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REVIEW ARTICLE

Update on andrological effects of SARS-CoV-2 infection and COVID-19: An overview review

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Abstract

Background: Evidence indicates a wide range of andrological alterations in patients with the Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) infection and Coronavirus Disease 2019 (COVID-19).

Aim: To provide an update on the andrological effects of SARS-CoV-2 infection and COVID-19.

Methods: PubMed/MEDLINE and Institutional websites were searched for randomized clinical trials, non-systematic reviews, systematic reviews, and meta-analyses.

Results: Fifty-four records were included from 2020 to 2024. The most representative paper categories were non-systematic reviews ($n = 26$) and systematic reviews/meta-analyses ($n = 27$). One randomized, prospective, phase 2 trial was also included. Eight topics were identified and discussed as follows: short- and long-term seminal changes attributable to SARS-CoV-2 infection or COVID-19; andrological effects of anti-SARS-CoV-2 vaccines; the potential impact of SARS-CoV-2 infection and COVID-19 on male fertility; the relationship between serum testosterone levels and COVID-19 prognosis in men; fertility care during the pandemic; urinary/genital male system tract impairment in SARS-CoV-2 infection and COVID-19; the effect of SARS-CoV-2 infection and COVID-19 on circulating levels of sex steroid hormones; the impact of SARS-CoV-2 and COVID-19 on sexual function and activity.

Discussion: SARS-CoV-2 can affect the whole testicular function through direct and indirect mechanisms, with a positive relation between the severity of SARS-CoV-2 infection and the level of deterioration of testicular function. Testicular function recovers along with the recovery from the disease. In vitro fertilization techniques ensure similar results in patients with or without previous SARS-CoV-2 infection or COVID-19. Immunization with anti-SARS-CoV-2 vaccines prevents andrological complaints due to naturally occurring infection. Erectile dysfunction and sexual dysfunction are frequently diagnosed in COVID-19 patients due to several contributing

factors, including hormonal imbalance and psychosocial complaints related to the pandemic.

KEYWORDS
COVID-19, SARS-CoV-2, sexual dysfunction, spermogram, testosterone, vaccines

1 | BACKGROUND

Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) is the etiological agent of the Coronavirus disease 2019 (COVID-19), a highly transmissible infectious disease, characterized by extensive localization into airways and lungs,[1] and difficult to predict clinical course.[2] SARS-CoV-2 exhibits a marked tropism for extrapulmonary tissues, including the central nervous system, myocardium, liver, kidney, gastrointestinal tract, and endocrine system.[3] Post-acute COVID-19 sequelae include sensorial disturbs in taste, eyesight, and hearing, chest pain, palpitations, cough, breathlessness, poor appetite, nausea, vomiting, diarrhea, constipation, weakness, muscle and joint pain, depression or anxiety, confusion, sleep disturbance, headache, dizziness and balance problems, tiredness, weight loss, and skin rash.[4] Post-acute signs and symptoms are reported in 7.5% and 5.4% of patients, respectively, 12 and 53 weeks after the infection.[5] Persistent symptoms are described more frequently after reinfection than following the first infection.[6]

Several papers have addressed the effect of SARS-CoV-2 infection on existing or new-onset endocrine disorders and the potential impact of existing endocrine disorders on COVID-19 prognosis.[7–14] A biologically interesting topic is related to the andrological effects of SARS-CoV-2 infection and anti-SARS-CoV-2 vaccines. This paper summarizes the most pertinent evidence on the topic 4 years following the pandemic.

2 | METHODS

PubMed/MEDLINE and Institutional websites were searched for randomized clinical trials, non-systematic reviews, systematic reviews, and meta-analyses. Keywords included the following terms: "covid-19," "sars cov 2," "male fertility," "semen," "sperm," "testosterone," and "erectile dysfunction." Records were searched from March 17, 2020, to September 19, 2024. No restrictions on languages were considered.

3 | RESULTS

3.1 | Data presentation

Fifty-four records were included (Figure 1). The most representative paper categories were non-systematic reviews ($n = 26$) and systematic reviews/meta-analyses ($n = 27$). One randomized, prospective, phase 2 trial was also considered. The foremost contributes were from China ($n = 13$), the USA ($n = 10$), Italy ($n = 7$), Iran, and India ($n = 3$). Based on keywords, topics were focused mainly on changes in seminal parameters during and after SARS-CoV-2 infection or COVID-19 ($n = 7$), andrological effects of SARS-CoV-2 vaccines ($n = 7$), effect of the COVID-19 pandemic on male fertility ($n = 6$), relationship between serum testosterone levels and COVID-19 prognosis ($n = 5$), effects of the COVID-19 pandemic on fertility care ($n = 5$), effects of SARS-CoV-2 or COVID-19 on a miscellaneous of andrological parameters, including serum testosterone and spermogram changes ($n = 5$), urinary/genital male system impairment due to SARS-CoV-2 infection or COVID-19 ($n = 4$), SARS-CoV-2 infection or COVID-19 and erectile dysfunction (ED) ($n = 4$).

