

MINI-REVIEW

Exploring spermatogenesis post-SARS-CoV-2: a comprehensive review of male reproductive health

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Abstract

The global health crisis induced by the COVID-19 pandemic, due to the novel SARS-CoV-2 pathogen, has cast widespread implications on public health, notably impacting the male fertility. This review intends to consolidate and analyze academic research up to the conclusion of 2021, highlighting the potential consequences of SARS-CoV-2 within the scope of reproductive health of male. This review scrutinizes potential underlying mechanisms, with a thorough look at the pertinent biochemical and physiological pathways that could be implicated, drawing upon evidence from both clinical and pre-clinical investigations. Furthermore, it considers the potential long-term consequences of these alterations in relation to assisted reproductive technologies. The precise effects of the severe respiratory condition, COVID-19, triggered by SARS-CoV-2, on fertility are still under investigation. Various potential risk factors have been identified that may link SARS-CoV-2 infection to complications in fertility. One such element is the presence of angiotensin-converting enzyme-2, the key receptor for viral entry, in the cells of the testes. This could potentially facilitate direct viral invasion, leading to subsequent damage. The evaluation of existing data is crucial in understanding the extensive effects of COVID-19, particularly in the sphere of family planning and management of reproductive health in the context of worldwide health crises. This review also intensifies gaps in our present understanding, suggesting areas for future exploration to more thoroughly understand the complex relationship between male reproductive health and SARS-CoV-2.

Keywords

ACE2 inhibitor; Fertility; Male; Semen; SARS-CoV-2

1. Introduction

In late 2019, the emergence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in Wuhan, China, marked the onset of a global health crisis. This pathogen rapidly evolved into a severe respiratory disorder, ultimately leading to the declaration of a pandemic by the World Health Organization (WHO) in March 2020. Gennaro *et al.* [1] conducted an extensive narrative review, exploring into the vast body of scholarly works related to Coronavirus Disease 2019 (COVID-19), epidemiological trends, biological reactions, detection methodologies, management strategies and future predictions [1–3].

1.1 Global impact and systemic manifestations

As the pandemic continues, this review provides a snapshot of the current understanding and challenges associated with this global calamity. It goes beyond respiratory effects, acknowledging the systemic impact of COVID-19, with rapid lung lesions leading to organ failure. Recognizing the emergence

of a novel pathogen, the review emphasizes the importance of assessing its potential impact on reproductive health, particularly male fertility [3].

It is essential to appreciate that when a novel pathogen emerges, appraising its potential influences on reproductive health becomes an essential component of the broader health risk evaluation. Gennaro *et al.* [1] strive to underscore potential apprehensions concerning male fertility in relation to coronavirus infection globally. They suggest that male fertility might be compromised due to two primary elements: firstly, the direct cytopathic effects emanating from the virus's replication and proliferation within the testes; and secondly, the indirect consequences on male fertility stemming from damage related to immune responses [1, 4].

1.2 Literature review and comparative analysis

For a comprehensive understanding of the possible effects of SARS-CoV-2 on male fertility, Gennaro *et al.* [1] draw on existing literature on fertility disruptions in humans and animals due to coronavirus infections. By comparing these

insights with current knowledge about SARS-CoV-2 and other coronaviruses, they provide an extrapolated view of the potential influence of the novel coronavirus on male fertility. This method of analysis considerably enhances our understanding of the complex pathophysiology related to the SARS-CoV-2 virus. In the past twenty years, two notable coronavirus-related pandemics have occurred: Severe Acute Respiratory Syndrome (SARS; 2002–2003) and Middle East Respiratory Syndrome (MERS; 2012), neither of which matched COVID-19 in terms of incidence and mortality. Both SARS-CoV and SARS-CoV-2 rely on angiotensin-converting enzyme 2 (ACE2) as a receptor for entering human cells, while MERS-CoV utilizes a different receptor, known as dipeptidyl peptidase-4 [5]. Coronaviruses, such as SARS-CoV-2, propagate through direct human interaction and *via* microdroplets dispersed from infected individuals [6]. Predominantly affecting the respiratory system, COVID-19 manifests an array of symptoms encompassing dry cough, fatigue, fever, respiratory distress and muscular discomfort. As the disease progresses, these symptoms can evolve into pneumonia, olfactory and gustatory disorders, digestive irregularities and lymphopenia [7, 8]. Lessons learned from the SARS-CoV outbreak in 2002 suggested that orchitis, a health complication which could interrupt spermatogenesis and induce germ cell apoptosis, consequently impairing semen quality, might be an unexpected sequela [9]. In fact, autopsy examinations of six male SARS-CoV victims from the 2002 outbreak revealed the presence of orchitis [9].

