A Review of Recent Studies on the Effects of SARS-CoV-2 Infection and SARS-CoV-2 Vaccines on Male Reproductive Health

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According to world statistics, men are more susceptible to the coronavirus disease 2019 (COVID-19) than are women. Considering the interconnection between infections and male infertility, investigation of the potential impact of COVID-19 on men’s reproductive health is now a particularly relevant topic. Published data indicate decreased sperm quality and orchitis development in patients with COVID-19, including reduced sperm count, decreased sperm motility, and elevated DNA fragmentation index. Although mass vaccination against COVID-19 is currently being carried out worldwide using available authorized vaccines, the effect of these vaccines on men’s reproductive health has not yet been investigated.

There is currently no evidence that SARS-CoV-2 can be transmitted in semen, but available data suggest that it can infect spermatogonia, spermatids, Leydig cells, and Sertoli cells. Therefore, SARS-CoV-2 orchitis and reduced male fertility may be long-term complications of COVID-19, which requires further investigation. Currently, there is also no evidence that vaccines against SARS-CoV-2 have any pathological effects on spermatogenesis or male reproductive health. Thus, further studies are needed to determine the effects of COVID-19 and COVID-19 vaccines on men’s reproductive health, which will help to optimize the management and rehabilitation of these patients. This review aims to discuss recent studies on the impact of the COVID-19 and COVID-19 vaccines on men’s reproductive health. The article addresses various issues such as the effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on testosterone biosynthesis, semen parameters, testicular tissue, and epididymis.

Keywords: COVID-19 • COVID-19 Vaccines • SARS-CoV-2 • Semen Analysis

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/935879
Background

According to world statistics, men are more susceptible to coronavirus disease 2019 (COVID-19) than are women. Various viral infections are known to be linked to decreased semen quality and male infertility [1]. Mumps is the best-known viral infection associated with orchitis and male infertility [2]. Human papillomavirus might be a risk factor for male infertility, as its presence in semen might be associated with decreased sperm motility, reduced sperm count, and increased DNA fragmentation rate [3]. Similar effects, as well as the higher proportion of apoptotic sperm, have been shown in patients with hepatitis B and hepatitis C infections [4,5]. Taking into account that various viral infections can affect male reproductive health, investigation of the potential impact of COVID-19 has now become a particularly relevant topic.

COVID-19 vaccines became one of the most important and critical tools for COVID-19 prevention. For safety assessment and to make sure that newly authorized vaccines have no negative impact on reproductive health, each adverse effect is currently reported and analyzed. The most commonly reported events are fever, fatigue, headache, local pain at the injection site, and myalgia [6]. To date, no cases of orchitis or abnormal semen parameters administration of COVID-19 vaccines have been described.

This review aims to discuss recent studies on the effects of SARS-CoV-2 infection and COVID-19 vaccines on male reproductive health and fertility, including what is known about any effects on spermatogenesis.

Expression Pattern of Factors Associated with the Entry of SARS-CoV-2 Into Reproductive Tissue Cells

To enter the cell, SARS-CoV-2 binds to cellular receptors with its S-protein. According to the available data, the receptor for angiotensin-converting enzyme 2 (ACE2) is the main receptor involved in this process. The binding of the S-protein to this receptor requires its activation (priming), which is provided by the transmembrane serine protease TMPRSS2 [7,8]. Corona et al found ACE2 receptor expression in spermatogenic cells and somatic cells of the testis, which suggests the high susceptibility of testicular tissue to SARS-CoV-2 infection [9]. A high level of TMPRSS2 expression was also found in spermatogonia and spermatids. Wang et al carried out transcriptomic analysis of testicular biopsies and found ACE2 expression predominantly in Leydig and Sertoli cells [10]. Coexpression of ACE2 and TMPRSS2 in spermatogonia and Leydig cells indicates the likelihood of infection and possible risk of degeneration of testicular tissue and male infertility. Researchers also determined a decreased expression of genes responsible for spermatogenesis in spermatogonia with a high level of ACE2 expression [10]. Sertoli cells are the only somatic cells in the convoluted tubules of the testes that come into direct contact with spermatogenic cells and regulate their differentiation [11]. ACE2 receptor expression in Sertoli cells determines the likelihood of these cells becoming infected by SARS-CoV-2.

Pan et al did not detect SARS-CoV-2 in semen samples of patients with COVID-19, which, according to the authors, may be explained by the low expression of ACE2 and TMPRSS2 in these cells [12]. TMPRSS2, an essential protease for SARS-CoV-2 entering and infecting cells, was found to be highly expressed in spermatogonia and spermatids. According to Huang et al, the coexpression of ACE2 and TMPRSS2 in spermatogonia and Leydig cells may be a risk factor for testicular degeneration and male infertility [13].