3.2 | Topic 1: Short- and long-term seminal changes attributable to SARS-CoV-2 infection or COVID-19

Histological studies showed a high expression of the angiotensin-converting enzyme 2 (ACE2) receptor in the testis as demonstrated by microarray revealing the presence of the ACE2 gene in Leydig and Sertoli cells.[15] ACE2 is essential for SARS-CoV-2 entry in host cells. At the testicular site, ACE2 was thought to mediate SARS-CoV-2 entry in both Leydig and Sertoli cells, consequently deteriorating intra-testicular steroidogenesis and spermatogenesis.[16]

One of the first reviews addressing the acute effect of SARS-CoV-2 infection on spermatogenesis included six original trials evaluating the presence of SARS-CoV-2 in semen and seminal alterations in individuals with acute SARS-CoV-2 infection or convalescents. SARS-CoV-2 was identified only in two out of six studies, and patients reported testicular discomfort and low sperm count.[17]

A systematic review published in September 2021 better investigated the possible presence of SARS-CoV-2 in the semen of men who had recovered from COVID-19. All had nasopharyngeal swabs negative for SARS-CoV-2 at least 2 weeks before the semen collection with a median time from recovery of 44 days. The presence of SARS-CoV-2 was demonstrated by real-time polymerase chain reaction, and no studies found the presence of SARS-CoV-2 genome in the semen.[18]

The results of a systematic review and meta-analysis conducted on seven studies, including 934 patients (mean age: 37.3 years) who had recovered from COVID-19, were published in December 2021. Compared to non-COVID and age-matched individuals, patients recovering from COVID-19 had a lower seminal volume (−0.2 mL), sperm concentration per mL (−16.6 million), total sperm count (−45.4 million), overall sperm motility (−10%), progressive sperm motility (−1.7%), and vitality (−3.5%).[19]

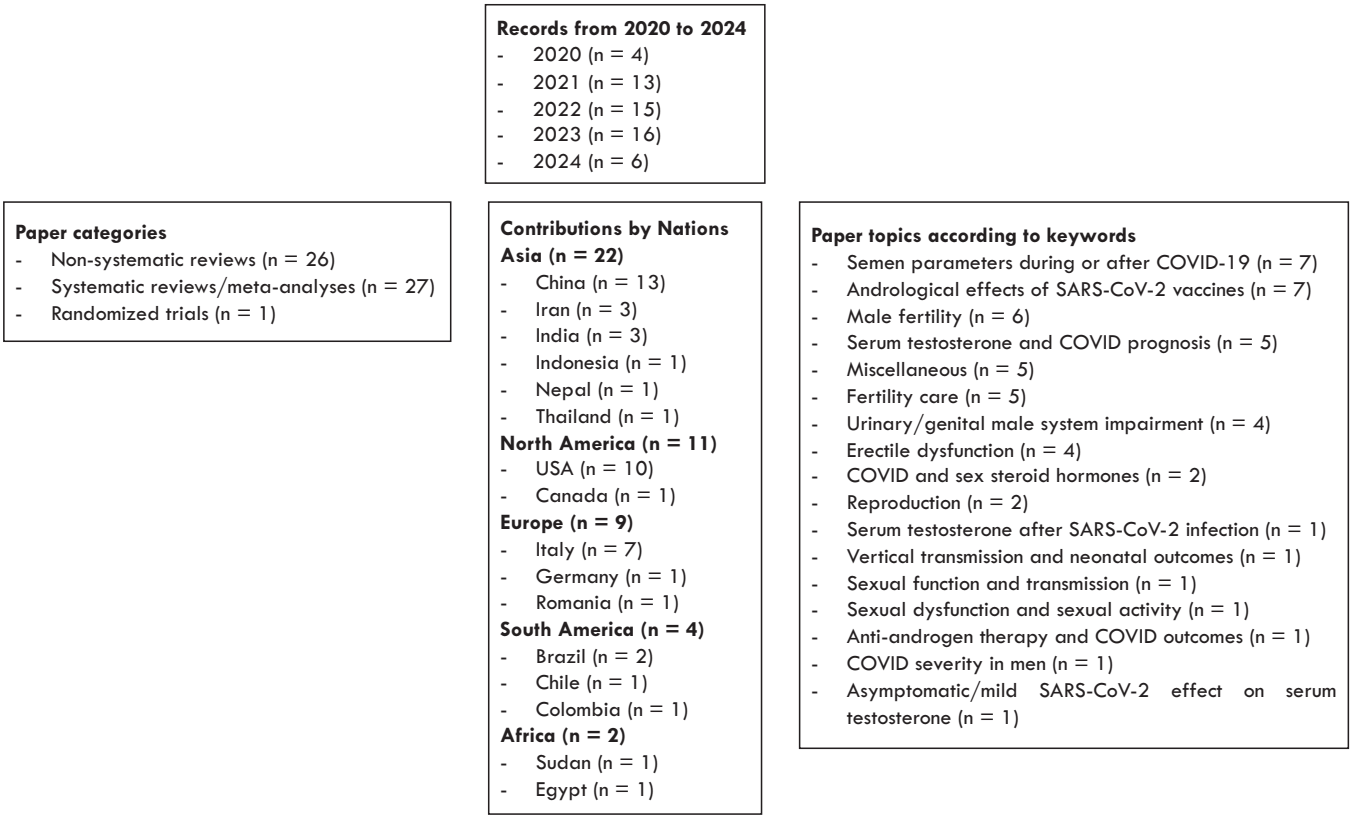

FIGURE 1 Schematic representation of included papers grouped according to the publication date (from 2020 to 2024), paper categories by titles and abstracts (not methodology), most frequent or relevant contributions by Nations ($n = 48$), and topics based on keywords.