1.3 Viral impact on male reproductive system

The male reproductive system and testicles may get affected with specific systemic viral illnesses, such as mumps orchitis. Immunogenic germ cells are normally protected from the host response by testicular immune privilege; however, certain viruses have the ability to cross the blood-testis barrier, enter male reproductive tract cells, and trigger an immunological response inside the testicle [10]. There is currently little knowledge on how viruses enter male reproductive tract cells and seed after contracting SARS-CoV-2. Among our goals are the description of the finding of SARS-CoV-2 in the semen of patients recuperating from COVID-19 and the identification of the ACE2 and Transmembrane Protease, Serine 2 (TMPRSS2) expression patterns in the human testicle. With these efforts, we hope to provide light on the mechanisms underlying viral entrance and its early effects on male reproductive function. The features of 34 Chinese men recuperating from COVID-19 are presented in the study by Pan *et al.* [11]. With a median body mass index (BMI) of 25.0 kg/m² (IQR: 23.2–26.9) and a median age of 37 years (interquartile range (IQR), 31–49 years), 17 males (50%) were classified as overweight (BMI >25 kg/m²). Nine percent of the patients had a history of hypertension, and it was unclear what their initial course of treatment had been. Remarkably, six individuals (19%) reported scrotal pain around the time of COVID-19 confirmation, which may indicate viral orchitis. However, because of the pandemic, a thorough genitourinary examination was not performed on the complete cohort. At the time of confirmation,

the majority of the cohort's patients had mild to moderate COVID-19 symptoms. The interval between the collection of a semen sample and the COVID-19 confirming diagnosis was 31 days on average (IQR: 29–36 days). Significantly, no ejaculated semen sample had severe acute respiratory syndrome-CoV-2 found in it after a median of 31 days.

The article by Pallotti *et al.* [12] offers a thorough examination of all the important aspects of how SARS-CoV-2 affects male reproductive health. It starts by explaining how the SARS-CoV-2 receptor, angiotensin-converting enzyme 2 (ACE2), is widely expressed in testicular cells. The context of this expression's facilitation of viral entry and infection within the testes is investigated. After that, the paper explores the controversial topic of SARS-CoV-2 discovery in COVID-19 patient semen samples and evaluates the possible effects on male fertility and sexual transmission. Furthermore, the paper summarizes research results from multiple investigations about the effects of COVID-19 on sperm quality, including changes in parameters like concentration, motility, morphology and DNA fragmentation in sick and recovered individuals. Lastly, the analysis looks at possible negative effects on spermatogenesis and testicular function caused by medications that are frequently used to treat COVID-19, such as tocilizumab, lopinavir/ritonavir, remdesivir and hydroxychloroquine [12].

1.4 Oxidative stress and male infertility

In terms of male reproductive functions, it is conjectured that SARS-CoV-2 may interfere through several potential mechanisms. One such mechanism might involve the activation of oxidant-responsive pathways through inflammation, thereby instigating oxidative stress—a common disruptor of various physiological functions *via* oxidative damage to host tissues. The role of oxidative stress in male infertility has been extensively studied and documented; it can compromise semen quality, alter sperm capacitation and form, and increase the DNA fragmentation index in semen [13]. Oxidative harm to sperm cells can induce lipid peroxidation of the sperm plasma membrane, DNA fragmentation, and initiate apoptotic cell death in spermatozoa [14]. With these in mind, this review aims to synthesize the broader implications on male reproductive health and evaluate the potential impact of the SARS-CoV-2 pandemic on male fertility.

2. Method

2.1 Screening of paper titles and abstracts

The selection of studies for this mini-review involved a comprehensive screening process conducted across multiple databases, namely Scopus, PubMed and Google Scholar. The search strings were meticulously constructed to generate a broad array of scholarly articles pertaining to the effects of SARS-CoV-2 on male fertility, focusing primarily on sperm quality and reproductive hormones.

In order to maintain the integrity and impartiality of the screening process, three independent authors carried out the initial screening of paper titles and abstracts. This ensured an unbiased representation of the current body of research, thereby minimising any potential for selection bias.

The first stage of screening involved the preliminary review of article titles. Subsequently, abstracts of potential studies were evaluated for relevance. Any discrepancies amongst the authors regarding the eligibility of a study were resolved through consensus. The screening process did not impose any restrictions on the language of the articles, widening the scope of research that could be incorporated in the review. This inclusivity, further bolsters the comprehensiveness and reliability of the findings of this review.

The selected studies were then analysed to derive the most relevant information pertaining to the impact of SARS-CoV-2 on male reproductive health, emphasizing on sperm quality and reproductive hormones. This included investigations of potential links between the coronavirus and any deleterious effects on the male reproductive tract, evidence regarding the presence of SARS-CoV-2 in semen, and the potential implications on male fertility.

The rigorousness of this screening process, coupled with the analytical expertise of the authors, ensures that this mini-review presents a comprehensive and robust examination of the current understanding of SARS-CoV-2's impact on male fertility (Fig. 1).

2.2 Data extraction

Following the comprehensive screening of articles, relevant data were extracted for qualitative synthesis. For each included study, relevant information was collected, such as study design, sample size, patient characteristics, methods of virus and semen detection, findings regarding the presence of SARS-CoV-2 in semen, effects on male fertility, and any associated

implications for male reproductive health.

