e7423. doi:10.7759/cureus.7423
40. Pan F, Xiao X, Guo J, Song Y, Li H, Patel DP, et al. There is no evidence of SARS-CoV-2 in the semen of males recovering from COVID-19. *Fertil Steril* 2020;113(6):1135–1139
41. Patel DP, Punjani N, Guo J, Alukal JP, Li PS, Hotaling JM. The impact of COVID-19 on male reproduction and men's health. *Fertil Steril* 2021;115:813–823
42. Raouf KS, Omar AM. COVID-19: a possible emerging impact on male fertility. *Int J Cancer Biomed Res* 2020;4(Special Issue):7–13
43. Rastrelli G, Di Stasi V, Inglese F, et al. Low testosterone levels predict clinical adverse outcomes in COVID-19 pneumonia patients. *Andrology* 2021;9(1):88–98
44. Ruan Y, Hu B, Liu Z, Liu K, Jiang H, Li H, Wang T. No detection of SARS-CoV-2 from urine, expressed prostatic secretions, or semen in 74 recovered COVID-19 male patients: a perspective and urogenital evaluation. *Andrology* 2021;9(1):99–106
45. Salonia A, Pontillo M, Capogrosso P, et al. Severely low testosterone in males with COVID-19: a case-control study. *Andrology* 2021;9(1):104–111
46. Giugliano S, Mozzarelli MA, Navarra A, et al. Impact of COVID-19 on the male reproductive tract: insights from semen analysis and cryopreservation. *Authorea* 2023. doi:10.22541/au.169511612.24040116/v1
47. Tian Y, Zhou LQ. Evaluating the impact of COVID-19 on male reproduction. *Reproduction* 2021;161(2):R37–R44
48. Tur-Kaspa I, Tur-Kaspa T, Hildebrand G, Cohen D. COVID-19 may affect male fertility but is not sexually transmitted: a systematic review. *F&S Rev* 2021;2:140–149
49. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the COVID-19 spike glycoprotein. *Cell* 2020;181:281–292.e6
50. Wang S, Zhang A, Pan Y, Liu L, Niu S, Zhang F, Liu X. Association between COVID-19 and male fertility: systematic review and meta-analysis of observational studies. *World J Mens Health* 2023;41(2):311–329
51. Yang M, Chen S, Huang BO, Zhong JM, Su H, Chen YJ, et al. Pathological findings in the testes of COVID-19 patients: clinical implications. *Eur Urol Focus* 2020;6(5):1124–1129.
52. Younis JS, Abassi Z, Skorecki K. Is there an impact of the COVID-19 pandemic on male fertility? The ACE2 connection. *Am J Physiol Endocrinol Metab* 2020;318(6):E878–E880
53. Zadeh AA, Arab D. COVID-19 and male reproductive system: pathogenic features and possible mechanisms. *J Mol Histol* 2021:1–10
54. Zhang H, Kang Z, Gong H, Xu D, Wang J, Li Z, Xu H. The digestive system is a potential route of 2019-nCoV infection: a bioinformatics analysis based on single-cell transcriptomes. *bioRxiv* 2020. doi:10.1101/2020.01.30.927806
55. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the receptor of COVID-19. *Am J Respir Crit Care Med* 2020;202(5):756–759
56. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020;579(7798):270–273
57. Zsichla L, Muller V. Risk factors of severe COVID-19: a review of host, viral and environmental factors. *Viruses* 2023;15(1):175

58. Yuanita E, Lestarini IA, Dharmayani NKT, Ningsih BNS, Septiyana M, Ulfa M, Sugara TH. Sulfonated hydroxyxanthone as anti-tuberculosis agent: one-step sequence synthesis, characterization, and molecular docking preevaluation. *Jordan J Pharm Sci* 2025;18(2):305–316
59. Mumtaz A, Hussain H, Umair M, Ali W, Sajid M. In-silico innovative mRNA vaccine development using multi-epitopes of SopD protein for enteric fever caused by *Salmonella enterica*. *Jordan J Pharm Sci* 2025;18(2):437–460
60. Khdair SI, Zarour S, Almajawleh M, Khudeir FA. Single nucleotide pleomorphisms of different cytokines among Jordanian patients with lupus nephritis: a pilot study. *Jordan J Pharm Sci* 2025;18(2):461–471.

تأثير مرض كوفيد-19 على مرضى العقم الذكري: مراجعة أدبية

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ملخص

يؤثر فايروس كوفيد-19، الفايروس المسبب لجائحة كوفيد-19، على العديد من الأعضاء، بما في ذلك الجهاز التنفسي، والكبد، والكلى، والقلب، والجهاز الهضمي، والجهاز التناسلي الذكري. يُعبر الجهاز التناسلي الذكري عن الإنزيم المحول للأنجيوتنسين 2، وهو مستقبل دخول الفايروس الرئيسي، في خلايا أمهات الحيوانات المنوية، وخلايا لايديغ، وخلايا سيرتولي. في حين أن العدوى الفيروسية يمكن أن تُلحق الضرر بخصوبة الذكور من خلال عواصف السيتوكين، إلا أن آثار كوفيد-19 على خصوبة الذكور لا تزال غير واضحة. يجب أن تأخذ الطرق العلاجية للوقاية من مرضى كوفيد-19 وعلاجهم في الاعتبار احتمالية حدوث خلل وظيفي متعدد الأعضاء. في حين أن المرضى الذكور قد يعانون من العقم، إلا أن المعلومات المتوفرة حول كيفية علاجهم قليلة. يمكن أن تضر الميكروبات المختلفة، بما في ذلك البكتيريا والفيروسات، بالوظيفة الإنجابية للذكور. تهدف هذه المراجعة إلى دراسة احتمالية العقم أو انخفاض الخصوبة لدى مرضى كوفيد-19 والآليات المسببة للأمراض التي قد تسبب العقم أثناء وبعد التعافي من كوفيد-19. وقد أظهرت هذه المراجعة تأثير كوفيد-19 على الصحة الإنجابية للذكور من خلال آليات متعددة، بما في ذلك دخول الفايروس عبر مستقبلات للأنجيوتنسين2، والتهاب الخصية، والتغيرات الهرمونية، واضطرابات في إشارات نظام الرينين-أنجيوتنسين .ومع ذلك، لا تتضمن آثار كوفيد-19 الطويلة عواقب ضارة طويلة المدى على إمكانية خصوبة الذكور، حيث كانت التغيرات الملحوظة قابلة للعكس بعد دورة أو دورتين من دورات تكوين الحيوانات المنوية.

الكلمات الدالة: الأنجيوتنسين 2، كوفيد-19، خلايا لايديغ وسيرتولي، هرمون الجنس، السائل المنوي، البروتيازعبرالغشاء سيرين 2.

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