A recently published systematic review of five studies on 118 cases of acute COVID-19 and 126 controls indicated a slight but significant impairment of total sperm count and sperm concentration per mL by 45.3 million and 15.6 million per mL, respectively.[20]

Another systematic review and meta-analysis of case-control studies, seven comparing acute COVID-19 cases with controls and five pre- and post-COVID-19, found relevant deterioration of seminal parameters in pre/post-COVID-19 but not case-control studies. The main changes were a reduction in semen volume (standardized mean difference or SMD = −0.27; $p = 0.00$), sperm concentration (SMD = −0.41; $p = 0.002$), sperm count (SMD = −0.30; $p = 0.00$), sperm motility (SMD = −0.66; $p = 0.00$), and progressive motility (SMD = −0.35; $p = 0.01$).[21]

In one systematic review, including 26 studies (2,060 cases and 1,960 controls), sperm concentration, overall and progressive sperm motility, and the number of sperm with normal morphology were lower in men with COVID-19 than controls. Seminal parameters were normal or near-normal after 3–6 months from the infection, depending on the duration and severity of COVID-19 symptoms.[22]

A systematic review and meta-analysis published in June 2023 addressed the effect of mild or asymptomatic SARS-CoV-2 infection, the most common clinical presentation, on sperm parameters. Mild or asymptomatic SARS-CoV-2 infection decreased sperm concentration and total sperm count, overall and progressive sperm motility, and the number of sperm with normal morphology. Sperm collected < 70 days compared to samples collected > 70 days from SARS-CoV-2 recovery had worse parameters.[23]

Another systematic review and meta-analysis found that patients with COVID-19, compared to healthy individuals or COVID-negative patients, had lower total sperm count (SMD, −0.411; $p = 0.012$), lower sperm concentration (SMD, −0.416; $p = 0.001$), lower total sperm motility (SMD, −0.605; $p = 0.001$), lower progressive sperm motility (SMD, −0.372; $p = 0.048$), and lower sperm viability (SMD, −0.665; $p = 0.031$). During the recovery phase (90 days, the authors observed a reduction in sperm concentration (SMD, −0.389; $p = 0.013$) and total sperm motility (SMD, −0.680; $p = 0.015$). Patients with febrile compared to non-febrile SARS-CoV-2 infection had lower sperm concentration (SMD, −0.457; $p = 0.022$) and progressive sperm motility (SMD, −0.697; $p = 0.010$).[24]

Restrictive measures imposed worldwide to tackle the spread of COVID-19, including limitations to regular access to healthcare facilities, have increased the number of at-home seminal collections, potentially affecting the reliability of sperm analysis. The topic was reviewed from seven studies with low or very low levels of evidence on 3,018 semen samples by comparing at-home with in-clinic semen collection. The results ruled out relevant differences in semen volume, sperm count, and sperm motility.[25]

Last, in a multicentric study conducted on 80 patients 3 months after they recovered from COVID-19, several andrological parameters were evaluated, including testicular ultrasound, semen analysis,

sperm deoxyribonucleic acid (DNA) integrity evaluation, anti-sperm antibodies testing, and sex hormone profile evaluation.[26] The mean percentage of sperm DNA fragmentation was 14.1 ± 7%, with 6.2% (five individuals) of patients showing total serum testosterone levels below the laboratory reference range. The mean bilateral testicular volume was normal (31.5 ± 9.6 mL) and the frequency of ED was 30%. Overall, the results of this study suggest that COVID-19 does not induce direct damage to the testicular function that, in turn, recovers entirely or almost completely to normal 3 months after the recovery from the infection.

Available evidence indicates that SARS-CoV-2 infection is associated with sperm deterioration. The magnitude and duration of sperm alterations depend on the duration and severity of SARS-CoV-2 infection.[27] Systemic inflammation, interference with pharmacological treatments of COVID-19, and the detrimental effect of SARS-CoV-2 on testis are probably the leading contributors to spermatogenesis impairment. However, sperm alterations are usually temporary and ameliorate during the recovery from COVID-19 in a period that coincides with the attenuation of acute inflammation and SARS-CoV-2 clearance. Sperm characteristics turn to normal or near-normal values in the long term due to the regenerative effect of the de novo spermatogenesis, which requires at least 3 months to become evident.

So, the evidence does not support persistent impairment of spermatogenesis after SARS-CoV-2 infection or COVID-19. Nevertheless, it is necessary to address the limitations of current evidence. First, most of the studies are limited to asymptomatic or mild-to-moderate cases of COVID-19 and are mainly focused on the acute or recovery phases. Consequently, there is a lack of information on spermatogenesis impairment in patients with and those who recovered from severe cases of COVID-19. Some patients do not completely recover after 3–6 months from the previous SARS-CoV-2 infection. The mechanisms involved in partial spermatogenesis failure due to an antecedent SARS-CoV-2 infection are unclear. Meanwhile, even if two observational studies have recently been published on the Omicron variant[28,29] indicating similar findings reported with previous variants, there is a need for more knowledge and, consequently, investigation on the effects of recurring SARS-CoV-2 infection by novel variants on sperm parameters.