Data were also extracted on secondary outcomes, including changes in hormone levels and the physiological state of testicular tissue, and any symptoms of orchitis or other inflammation in the reproductive system. Where available, data on semen quality were also noted, including any changes in sperm count, sperm motility, and sperm morphology.

Data extraction was conducted independently by two authors to ensure the accuracy and completeness of the data extracted. Discrepancies were resolved through discussion until a consensus was reached.

2.3 Quality appraisal

The quality of the included studies was assessed using an appropriate tool, such as the Newcastle-Ottawa Scale for non-randomized studies or the Cochrane risk of bias tool for randomized controlled trials. The quality appraisal considered several domains such as selection bias, comparability of groups, exposure or outcome assessment, and handling of missing data.

Critical evaluation of the methodological quality of each study was conducted independently by two reviewers. Disagreements between the reviewers were resolved by consensus or by consulting a third reviewer.

The quality assessment helped to ensure that the review's findings were based on studies with sufficient scientific rigour. It also allowed us to identify potential sources of bias and limitations in the included studies, providing context for the interpretation of the review's findings.

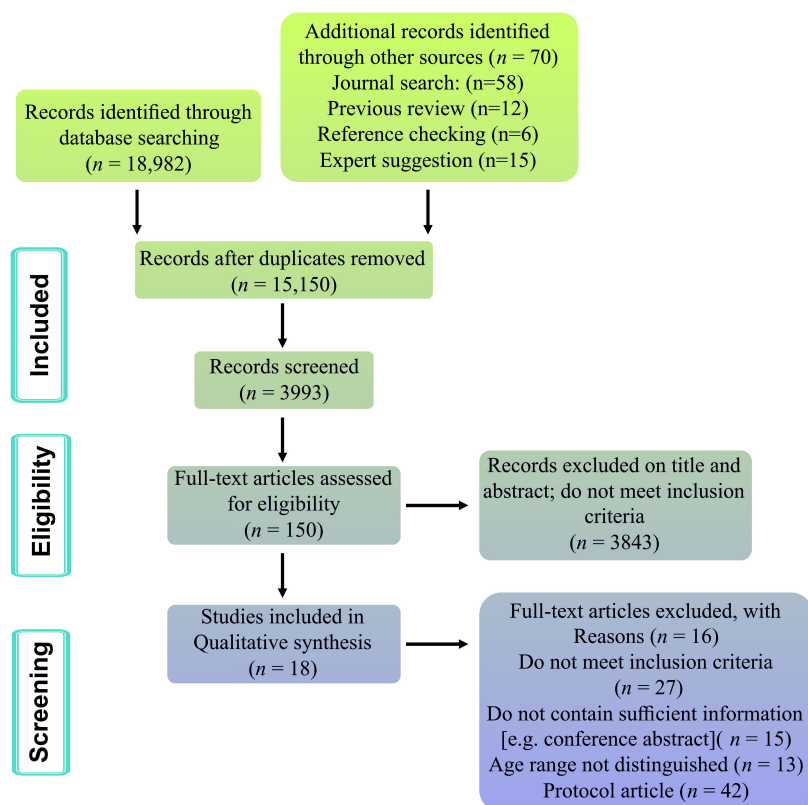


FIGURE 1. PRISMA flow chart of search strategy and study selection.

2.4 Synthesis

The process of synthesis in a systematic review involves bringing together the findings of multiple studies to draw overarching conclusions or highlight consistent patterns.

In this review, the synthesis of evidence primarily involved a narrative synthesis, given the diversity of the studies in terms of their design, populations and outcomes measured. The narrative synthesis focused on comparing and contrasting the findings across studies, noting areas of consistency and inconsistency, and considering potential explanations for any conflicting results.

Firstly, findings related to the presence of SARS-CoV-2 in semen were synthesized. These findings varied across studies, with some reporting no detectable virus in semen and others reporting a percentage of positive samples. Where possible, factors such as the stage of infection and recovery, and the method of detection used, were considered in understanding these differences. Shuibo Shi *et al.*'s [15] most recent study found that COVID-19 infection had a major impact on semen quality. Sperm DNA fragmentation index (DFI), concentration, progressive motility, overall motility and other semen characteristics were significantly reduced. The increase in sperm DFI is especially concerning because it affects male fertility significantly. Therefore, in order to reduce the possibility of unfavourable reproductive results, it is recommended that men receive reproductive guidance after contracting COVID-19. It is specifically advised against arranging a pregnancy during a spermatogenic cycle, which lasts for three months [16].