ACE Role in the Male Reproductive System

Many studies have been devoted to the role of the “angiotensin-converting enzyme ACE2 – angiotensin (1-7) – Mas receptor” axis in the male reproductive system [14-16]. Angiotensin (1-7) is a product of ACE2 hydrolysis of angiotensin II and is an endogenous ligand of the Mas receptor, and significant expression of this Mas receptor was detected in the endothelium and testicular tissue [17,18].

Similar to the ACE2 expression pattern, Mas receptor expression was also found in Leydig and Sertoli cells and to a much greater extent in Leydig cells [15]. Xu et al carried out a study on mice with Mas gene knockout and demonstrated that such deletion affects the expression of enzymes involved in testosterone biosynthesis in Leydig cells (steroidogenic acute regulatory protein and 3β-hydroxysteroid dehydrogenase 1 and 6), which theoretically indicates the role of Mas in the regulation of androgen metabolism in men [19]. De Gendt et al also revealed errors at late stages of meiosis during spermatogenesis in mice with androgen receptor gene knockout in Sertoli cells [20].

As both angiotensin II and SARS-CoV-2 interact with ACE2 receptor, it might be assumed that SARS-CoV-2 competes with angiotensin II for this receptor. This theoretically leads to a decreased rate of angiotensin II to angiotensin 1-7 conversion and therefore decreased activation of Mas receptor, which is potentially associated with decreased production of testosterone. This might explain the decreased testosterone level in COVID-19 patients.

At the beginning of the COVID-19 pandemic, it was suggested that patients taking ACE inhibitors are more susceptible to...
infection with SARS-CoV-2 due to increased expression of the ACE2 receptor [21]. Theoretically, an increase in viral load may be associated with a subsequent decrease in the expression of the ACE2 receptor. Such a change in the balance of factors in the “angiotensin-converting enzyme ACE2 – angiotensin (1-7) – Mas receptor” axis might affect the regulation of the male reproductive system. Further research is undoubtedly needed to confirm the existing hypotheses.

**SARS-CoV-2 Effect on Testosterone Biosynthesis**

In addition to ACE2 and TMPRSS2, alternative Basigin receptor (BSG) and Cathepsin L protease (CTSL) were found in Leydig cells and can also mediate SARS-CoV-2 entry into cells [22]. Interestingly, testicular autopsy analysis of patients with COVID-19 showed a significant decrease in the number of Leydig cells in the interstitial tissue of the testes, which indicates that these cells were infected by SARS-CoV-2, leading to ultrastructural cell damage [23].

SARS-CoV-2 replication in Leydig cells can lead to impaired testosterone production. Pozzilli et al revealed a dramatic decrease in serum testosterone levels in patients with severe COVID-19. Moreover, they suggest that this may be a predictor of COVID-19 progression [24]. Rastrelli et al and Warmbier et al described clinical cases of hypogonadotropic hypogonadism in patients with COVID-19, which confirms the assumption of impaired testosterone production in those patients [25,26].

Testosterone is an important factor involved in the regulation of spermatogenesis and maturation of Sertoli cells [27]. Many studies have shown that testosterone deficiency can lead to atrophy of the testicular parenchyma and seminiferous tubule degradation [28]. Thus, the change in testosterone levels caused by SARS-CoV-2 can negatively affect men’s reproductive function. In this regard, special attention should be given to andrological examination and sex hormone level assessment in patients who have a history of COVID-19.

**SARS-CoV-2 RNA Detection in Semen Samples**

Findings regarding SARS-CoV-2 present in semen samples are highly controversial [29]. SARS-CoV-2 RNA was detected in semen samples in only 2 studies. The majority of published data indicates an absence of COVID-19 RNA in semen samples. Holtmann et al did not find SARS-CoV-2 RNA in semen samples in the acute phase of COVID-19 and at 8-54 days after the infection [30]. Kayaaslan et al also did not detect SARS-CoV-2 RNA in semen samples in the acute phase of COVID-19 [31]. Researchers collected semen samples from patients with acute COVID-19, with most of the samples obtained 1 day after a positive nasopharyngeal test. SARS-CoV-2 RNA was not detected in any of the analyzed samples [31]. Guo et al described the absence of SARS-CoV-2 RNA in the semen samples of 12 patients with COVID-19 and 11 fully recovered patients [32]. Ning et al also reported no SARS-CoV-2 RNA in semen samples of 9 COVID-19 patients and 8 recovered patients, but reported that orchidoptosis was diagnosed in 3 patients with severe COVID-19 [33].