3.3 | Topic 2: Andrological effects of anti-SARS-CoV-2 vaccines

The first anti-SARS-CoV-2 messenger ribonucleic acid (mRNA)-based vaccine was approved at the end of December 2020.[30] The approval symbolized an unprecedented event in modern Medicine and Science, as it occurred after one of the fastest steps between the preclinical development of a specific molecule and the approval for clinical use. Thanks to the potential of mRNA-based vaccines to reduce the severity of COVID-19 clinical presentation and related outcomes,[31] these were authorized for emergency use worldwide, generating an ambivalent reaction among the population: on the one hand, enthusiasm to receive a safe-life treatment, especially for high-risk patients; on the other hand, concerns and distress because of fear of adverse events and consequent vaccine hesitancy.

Shortly after the introduction of anti-SARS-CoV-2 vaccines, evidence indicated that SARS-CoV-2 infection had potentially relevant andrological effects. Therefore, growing interest has been increased in comprehending the impact of anti-SARS-CoV-2 vaccines on andrological outcomes.

The first systematic review on the effect of anti-SARS-CoV-2 vaccines on male fertility was conducted by an Italian Center and published in October 2022. The systematic review included 29 studies with poor-to-moderate quality. Trials were from Israel (34.5%), the USA (24.1%), Russia (20.7%), and China (10.3%), and included data on mRNA-based vaccines (BNT162b2 and mRNA-1273), the adenovirus-vector vaccine Gam-COVID-Vac (Sputnik V), Sinopharm/Sinovac, and viral vector-based vaccines. The results of this systematic review demonstrated no significant changes in sperm concentration or progressive motility before and after vaccination. At the same time, the pregnancy rate was similar between the two time points, and no difference in sperm parameters, testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels was found among vaccine users.[32]

A non-systematic review addressed the effects of anti-SARS-CoV-2 vaccines on the whole endocrine system. While focusing on the male reproductive system, the authors considered one case report and 11 studies and found that SARS-CoV-2 vaccines had no laboratory and clinical effects on sperm parameters and fecundability rate, respectively.[33]

A systematic review and meta-analysis, published at the end of 2022 and conducted on 12 observational independent studies, investigated the effects of anti-SARS-CoV-2 vaccines (mRNA-based vaccines for most) on sperm count by comparing sperm parameters before and after vaccination. Around 1,500 healthy individuals aged 22–45 years were included. The authors found that total sperm count (SMD, 0.11 [0.18–0.24]) was slightly increased after vaccination, while progressive sperm motility (SMD, −0.43 [−0.54 to −0.32]), total motile sperm count (SMD, −0.38 [−0.44 to −0.31]), and the number of sperm with normal morphology (SMD, −0.42 [−0.54 to −0.3]) were reduced post-vaccination. The magnitude of these changes was clinically irrelevant, as all the parameters were in the normal range before and after vaccination.[34]

A systematic review and meta-analysis, published in January 2023, focused on the effect of anti-SARS-CoV-2 vaccines on several sperm parameters. Despite some heterogeneity in the results, the authors found that semen parameters did not change by comparing pre-vaccination with post-vaccination spermograms (inactivated, viral-vector, and mRNA vaccines) and after comparing sperm parameters of vaccinated with unvaccinated healthy men.[35]

Similar results were reported by a Chinese group evaluating the effects of inactivated and mRNA-based vaccines on total sperm motility, semen volume, sperm concentration per mL, sperm morphological changes, and total sperm count, thus confirming that both vaccines were safe for male fertility.[36]

In December 2023, Edele Santos et al. published a systematic review on the effects of SARS-CoV-2 infection or COVID-19 and anti-SARS-CoV-2 vaccines on sperm parameters. The authors confirmed that SARS-CoV-2 infection and COVID-19 deteriorate seminal concentration, total and progressive motility, and morphology; meanwhile, the examined evidence (five studies) revealed that seminal parameters were not likely to be impaired after anti-SARS-Cov-2 vaccination (mRNA-based for most).[37]

Overall, data indicate that anti-SARS-CoV-2 vaccines, compared to naturally occurring SARS-CoV-2 infection, prevent any possible deterioration of the male reproductive function as they have clinically irrelevant effects on seminal parameters and testosterone concentration.[38]

3.4 | Topic 3: The potential impact of SARS-CoV-2 infection and COVID-19 on male fertility

ACE2 expression is relevant in the germ, Sertoli, and Leydig cells, indicating that the testis is a potential target of the infection.[39] Apart from the direct mechanism of testicular injury induced by coronaviruses, several other factors facilitate the SARS-CoV-2-mediated testicular damage. Persisting fever increases the body temperature sufficiently to affect spermatogenesis and induce germ cell apoptosis with potentially persisting sequelae. Intra-testicular leukocyte infiltration may impair the Leydig cell function, thus dropping testosterone synthesis. Moreover, leukocytes disrupt the blood-testis barrier, leading to immune-mediated inflammation of seminiferous tubules. Infections result in relevant disruption of the redox balance.[40] Studies indicated that testicular involvement in patients with SARS-CoV-2 infection is also the result of indirect mechanisms, as typical signs of orchitis and microvasculature thrombosis were also found regardless of the isolation of SARS-CoV-2 in testis samples in all examined fatality COVID-19 cases (11 patients).[41] SARS-CoV-2 mRNA is rarely identified in the semen of patients with acute or resolving SARS-CoV-2 infection. These are the results of a systematic review reporting six positive samples from 38 men only in one out of six examined studies.[42] As reported by Lucio Carrasco et al. from an animal model, a weekly inoculation of one of the most immunogenic components of SARS-CoV-2, the nucleocapsid (N) protein, in seminiferous tubules for 4 consecutive weeks induces a relevant reduction of the total number of spermatozoa and significantly lower serum testosterone levels than controls, regardless of other histological and biochemical changes.[43] The results of this study emphasized the pathophysiological importance of a small component, rather than the entire virus, of SARS-CoV-2 in impairing the whole testicular function in mammalians.