The results of the study showed a considerably larger DFI ($p < 0.001$) in the COVID-19 positive group, suggesting a negative impact on sperm DNA. According to Haghpanah *et al.* [17], sperm DFI may be a significant and important role in male infertility linked to COVID-19 infection. This is in line with the most recent guidelines from the extended examination in World Health Organization (WHO), which suggest using sperm DFI as a vital addition when evaluating male fertility. Furthermore, in line with Caliskan *et al.* [18], an examination of sperm samples from 743 infertile men revealed a negative connection between sperm DFI, sperm concentration and the percentage of motility. The claim that COVID-19 can impact male infertility and that DNA damage in sperm plays a major role in this process is further supported by the findings of Dipankar *et al.* [19], who found that all 30 COVID-19 positive respondents in their survey had a DFI over 30%.

In the COVID-19 positive group, the study also looked into the effect of an unhealthy lifestyle on sperm quality, but no statistically significant differences were found. This implies that although COVID-19 has a significant effect on sperm quality, the study's findings did not clearly show how specifically an unhealthy lifestyle affects sperm quality in this situation.

Next, evidence on the effects of COVID-19 on male fertility was synthesized. This involved bringing together data from different studies on various parameters of semen quality, including sperm count, sperm motility and sperm morphology, and considering how these might be related to infection.

In addition, findings related to changes in hormone levels,

testicular tissue damage, and symptoms of orchitis were collated and discussed, considering the possible implications for male reproductive health.

Finally, all these findings were integrated into an overall interpretation of the potential impact of COVID-19 on male fertility, taking into account the limitations of the available evidence, the variability in findings, and the potential for confounding factors.

Throughout the synthesis, the quality of the included studies and potential for bias were considered in interpreting the findings. Findings from higher-quality studies were given more weight in the synthesis, and potential sources of bias were highlighted.

To methodically garner relevant literature regarding SARS-CoV-2, a search strategy was assembled using a combination of specific keywords. The search was executed across three diverse databases, namely Google Scholar, PubMed and Scopus, to ensure a comprehensive coverage of scholarly articles. To maintain the integrity of the selection process, three independent researchers (AJ, KS and MKR) undertook the initial screening of the article titles and abstracts, thus promoting objectivity in the selection process. The scope of this concise review was restricted to original human studies that examined the impact of SARS-CoV-2 on sperm quality and reproductive hormones, imposing no restrictions based on the language of publication.

3. Mode of infection

The process of infection is initiated when the Spike (S) glycoprotein, a protein embedded on the viral surface, latches onto the angiotensin-converting enzyme 2 (ACE2) receptor that is present on the membrane of the host cell [20]. Within the body's renin-angiotensin-aldosterone system (RAAS), another enzyme, the angiotensin-converting enzyme (ACE), facilitates the conversion of angiotensin I into angiotensin II [21]. The S glycoprotein comprises two distinct domains: S1 and S2. Each domain contributes uniquely to the progression of infection. The S1 domain enables the virus to bind directly with the ACE2 receptor of the host, the S2 domain promotes the fusion of the viral entity with the membrane of the target cell, utilizing its functional components [22]. The execution of this process is aided by the transmembrane serine protease 2 found on the target cell membrane, which primes the S protein and triggers the entry of the virus [23]. Following the fusion of the virus with the cell membrane, the viral genome is released, facilitating the hijacking of the host cell's machinery to replicate its RNA and assemble new virions for further infection [24, 25]. The ACE2 receptor is predominantly found in areas such as respiratory epithelial cells, type I and II alveolar cells, the oral cavity, kidneys, testes and intestines [26]. Thus, human cells featuring ACE2 expression become probable targets for SARS-CoV-2 infection [27] (Fig. 2).

4. COVID-19 diagnosis and symptoms

COVID-19 manifests primarily through symptoms such as fever, dry cough, fatigue, dyspnoea, sputum production, diarrhoea, loss of smell (anosmia), taste dysfunction (ageusia),