Paoli et al published a case report of a patient with COVID-19 who voluntarily provided semen and urine samples 8 days after testing positive for SARS-CoV-2. Both types of samples were negative for SARS-CoV-2 RNA [34]. Song et al reported the absence of SARS-CoV-2 RNA in semen samples of 12 patients recovering from COVID-19 [35].

Zhang et al found no SARS-CoV-2 RNA present in prostatic secretions of 10 patients [36]. Similar results were reported by Pan et al, who did not find SARS-CoV-2 in semen samples of 34 patients 1 month after COVID-19 diagnosis. Moreover, the authors performed single-cell transcriptome analysis of semen samples and found only sparse ACE2 and TMPRSS2 expression [12].

The relevance of genetic studies is beyond doubt since the analysis of a wide range of genetic abnormalities in the semen of patients with COVID-19 allows the analysis of the molecular changes underlying SARS-CoV-2 infection and its complications. Adamyan et al profiled gene expression in semen samples of 10 patients who recovered from COVID-19. Researchers used RNA sequencing, Gene Ontology analysis of differentially regulated genes, and analysis of signaling pathway activation levels, which demonstrated decreased expression of genes linked to Toll-like receptor (TLR) pathways and energy production pathways in the mitochondria. Moreover, all protein-coding genes encoded by the mitochondrial genome were found to be significantly downregulated in semen samples collected after complete recovery from COVID-19. Reduced expression of these genes might be associated with the previously common decreased sperm motility in patients who recovered from COVID-19 [37].

Thus, most of the published manuscripts describe no SARS-CoV-2 RNA detected in the semen samples of patients with acute COVID-19 or in patients who have recently recovered from this disease. Nevertheless, Li et al reported that semen samples of 6 COVID-19 patients tested positive for SARS-CoV-2 RNA, including 4 from patients with acute COVID-19 and 2 from fully recovered patients [38]. In the study published by Machado et al, SARS-CoV-2 RNA was detected in 1 out of 15 patients with mild COVID-19 [39].
Another interesting result was published by Amaro N Duarte-Neto et al, who detected SARS-CoV-2 antigen in Leydig cells, Sertoli cells, spermatogonia, and fibroblasts by immunohistochemistry in 11 autopsied testicular tissue samples. Using electron microscopy, they detected viral particles in the cytoplasm of endothelial cells fibroblasts, spermatids, Sertoli cells, Leydig cells, and cells of the rete testis in 4 out of 11 samples, and in 3 cases they were able to detect SARS-CoV-2 RNA using RT-PCR [40].

**SARS-CoV-2 Impact on Semen Parameters**

According to Holtmann et al, mild COVID-19 disease did not impair testicular and epididymal function, while moderate disease was associated with decreased sperm concentration, decreased total number of sperm in the ejaculate, and decreased sperm motility [30].

Ma et al found several abnormal findings in the semen of patients who had recovered from COVID-19, including DNA fragmentation and reduced sperm motility. They also described cases of decreased libido and loss of morning erection in patients with COVID-19 [41]. Ruan et al analyzed semen samples from 55 COVID-19 patients and 145 controls, and found reduced sperm concentration and motility in patients with COVID-19 [42].

The impact of COVID-19 on spermatogenesis was also determined in a hospital-based observational study by Honggang Li et al, who enrolled 23 recovering COVID-19 patients. Semen analysis demonstrated oligozoospermia, leukocytospermia, decreased sperm concentration, and increased seminal levels of IL-6, TNF-α, and MCP-1 in patients who recovered from COVID-19 compared to the control group. The authors did not specify the timeline of biosample collection, so the long-term effect of SARS-CoV-2 on semen remains unclear [43]. Leukocytospermia is not evidence of inflammation in the testes, as it can be a sign of either a bacterial or viral infection, systemic inflammation, or infrequent ejaculation [44].

The longest longitudinal studies to date were conducted by Guo et al and Falahieh et al. Guo et al analyzed semen samples of recovered COVID-19 patients 56 days (n=41) and 84 days (n=21) after discharge. Researchers revealed significantly reduced total sperm count, sperm concentration, and motility on the first analysis, but all these parameters significantly increased at the second sampling. These findings suggest only temporary alterations in sperm parameters after COVID-19, with the potential recovery of semen quality over time [45]. Falahieh et al investigated semen samples of 20 patients at 2 time points – 14 and 120 days after laboratory confirmation of COVID-19, finding improvement of semen parameters and semen oxidative status by day 120, which indicates there is only temporary deterioration of semen quality after COVID-19 [46].