Delle Fave et al. (March 2021) reported that all testicular samples from patients who died with or due to COVID-19 displayed relevant signs of histological damage, including necrosis of both Sertoli and Leydig cells, seminiferous tubules, edema, and intra-testicular infiltration of T-lymphocytes, indicating that testicular injury can be considered a genital manifestation of sepsis in severe COVID-19. Similar findings were also reported in patients with mild or moderate COVID-19, but tracks of SARS-CoV-2 were rarely described in the testis. Testicular signs of inflammation were associated with impaired spermatogenesis and reduced serum testosterone levels, possibly indicating that pathological signs of testicular injury are consistent with anatomical changes of both secretive and endocrine functions.[44] Also, in a post-mortem series of cases, fatal COVID-19 was associated with signs of interstitial orchitis, such as congestion, interstitial edema, thickening of the tubular basal membrane, decreased Leydig and Sertoli cells, reduced spermatogenesis, and strong expression of vascular cell adhesion molecules in micro-vessels.[45]

A few data indicated that low viral clearance, persisting symptoms, and residual inflammation due to the so-called long-COVID syndrome can result in persisting impairment of spermatogenesis and testosterone synthesis and related disorders, such as poor libido, ED, low mood and strength.[46,47]

As indicated by an observational study on 26 young adults with mild-to-moderate COVID-19, epididymitis was a frequent finding (43% of cases) with either monoliteral or bilateral presentation and with disseminated micro-abscesses or inhomogeneous echogenicity with reactional hydrocele.[48] The relevance of such findings requires more investigation, as epididymitis can be a frequent cause of male infertility, even in the absence of testicular complaints.

Overall, evidence indicates that SARS-CoV-2 infection and COVID-19 are associated with a relevant injury of germinal and non-germinal compartments in the testis and epididymitis. Although pathological changes can be a direct or indirect consequence of SARS-CoV-2, effective measures to prevent SARS-CoV-2 infection are desirable to reduce the risk of testicular and epididymal damage.

3.5 | Topic 4: The relationship between serum testosterone levels and COVID-19 prognosis in men

Since the beginning of the pandemic, there has been evidence of a more severe prognosis of COVID-19 in men than women. Gender disparity in terms of hospital admission and mortality due to COVID-19 was attributable to several factors, including the physiological dimorphism in the levels of serum testosterone.[49] Even if normal/high levels of serum testosterone enhance the expression of ACE2 and transmembrane protease serine 2 (TMPRSS2), thus predisposing men compared to women to a more extended SARS-CoV-2 internalization into host cells and spread to pulmonary and extrapulmonary tissues, testosterone deficiency facilitates systemic inflammation, impairs the adaptive immune system, increases the pro-thrombotic risk, and is associated to more extended lung injury in COVID-19.[50]

Several observational studies have confirmed an inverse relationship between serum testosterone levels and COVID-19 prognosis in men. One study found low levels of serum testosterone in patients aged < 40 years with severe COVID-19, and men with lower values of serum testosterone had a more severe clinical presentation and related prognosis.[51]

The results of a systematic review indicated that serum testosterone concentration was significantly reduced during SARS-CoV-2 infection, and a significant impairment of serum testosterone levels

was also observed in moderate and severe COVID-19 cases and during the convalescence.[52]

Serum testosterone impairment was initially attributable to secondary hypogonadism due to the direct and indirect effects of SARS-CoV-2 on the hypothalamic-pituitary axis. A recent paper reviewing 18 series for more than 1,500 patients between 2020 and 2022, found a significant decrease in total serum testosterone levels in patients with COVID-19 compared to controls (SMD, −3.25 nmol/L; 95% CI −0.57, −5.93). The reduction in serum total testosterone concentration was more significant among severe cases than healthy controls (SMD, −5.04 nmol/L; 95% CI −1.26, −8.82) but no changes in the LH levels were found, suggesting a wide range of mechanisms being involved in COVID-19-related male hypogonadism.[53]

A systematic review with meta-analysis, published in 2023, found a relationship between low levels of serum testosterone and worse clinical presentation, higher levels of circulating markers of inflammation, and higher probability of being admitted to hospital care and intensive care units because of significant impairment of pulmonary function,[54] as previously demonstrated by observational studies.[55,56]

Preclinical evidence confirmed that antiandrogen treatment was ineffective in reducing the replicative potential of SARS-CoV-2.[57] Also, a phase 2 prospective intervention trial with a retrospective analysis of patients with prostate cancer who tested positive for SARS-CoV-2 found similar results. The study was designed to evaluate the effect of antiandrogen treatments on COVID-19 prognosis and found that antiandrogen treatment increased the duration of hospital stay and the risk of mortality (relative risk of 2.5).[58]