ACE 2 Receptor and Sperm Disruption Mechanism

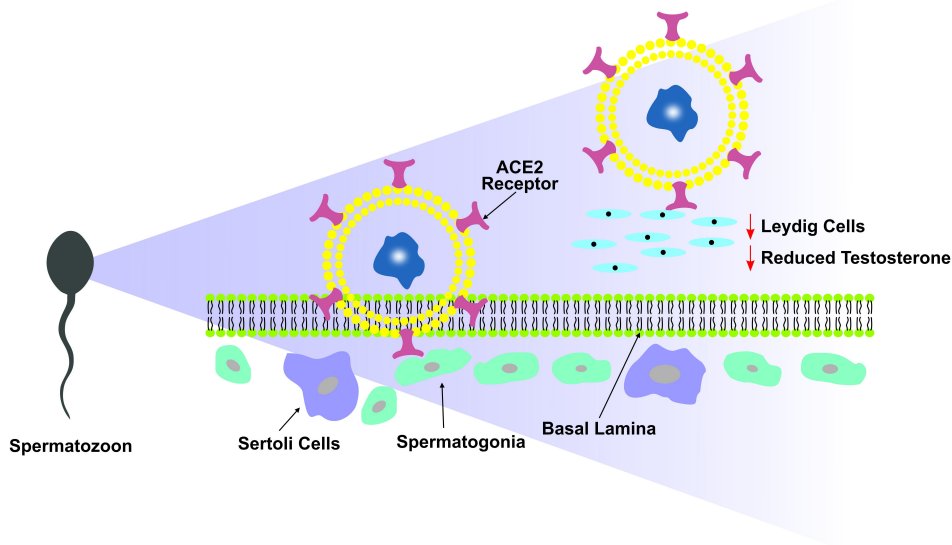


FIGURE 2. ACE-2 receptor and sperm disruption mechanism: this illustrative depiction provides a comprehensive overview of the intricate ACE-2 receptor and sperm disruption mechanism, particularly in the context of SARS-CoV-2 viral infections in males, with a specific emphasis on the impact on human Leydig cells. The image showcases the distribution of ACE-2 receptors on the surface of cells within the male testes. These receptors, known for their role in regulating blood pressure and inflammation, have been identified as potential targets for viral entry, including by certain coronaviruses. A depiction of a viral particle, possibly a coronavirus, approaching and binding to the ACE-2 receptor on the surface of a sperm cell is highlighted. The interaction between the viral spike protein and the ACE-2 receptor is a critical step for the virus to gain entry into the host cell. Upon binding, the viral particle is internalized into the sperm cell through endocytosis. This internalization triggers a cascade of events within the sperm, potentially leading to disruptions in its normal functioning. The image could show the release of viral genetic material into the sperm cell or the interference with essential cellular processes [28]. ACE2: angiotensin-converting enzyme 2.

headache, insomnia, anxiety and muscle pain (myalgia). Less common symptoms may include manifestations in the eyes and connective tissues [29]. Studies exploring the presence of SARS-CoV-2 in the semen of infected individuals found no traces of the virus's RNA in the semen samples. However, around 19% of the infected individuals reported experiencing discomfort in the testes, correlating with the COVID-19 infection [11, 30]. COVID-19 patients can be categorized into different classes, namely asymptomatic, mild (stage 1), severe and critical. Patients with mild stage 1 symptoms typically experience mild pneumonia, while severe patients may present with difficulty breathing and increased respiratory frequency within a span of 24–48 hours. Critical patients experience serious complications such as respiratory failure, acute cardiac injury, septic shock and multiple organ dysfunction [3]. The highly pathogenic nature of SARS-CoV-2 may be associated with an unregulated cytokine release, known as a “cytokine storm”, causing capillary leakage, tissue damage, edema, organ dysfunction and septic shock [31]. COVID-19 patients typically exhibit increased levels of various cytokines (interferon, tumour necrosis factor, interleukin (IL)-1, IL-2, IL-6, IL-10 and others) and a decreased number of lymphocytes. Severe cases primarily present with elevated IL-6 levels [32]. While clinical symptoms and results from computed tomography scans can suggest a COVID-19 infection,

a definitive diagnosis requires virus detection using real-time polymerase chain reaction (RT-PCR). The U.S. Centres for Disease Control and Prevention, as well as the World Health Organization, recommend RT-PCR for diagnosing acute infection. While false positives are rare, false negatives can arise due to improper sample collection or early infection stages. RT-PCR tests can utilize samples from nasal swabs, tracheal aspirates and nasopharyngeal exudates, with a set of nucleotide primers aiding in the identification of SARS-CoV-2. Serum-based tests, which determine the presence of immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies, are not typically used for diagnosing acute infection, despite growing evidence of their potential role in immunity or reducing reinfection risk. When conducted through Enzyme-Linked Immunosorbent Assay (ELISA), serologic tests exhibit over 95% specificity for the virus, but their sensitivity and specificity can vary, ranging from 60% to 98% [32].

5. SARS-CoV-2 and the male reproductive tract

The Impacts of SARS-CoV-2 on the male reproductive system, the complete understanding of how SARS-CoV-2 might influence male reproductive health remains unclear and controversial [20, 33–36]. The primary method of coronavirus

transmission is *via* respiratory droplets. Still, traces of the virus have also been detected in the sputum, urine, feces [33], and conjunctival secretions [37] of those infected. Due to its systemic propensity to bind to ACE2 receptors, SARS-CoV-2 may potentially infect tissues where these receptors are expressed, including those within the reproductive system. Notably, high levels of ACE2 expression have been observed in testicular cells, more specifically in the cells of the seminiferous ducts, spermatogonia and the Leydig and Sertoli cells [34].