**SARS-CoV-2 Impact on Testicular Tissue and Epididymis**

The epididymis is an important paired organ in which maturation and accumulation of spermatozoa occur. Infection of the epididymis can have a negative effect on the sperm maturation process and lead to decreased sperm motility, an increase in the frequency of DNA damage, a change in the lipid composition of the membrane, and abnormal acrosomal reaction [47]. Due to the potential adverse effects of COVID-19 on male reproductive health, Huang et al recommend a comprehensive assessment of the genitourinary system for all male patients who have a history of COVID-19 [13].

Honggang Li et al analyzed autopsied testicular and epididymal tissue samples and revealed interstitial edema, red blood cell exudation in testicular tissue and epididymis, and seminiferous tubule thinning [43]. According to Yang et al, analysis of testicular samples of 12 deceased patients with COVID-19 demonstrated significant seminiferous tubular injury, a decreased number of Leydig cells, and Sertoli cell swelling [23].

**Influence of Inflammatory Reactions and Endothelial Dysfunction in COVID-19 on the Male Reproductive System**

Many studies have demonstrated dramatic increases in interleukin 6 (IL6) levels in COVID-19 patients [48,49]. From the standpoint of the immune response, elevated IL6 expression correlates with a systemic inflammatory response, which can lead to disruption of blood–testicular barrier integrity [50], which can facilitate dissemination of SARS-CoV-2 and direct damage to testicular tissue.

Peirouvi et al investigated autopsied testicular specimens of 10 deceased COVID-19 patients, and found significant changes in the spatial arrangement of testicular cells and a decreased number of Sertoli cells. They reported increased expression of pro-inflammatory cytokines and decreased expression of junctional proteins of the blood–testicular barrier, including occludin, claudin-11, and connexin-43 in testicular tissue samples of COVID-19 patients when compared to living patients of a control group. The authors concluded that these changes can potentially lead to disruption of blood–testicular barrier integrity and subsequent impaired spermatogenesis [51].

The mobilization of white blood cells as a part of the immune response to a viral infection can lead to the localization of leukocyte infiltration in the interstitial tissue of testes, which is a sign of orchitis and can lead to male infertility [13]. Pan et al detected orchitis in 19% of COVID-19 patients [12]. Analysis of autopsies of patients with COVID-19 has also shown the
characteristic features of viral orchitis with testicular parenchyma T-lymphocyte infiltration and significant damage to the seminiferous tubules [23].

As was previously shown, SARS-COV-2 contributes to damage and diffuse inflammation of the vascular endothelium [52]. In theory, testicular injury can result from segmental vascularization associated with COVID-19-associated vasculitis [53]. Local ischemia can lead to endothelial dysfunction, which can contribute to priapism (prolonged, painful erection) in COVID-19 patients [54].

**COVID-19 Vaccines and Men’s Reproductive Health**

Currently, there is no evidence that any COVID-19 vaccines cause fertility problems in men. According to the CDC, COVID-19 vaccination is recommended for all people who are trying to get pregnant now or might become pregnant in the future [55].

The Society for Male Reproduction and Urology (SMRU) and the Society for the Study of Male Reproduction (SSMR) released a Joint Statement regarding the COVID-19 vaccine in men desiring fertility, which includes the following:

- the COVID-19 vaccine should not be withheld from men desiring fertility who meet the criteria for vaccination;
- COVID-19 vaccines should be offered to men desiring fertility, similar to men not desiring fertility when they meet the criteria for vaccination [56].

Fever was shown to be one of the most common adverse effects of any vaccination. According to the literature, fever can have a temporary negative effect on sperm parameters [57]. Therefore, male patients who reported fever after getting the COVID-19 vaccine might experience a temporary decline in sperm production, but that would be similar to the effect of fever caused by other registered vaccines [56].

Zhao et al analyzed urologic adverse effects reported to the FDA Vaccine Adverse Event Reporting System (VAERS) after vaccination with the Pfizer-BioNTech and Moderna COVID-19 vaccines. Researchers demonstrated that out of 15,785 adverse events, only 113 (0.7%) described urologic symptoms, including lower urinary tract symptoms (34 cases), hematuria (22 cases), and urinary infection (41 cases). The median age of the patients with urologic symptoms was 63 years and only 46% of the patients were male [58].