Last, evidence indicates that impaired androgen signaling associated with the presence of androgen receptor gene polymorphisms may contribute to testosterone deficiency and spermatogenesis impairment.[59] To confirm the relevance of such a phenomenon, also in driving poor prognosis in men with COVID-19 as similarly observed for those with low levels of serum testosterone, an Italian study found that impaired androgenic signaling due to androgen receptor polymorphism with reduced activity, especially when associated with CAG expansion (> 23), exposes the host to more severe inflammatory response, and higher chance to develop sepsis and multi-organ failure as described in severe COVID-19 cases.[60]

Overall, current evidence indicates a relevant deterioration of total serum testosterone levels in patients with COVID-19.[61] There is also a negative relationship between serum testosterone concentration and the clinical presentation and progression of COVID-19, indicating total serum testosterone as a biomarker of disease severity and poor prognosis. According to the levels of gonadotropins, most cases of hypogonadism are related to the impairment of the hypothalamic-pituitary axis (tertiary/secondary hypogonadism), but there is a coexistence of testicular injury in severe COVID-19 (primitive hypogonadism). A few data have so far been published demonstrating that testosterone levels were seen to completely recover or arise closely around the pre-COVID levels. However, data cannot depict the phenomenon since the relative lack of evidence is attributable to a methodological limitation. Particularly, serum testosterone is not routinely measured in the absence of signs or symptoms of male hypogonadism. Therefore, baseline levels of serum testosterone concentration are unknown for most, especially young and healthy individuals, and consequently, we cannot completely understand the effect of SARS-CoV-2 infection and reinfections on the entire hypothalamic-pituitary-testicular axis.

3.6 | Topic 5: Fertility care during the pandemic

The initial concerns about the possible impact of SARS-CoV-2 on gonadal health, sexual transmission, and pregnancy safety raised unpleasant psychosocial burdens and relevant interests in fertility and assisted reproduction technology.[62,63]

Generally, coronaviruses have the potential to affect gametogenesis, and infections during pregnancy were found to be associated with preterm delivery and peripartum mother-to-neonatal transmission.[64]

Early data on SARS-CoV-2 biology also indicated that the virus could infect the placental tissue, as it expresses the ACE2 receptors, and it could influence the early stages of embryogenesis.[65]

Although evidence has confirmed a SARS-CoV-2-mediated testicular injury,[66,67] subsequent studies indicated that TMPRSS2, an essential protease for SARS-CoV-2 entry, was not expressed on germ and non-germ cell surfaces.

The results of a systematic review corroborated the biological importance of TMPRSS2 on the infectious potential of SARS-CoV-2, as they found that SARS-CoV-2 RNA was undetectable in tissues with physiologically low expression of the protease, such as prostatic fluid, cervical smears, and oocyte samples (100%), vaginal and seminal fluids (98%), and testicular biopsy (94%).[68]

One systematic review with meta-analysis addressing the effect of a previous SARS-CoV-2 infection on in vitro fertilization technique clinical outcomes did not find any difference in terms of pregnancy (OR 0.97; $p = 0.82$), implantation (OR 0.99; $p = 0.96$), or miscarriage (OR 0.64; $p = 0.53$) rates.[69]

Similar results were recently published, starting from 12 observational studies. The clinical pregnancy rate was similar among patients immunized against SARS-CoV-2 (naturally occurred infection compared to vaccination) and never-had COVID-19 patients, including data from in vitro fertilization procedures carried out before the pandemic (odds ratio or OR 0.90; 95% CI 0.67, 1.21; $I^2 = 29\%$). Similarly, there was no significant effect on the implantation rate (OR 0.92; 95% CI 0.68, 1.23; $I^2 = 31\%$) and ongoing pregnancy rate (risk ratio or RR 0.96; 95% CI 0.79, 1.15; $I^2 = 21\%$).[70]

Evidence indicates that the gonadal localization of SARS-CoV-2 is uncommon, and a previous infection is not a risk factor for poor outcomes in couples undergoing in vitro fertilization procedures.

3.7 | Topic 6: Urinary/genital male system tract impairment in SARS-CoV-2 infection and COVID-19

Limited evidence indicated a possible localization of SARS-CoV-2 at the urinary/genital male system tract, other than gonads.

In a systematic review involving 575 patients (479 with acute COVID-19 and 53 recovering cases), lower urinary tract symptoms (LUTS) were detected in 43 naïve patients and seven displayed a deterioration of pre-existing symptoms. Signs of urinary or genital tract injury were observed less frequently than LUTS; these included bladder bleeding, acute urinary retention, scrotal swelling, priapism, and orchitis.[71]

Another systematic review found a low frequency of signs and symptoms of urinary/genital inflammation, reporting a temporary reduction in serum testosterone levels and sperm count.[72]

According to Kloping et al., the frequency of clinical manifestation of orchitis or orchiepididymitis in patients with SARS-CoV-2 infection is around 7%. The authors also found low semen volume and sperm concentration in patients with worse progression of COVID-19.[73]

Evidence indicates that the urinary/genital male system tract can be an infrequent but possible target of SARS-CoV-2. It is unclear whether the frequency of urinary/genital signs and symptoms are associated or not with the severity of SARS-CoV-2 infection, but in most cases, the clinical presentation is mild or moderate.