Many publications have highlighted the detrimental consequences of SARS-CoV-2 infection on the male reproductive system, even if their findings have been inconclusive. The fundamental mechanisms driving these impacts are still not well known, though. Studies that have made use of publicly available single-cell RNA sequencing datasets have revealed increased expression levels of ACE2 and TMPRSS2 in spermatogonia, peritubular myoid cells, testis somatic cells, and spermatogonial stem cells, among other components of the testicles [38]. However, other research has not shown ACE2/TMPRSS2 co-expression in any kind of testicular tissue, indicating that there may not be much of a chance for viruses to enter and infect testicular cells. It has been suggested that indirect mechanisms, such as fever and inflammation brought on by the cytokine storm, may be responsible for reduced testicular function. Additionally, some studies have demonstrated that SARS-CoV-2, like other viruses such as H1N1, Zika, HIV, hepatitis and papilloma, may cause an oxido-inflammatory response, atrophy of the seminiferous tubule and Sertoli cells, and a decrease in Leydig cell mass with hypotestosteronemia, all of which can impair testicular function [39]. Furthermore, certain viruses may be sexually transmitted by using extracellular vehicles (EVs) to evade the host immune response. It is still unclear, nevertheless, if EVs protect SARS-CoV-2 virions from testicular immune surveillance. The issue of SARS-CoV-2 sexual transmission is still unclear because the research that is now accessible yields contradicting results. However, consistent findings in the literature show that male fertility is negatively impacted by SARS-CoV-2 infection [40].

This study aims to provide a concise overview of the existing knowledge regarding the impact of SARS-CoV-2 on the male urogenital tract, specifically the testes. It delves into how such an impact compromises testicular function, leading to diminished testosterone production and impaired spermatogenesis.

6. Results

COVID-19 and its Implications on Male Fertility? Scientific publications and social media platforms have provoked questions about the potential influence of the coronavirus on male fertility. Nonetheless, up to this point, there's no conclusive proof linking COVID-19 infection with a decrease in male fertility [41].

6.1 Testicular implications

Orchitis, denoting inflammation in one or both testicles, is recognized as a possible clinical consequence of viral infection. Initial indications suggest COVID-19 may inflict harmful

effects on testicular cells. The predominant mechanism seems to involve an increased body temperature due to persistent fever, which in turn induces a secondary autoimmune response, leading to autoimmune orchitis [42]. The ACE2 receptor, akin to its role with SARS-CoV, holds a pivotal part in the pathophysiology of SARS-CoV-2 infection. In the context of the renin-angiotensin-aldosterone system (RAAS), angiotensin I undergoes conversion to angiotensin II *via* the action of the angiotensin converting enzyme (ACE) [43]. ACE2 functions as a counterbalance to the ACE system, impeding the synthesis of angiotensin II. Given the accumulating evidence suggesting potential testicular infection with SARS-CoV-2, it becomes critical to monitor reproductive function in these individuals. Additionally, inflammation-related complications were reported in 19% of patients [4] (Table 1).

6.2 Prostate

The influence of SARS-CoV-2 on prostate-specific antigen (PSA) levels remains uncertain [44]. There is only one study, to date, which reported detecting COVID-19 in prostatic secretions. In this investigation, 18 males were evaluated for COVID-19, but viral RNA amplification in prostatic secretion was not observed in any of the subjects [35].

6.3 Seminal fluid

Despite the existence of the protective blood-testicular barrier, a myriad of viruses, encompassing HIV, Ebola, Zika, mumps, influenza and hepatitis B and C, have been detected and transmitted through semen. Initial studies could not locate SARS-CoV-2 in semen, however, these investigations involved limited patient numbers at varied stages of infection and recovery [4]. The maiden study assessing semen from men diagnosed with COVID-19 encompassed 34 Chinese males. Among these, six (19%) reported experiencing testicular discomfort and inflammation, yet none had detectable SARS-CoV-2 in their semen [4]. A second study focused on 12 patients in the recovery phase of COVID-19 and found no detectable SARS-CoV-2 RNA in any of their semen samples. A third study scrutinized semen samples from 38 men with COVID-19 and found that six (15.8%) had SARS-CoV-2 present in their semen, including some who were in the recovery phase. Nonetheless, this study did not determine the viral load in the samples or the virus's survival duration.

7. Discussion

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has far-reaching implications beyond the well-known respiratory illness. Given the virus's pervasive nature and its systemic affinity for ACE2 receptors found in various organs, the scientific community has started investigating its potential impact on the male reproductive system [45]. This discussion will synthesize current findings from existing literature on the subject, covering aspects like direct viral infection of the testes, the indirect effects of the body's response to the virus, and the outcomes of clinical studies regarding the presence of the virus in the semen.

SARS-CoV-2 primarily enters host cells *via* the ACE2 re-

TABLE 1. Viruses-taxonomy, clinical presentation, and impact on male reproductive health and target organs.

Viruses	Family	Genus	Genome	Clinical presentation	Male reproductive health and target organ
SARS-CoV-2	Coronaviridae	Betacoronavirus	ssRNA (+)	Severe acute respiratory syndrome	Testicle and Prostate

ceptor, which is highly expressed in various organs, including the testes. Specifically, ACE2 has been found in high concentrations in spermatogonia, Leydig and Sertoli cells, all crucial in the process of spermatogenesis. The presence of these receptors presents a pathway for the virus to potentially infiltrate the male reproductive tract and affect its function [46, 47].