The results of the first study on the impact of the COVID-19 vaccine on sperm parameters were published by Safrai et al, who demonstrated that the BNT162b2 mRNA vaccine (Pfizer/BioNTech) was not associated with a deterioration of semen quality. The study included 43 patients (14 of them were diagnosed with infertility and 29 had normal sperm parameters). The authors noted that none of the sperm parameters has changed significantly after COVID-19 vaccination [59]. Despite the significance of the study, it is important to note that it was published as a preprint and has not been peer-reviewed. Moreover, the authors did not indicate the time interval from vaccination to the semen collection and analysis.

Gonzalez et al published a research report on the effect of mRNA vaccines (BNT162b2/Pfizer-BioNTech and mRNA-1273/Moderna) on semen quality; 45 healthy men were enrolled in the study and provided semen samples prior to vaccination and at a median of 75 days after administration of the second dose. They found no statistically significant changes in any sperm parameters after vaccination [60].

Adamyan et al assessed sperm parameters and serum level of hormones (total testosterone, estradiol, FSH, LH, and prolactin) before and after administration of vector-based COVID-19 vaccine “Gam-COVID-Vac” (“Sputnik-V”) of the National Research Center for Epidemiology and Microbiology, named after N.F. Gamaleya of the Russian Federation. They found no negative effects of the “Gam-COVID-Vac” (“Sputnik-V”) vaccine on semen parameters and serum level associated with these hormones in men of reproductive age [61].

Moreover, for the first time, the effect of the COVID-19 vaccine “Sputnik-V” on molecular features of semen samples was also investigated. The same group of authors enrolled 10 men of reproductive age, 6 of whom were planning to get the COVID-19 vaccine, and the other 4 were included in the control group. Semen samples were collected prior to the vaccination and 75 days after administration of the second dose of the “Gam-COVID-Vac” vaccine. They did not find any statistically significant changes in the gene expression and functioning of intracellular molecular pathways in semen samples collected after vaccination with the “Gam-COVID-Vac” (“Sputnik-V”) vaccine [62].

The limitations of the above-mentioned studies include the small number of participants and short follow-up period. Therefore, further studies need to be conducted prior to the implementation of relevant recommendations into clinical practice.

**Future Studies on the Effects of SARS-CoV-2 Infection on Male Reproductive Health**

Currently, studies are being actively carried out to identify the effect of COVID-19 on the male reproductive system. There are no available data on SARS-CoV-2 RNA detection in semen samples of COVID-19 patients, which suggests that there is no risk of sexual transmission of this virus.
According to the literature, testicular tissue infected with SARS-CoV-2 can lead to the development of orchitis and epididymitis. Given the expression of factors associated with the penetration of SARS-CoV-2 into cells (eg, ACE2 and TMPRSS2) in spermatogonia, spermatids, Leydig cells, and Sertoli cells, these cells might be targets for SARS-CoV-2. Infection of these cells can be associated with impaired spermatogenesis and corresponding changes in sperm parameters (eg, decreased sperm concentration, decreased total number of spermatozoa in the ejaculate, decreased sperm motility, and increased DNA fragmentation rate). The available data were obtained from the analysis of small groups of patients, and no semen analysis was carried out after approximately 75 days (a period of time corresponding to the spermatogenic cycle) after COVID-19. These factors necessitate further large-scale studies aimed at identifying the potential effect of SARS-CoV-2 on the male reproductive system.

Regarding the effect of COVID-19 vaccines on men’s reproductive health, all published manuscripts suggest that there is no negative effect of those vaccines on sperm parameters and serum level of hormones in male patients. The available data on decreased semen quality in COVID-19 survivors outweighs theoretical concerns about the potential negative effect of COVID-19 vaccines on sperm parameters.

Further large-scale clinical studies on the effects of COVID-19 vaccines on men’s reproductive health still need to be conducted. However, considering the risk/benefit analysis of COVID-19 complications and the benefits of getting a COVID-19 vaccine, vaccination should be highly recommended to all men, especially those of reproductive age.

Conclusions

This review has presented the findings from recent studies on SARS-CoV-2 infection and SARS-CoV-2 vaccines on male reproductive health and fertility. There is no evidence that SARS-CoV-2 can be transmitted in semen, but SARS-CoV-2 can infect spermatogonia, spermatids, Leydig cells, and Sertoli cells. Therefore, SARS-CoV-2 orchitis and reduced male fertility may be long-term complications of COVID-19, which requires further study. Currently, there is no evidence that vaccines against SARS-CoV-2 have any pathological effects on spermatogenesis or male reproductive health.

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