3.8 | Topic 7: The effect of SARS-CoV-2 infection and COVID-19 on circulating levels of sex steroid hormones

As clinical and pathological evidence demonstrated a wide range of structural and functional testicular alterations, specific studies aimed to address the effect of SARS-CoV-2 infection and COVID-19 on the hormonal function of the testis.

One review, published in October 2022, investigated the effect of SARS-CoV-2 infection and COVID-19 on sex hormone levels in more than 3,000 individuals by including case-control studies (COVID-19 vs. no-COVID-19 cases), comparisons between more vs. less severe COVID-19 cases, and survivors vs. non-survivors.[74] Overall, the main patterns of hormonal imbalance were synthetized in low total serum testosterone-to-LH and FSH-to-LH ratios, low levels of sex hormone binding globulin, and high levels of LH and estradiol-to-total testosterone ratio. The imbalance was more evident in severe than mild or moderate COVID-19 cases, but survivors and non-survivors had a similar hormonal profile.

A systematic review of prospective studies involving more than 2,000 COVID-19 cases and more than 1,000 controls (mean age 44 years) found a relevant deterioration of serum testosterone levels during the acute phase, with low levels of serum testosterone being a biomarker of COVID-19 severity and a predictor of the risk of admission to intensive care units.[75]

Cannarella et al. conducted a systematic review and meta-analysis on 1,250 patients with recent SARS-CoV-2 infection or COVID-19 (acute phase to 80 days after the diagnosis) and 1,232 healthy controls. Apart from seminal changes in line with other reports, the authors found lower levels of total serum testosterone and higher levels of LH, estradiol, and prolactin in COVID-19 cases compared to controls.[76]

A few studies have examined serum testosterone changes after exposure to COVID-19. A recently published systematic review and meta-analysis, conducted on 256 adult patients (< 60 years) from four observational studies, found that serum testosterone levels improved significantly 1–7 months after COVID-19 recovery with an SMD of 158.7 ng/dL compared to baseline.[77]

These data indicate that SARS-CoV-2 infection impairs serum testosterone concentration, even in young and healthy individuals. Most importantly, the more severe the COVID-19 presentation is, the more the impairment in serum testosterone levels will be. Testosterone decline during the acute phase of SARS-CoV-2 infection is related to primitive testicular impairment, even if a not negligible percentage of individuals experienced male hypogonadism because of COVID-19-related deterioration of the hypothalamic-pituitary axis as a consequence of systemic inflammation rather than a direct virus-mediated injury. Testosterone impairment is temporary with patients recovering in the post-COVID phase (up to 7 months), but it is unclear whether the recovery is complete or not because of missing information.

3.9 | Topic 8: The impact of SARS-CoV-2 and COVID-19 on sexual function and activity

SARS-CoV-2 has the potential to impair testicular function, induce urinary and genital complaints, and deteriorate male fertility. Psychosocial and economic concerns and disparity in the opportunity to access healthcare systems because of signs and symptoms of sexual dysfunction have also contributed to the deterioration of sexual function and activity, especially in the earliest phases of the pandemic.[78]

The frequency of ED during the COVID-19 pandemic ranged from 32% to 87%, according to the results of an Egyptian non-systematic review, with ED being more commonly diagnosed among healthcare providers than the general population.[79]

One explorative review[80] confirmed a higher frequency of ED among healthcare than non-healthcare providers (63.6% vs. 31.9%), probably because of a higher burden of psychological discomfort in the former compared to the latter.

In a recently published systematic review with meta-analysis, the authors investigated the frequency of ED among 250,000 COVID-19 cases and over 10 million aged-matched healthy individuals. ED was diagnosed in 33% of patients with COVID-19 with an estimated relative risk of developing ED 2.6 times higher in COVID-19 cases than healthy controls. Despite a relevant heterogeneity in the results, the frequency of ED was significantly higher in reports from 2021 (50%) than those from 2022 (17%) with anxiety due to COVID-19-related concerns being a risk factor for ED (OR 1.13; 95% CI 1.03, 1.26).[81]

A systematic review with meta-analysis, published in 2022, summarized the results of sexual function, assessed with the 5-item International Index of Erectile Function and the Female Sexual Function Index, in 3,765 men and 2,454 women. As depicted by scores, women displayed a relevant deterioration of sexual function. Men also had a statistically significant, but less evident than women, weakening of sexual function by comparing the period before to the 2 years after

the beginning of the pandemic.[82] The authors concluded that COVID-19-related concerns and restrictions were associated with higher rates of sexual dysfunction and reduced sexual activity in women than men.