Evidence is emerging that suggests that SARS-CoV-2 may have deleterious effects on testicular cells. Orchitis, or inflammation of one or both testes, has been observed in some COVID-19 patients, which may arise due to the body's immune response to the virus. Persistent fever associated with the infection could instigate an autoimmune response, resulting in autoimmune orchitis. Moreover, studies have found that around 19% of male COVID-19 patients had inflammation-related complications [48].

Nevertheless, the relationship between SARS-CoV-2 infection and male fertility remains a complex and multifaceted issue. Current literature presents a mixed picture, with some studies reporting negative impacts on various markers of fertility, while others find no significant effects. For instance, while Rastrelli *et al.* [49] (2020) linked severe cases of COVID-19 with low total testosterone levels, Paoli *et al.* [50] (2020) found no presence of viral RNA in either urine or sperm samples. These conflicting findings highlight the need for further research to elucidate the exact effects of the virus on male fertility (Table 2).

Even though the majority of the studies did not detect SARS-CoV-2 in semen samples, some reports indicate its presence. A study by Li *et al.* [54] (2020) showed SARS-CoV-2 positivity in 15.8% of the total cohort. Yet another research by Pan *et al.* [11] (2020) identified no viral RNA in the semen but reported orchitis in 19% of the patients. It is important to note that the presence of SARS-CoV-2 in semen does not necessarily equate to sexual transmission. Nonetheless, the potential for sexual transmission of COVID-19 remains a concern and warrants further investigation.

Moreover, several studies have pointed to potential changes in hormonal profiles in COVID-19 patients. Studies by Rastrelli *et al.* [49] (2020), Mustafa *et al.* [58] (2021) and Okçelik S. (2021) [59] indicate a decrease in testosterone levels, particularly in severe cases or those with concurrent pneumonia. As testosterone plays a crucial role in sperm production, a decrease could potentially affect male fertility. Concurrently, Luteinizing Hormone (LH) levels were observed to rise, suggestive of a compensatory response to low testosterone levels.

Multiple studies also reported the influence of COVID-19 on seminal parameters. Holtmann *et al.* [56] (2020) found a significant reduction in sperm quality in moderate COVID-19 cases, and Hajizadeh *et al.* [62] (2021) reported a decline in semen volume, sperm concentration, and motility. Li *et al.*

[54] (2020) found increased seminal levels of inflammatory markers, which may also impact sperm function.

However, despite these findings, there is currently no definitive evidence linking COVID-19 infection to decreased male fertility. The research community has been grappling with several challenges, including small sample sizes, lack of long-term follow-up, and varying disease severity among study participants. Furthermore, some of the observed effects could also be attributed to the general stress and systemic illness caused by the infection rather than a direct effect of the virus on the reproductive system.

Nonetheless, the potential impact of COVID-19 on male fertility should not be overlooked. With millions of men worldwide affected by the virus, even a minor effect on fertility could have significant public health implications. Therefore, it is crucial to conduct more comprehensive, large-scale and long-term studies to fully understand the impact of COVID-19 on male reproductive health.

The SARS-CoV-2 pandemic's effects on semen parameters and the existing data on male reproductive health treatment strategies are both somewhat restricted. However, a thorough analysis of the research on men's reproductive role in COVID-19 suggests that men are more vulnerable to SARS-CoV-2 infection than women are. Research has shown that testosterone regulates the expression of ACE2 and TMPRSS2, which are strongly linked to the clinical signs of COVID-19 in the testis and male reproductive system. Notably, mature spermatozoa have all the components needed to bind SARS-CoV-2, indicating that spermatozoa may act as vectors for this extremely contagious illness [65].

It has been noted that sperm parameters, spermatogenesis, and semen quality are negatively impacted by SARS-CoV-2 infection. Furthermore, the infection may alter the expression of gonadal hormones and cause harm and damage to the testicles [65]. On the other hand, no evidence has been found in two published studies to suggest that men's history of SARS-CoV-2 infection has a negative impact on fertility or performance in subsequent cycles of assisted reproductive technology (ART) [66].

8. Conclusion

In conclusion, even though the evidence to date has not established that SARS-CoV-2 has a negative impact on male fertility, the signs that are currently available highlight the urgent need for more research. A complex scenario of potential reproductive disruption is presented by the delicate interplay of direct cellular damage through ACE2 receptors, indirect repercussions resulting from fever-driven immunological responses, and probable hormonal imbalances generated by the virus. In light of the ongoing global COVID-19 pandemic, it is critical to expand our knowledge of the disease's more

TABLE 2. Available literature investigating SARS-CoV-2 infection on semen quality.

SN.	Study	Reported outcome
1	Pan <i>et al.</i> [11] (2020)	No semen sample tested positive for the virus; 19% of COVID-19 patients exhibited orchitis at the time of diagnosis; ACE2 and TMPRSS2 expression was found to be weak according to single-cell RNA-seq.
2	Pan <i>et al.</i> [11] (2020)	Orchitis was suggested by scrotal pain in 19% of patients.
3	Rastrelli <i>et al.</i> [49] (2021)	Low total testosterone levels were linked with severe COVID-19 cases.
4	Rastrelli <i>et al.</i> [49] (2021)	Total and free testosterone levels were lower in patients who deteriorated or died compared to those who improved or remained stable.
5	Paoli <i>et al.</i> [50] (2020)	Neither urine nor sperm showed positive viral RNA.
6	Li <i>et al.</i> [51] (2020)	SARS-CoV-2 positivity was found in 15.8% of the total cohort, 66.7% of patients with an acute infectious illness, and 33.3% of those deemed to be recovering.
7	Ma <i>et al.</i> [52] (2020)	Recovered patients exhibited significantly higher serum LH levels and lower testosterone:LH and FSH:FSH ratios compared to healthy controls.
8	Ning <i>et al.</i> [53] (2020)	Neither the <i>N</i> gene nor <i>ORF1ab</i> gene was found in any of the samples.
9	Song <i>et al.</i> [54] (2020)	The virus was not detected in any of the sperm samples.
10	Schroeder <i>et al.</i> [55] (2020)	Most males with COVID-19 exhibited elevated levels of inflammatory cytokines such as interferon-gamma (IFN- γ) and interleukin-2 (IL-2).
11	Holtmann <i>et al.</i> [56] (2020)	Sperm quality (concentration, progressive motility, and total motile count) was significantly lower in men with moderate illness compared to those recovering from mild infection or the control group.
12	Holtmann <i>et al.</i> [56] (2020)	Viral RNA was not detected in any of the analyzed sperm samples.
13	Li <i>et al.</i> [57] (2020)	Elevated seminal levels of IL-6, TNF- and MCP-1 were noted relative to controls, while sperm concentration was lower; 39.1% of recovered patients showed oligozoospermia and 60.9% showed increased leucocytes.
14	Mustafa <i>et al.</i> [58] (2021)	Testosterone levels decreased, whereas LH and prolactin levels increased, and FSH remained unchanged.
15	Okçelik S. [59] (2021)	No difference was observed in testosterone, LH or FSH levels between positive and negative subjects. Patients with COVID-19 with pneumonia had lower testosterone levels compared to those with COVID-19 but no pneumonia.
16	Caner <i>et al.</i> [60] (2021)	10.98% of patients (n = 91) experienced severe testicular pain, and one case of clinical epididymo-orchitis was recorded.
17	Abdallah <i>et al.</i> [61] (2021)	Compared to chronic damage in controls (decreased spermatogenesis and Leydig cells), the effects of oxidative stress on the testicles are apparent early on (elongation and sloughing of spermatocytes with Sertoli cell enlargement). No evidence of SARS-CoV-2 RNA in the testes was seen in autopsy results.
18	Maleki <i>et al.</i> [62] (2021)	Seminal plasma ACE2 enzymatic activity was significantly higher, and there were substantial decreases in semen volume, sperm concentration, progressive motility, and sperm morphology compared to the control group.
19	Gacci M <i>et al.</i> [63] (2021)	A correlation was observed between COVID-19 severity and the prevalence of oligo-crypto-azoospermia (25%), and elevated seminal IL-8 levels (76%).
20	Liao <i>et al.</i> [64] (2021)	Twenty-five percent of COVID-19 patients experienced orchitis, epididymitis, or epididymo-orchitis, with thicker tunica albuginea and increased vascular flow as common findings.

ACE2: Angiotensin-Converting Enzyme 2; TMPRSS2: Transmembrane Protease Serine 2; LH: Luteinizing Hormone; FSH: Follicle-Stimulating Hormone; TNF: Follicle-Stimulating Hormone; MCP: Monocyte Chemoattractant Protein.

extensive physiological effects. It takes this knowledge to improve clinical procedures and guarantee that patients receive the best care possible.

It is imperative to investigate the processes by which SARS-CoV-2 negatively impacts male fertility, with a focus on treatment outcomes. A targeted investigation is required to pinpoint the exact mechanisms and processes that the virus uses to impede male fertility. This entails looking at direct impacts on testicular cells and figuring out the complex biochemical mechanisms that underlie the adverse effects that have been noted. Scientists can reduce the negative effects of SARS-CoV-2 on male fertility by developing focused and efficient therapy approaches through a thorough understanding of these complex pathways.

ABBREVIATIONS

ACE2, Angiotensin-Converting Enzyme 2; COVID-19, Coronavirus Disease 2019; DNA, Deoxyribonucleic Acid; ELISA, Enzyme-Linked Immunosorbent Assay; HIV, Human Immunodeficiency Virus; IgG, Immunoglobulin G; IgM, Immunoglobulin M; IL, Interleukin; MERS, Middle East Respiratory Syndrome; RAAS, Renin-Angiotensin-Aldosterone System; RNA, Ribonucleic Acid; RT-PCR, Reverse Transcription Polymerase Chain Reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; WHO, World Health Organization.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

AJ—conceptualization; AJ, KS—data curation, writing—original draft; MKR, KS—formal analysis. MKR—validation. AJ, MKR, KS—Writing—review and editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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