Evidence suggests that sexual health has been significantly impaired during the COVID-19 pandemic. Despite most of the summarized evidence indicating a relevant psychosocial component in the genesis of ED and other signs and symptoms of sexual dysfunction, more investigation is needed to better understand the short- and long-term effects of SARS-CoV-2 infection and COVID-19 compared to other infectious diseases. For instance, men with COVID-19 are more likely to develop ED than those with no acute viral illness (RR 1.33; 95% CI 1.25, 1.42). However, they are less likely to be diagnosed with ED than men with herpes zoster (RR 0.37; 95% CI 0.27, 0.49).[83] It means that viral agents, inflammation, and specific immune responses play, to a variable degree, a significant role in the pathogenesis of ED by affecting penile hemodynamics. Another observational study found similar conclusions, indicating a negative causal association between COVID-19 hospitalization and ED, which can be mediated by the combined effect of systemic inflammation and impaired testosterone synthesis.[84]

4 | DISCUSSION AND CONCLUSION

Evidence on the COVID-19 effect on andrological parameters could be summarized in eight topics that include the essential impact of SARS-CoV-2 infection on secretive and hormonal testicular function, male urinary/genital tract disturbs, ED and sexual dysfunction, serum testosterone impairment and its effect on COVID-19 prognosis, male fertility and fertility care, and the impact of anti-SARS-CoV-2 vaccines on andrological parameters.

Most of the evidence has been summarized by papers that do not have the essential characteristics of systematic reviews, thus generating a relevant heterogeneity of the results.

Besides the bias mentioned above, SARS-CoV-2 affects the whole testicular function through direct and indirect mechanisms, with a positive relation between the severity of SARS-CoV-2 infection and the level of testicular impairment. Patients with severe COVID-19 would benefit from a closer monitoring of their reproductive health during and after recovery. Evidence indicates that these alterations are temporary, but the weight of their clinical meaning is unclear because of methodological limitations, including the lack of baseline data. Moreover, as a recent paper suggests, electron microscopy has revealed the presence of SARS-CoV-2 in spermatozoa of patients who were recovering from COVID-19 until 3 months after discharge. Spermatozoa were found to produce nuclear DNA-based extracellular traps in a cell-free DNA-dependent manner indicating that SARS-CoV-2 could use the epididymis as an additional route to bind and fuse to the mature spermatozoa and accomplish the reverse transcription of the single-stranded viral RNA into DNA, thus eliciting the extracellular cell-free DNA formation.[85]

Even if we do not know the effect of SARS-CoV-2 infection on the fertility background, especially for young individuals, evidence is enough to confirm that in vitro fertilization techniques ensure similar results in patients who had SARS-CoV-2 infection or COVID-19 compared to those who did not.

Immunization with anti-SARS-CoV-2 vaccines has been demonstrated to prevent andrological complaints due to naturally occurring SARS-CoV-2 infection. It is an important point, also considering that it is not known the weight of recurring SARS-CoV-2 infections on male sexual health and fertility.

Although off-topic, mainly because of a lack of systematic reviews and meta-analysis, it should also be considered that there is no clear evidence on the effect of approved drugs for SARS-CoV-2 infection and COVID-19[86] on sperm characteristics and testosterone synthesis. Protease inhibitors, such as ritonavir, nirmatrelvir, and darunavir, can be conveyed to the seminal compartment[87] and affect the spermatogenesis by impairing the PI3K/PDK1/AKT signaling pathway[88,89] and reduce sperm capacitation as demonstrated in an animal model.[90] Dexamethasone, a long-acting potent glucocorticoid agent with marked immunosuppressive activity, is usually administered in severe cases of COVID-19 when serious pulmonary complaints (such as acute respiratory distress syndrome) or septic shock complicate the clinical presentation. Therefore, the gonadal background of men receiving dexamethasone, as abundantly presented and discussed before, is poor and it is expected that low levels of serum total testosterone and poor sperm count, and motility can be attributed to severe COVID-19 per se. Nevertheless, mechanistic studies demonstrated that dexamethasone may impair both the intra-testicular testosterone synthesis and spermatogenesis with several mechanisms that include the inhibition of the GR/KDM1B/FSTL3/TGFβ signaling,[91] cellular proteasome,[92] and the enzyme aromatase.[93] Immune modulators, such as baricitinib (a Janus Kinase or JAK2, 3 inhibitor) and tocilizumab (an anti-interleukin-6 or IL-6 agent), may have a positive effect on both the testosterone synthesis and spermatogenesis as demonstrated by mechanistic studies. On the one hand, the inhibition of the JAK2/STAT3 pathway in an animal model of testicular ischemia-reperfusion injury is associated with reduced oxidative stress, improved spermatogenesis and testosterone synthesis, reduced apoptosis, and prolonged survival of seminal and non-seminal cells.[94] On the other hand, the inhibition of the IL-6 pathway increases the expression of the suppressor of cytokine signaling 3 gene in mice testicles, which in turn stimulates the intra-testicular synthesis of testosterone and dihydrotestosterone with positive effects on spermatogenesis.[95] So, antagonizing the IL-6 signaling pathway would preserve testicular function, especially in cases of severe COVID-19.

More research is needed to better understand the relationship between SARS-CoV-2 infection or COVID-19 and ED and sexual dysfunction, as well as their effects on general health and reproduction.

AUTHOR CONTRIBUTIONS

G.L. and A.D.T. conceived the study; G.L. and A.D.T. searched databases, identified and extracted the records of interest; V.A.G. provided additional references; G.L. and A.D.T. drafted the original manuscript; M.M., V.A.G., E.G., G.D.P., G.P., and V.T. read the original draft and provided feedback and adjustments. All the authors read the final version of the manuscript and approved the submission to the journal.

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CONFLICT OF INTEREST STATEMENT

The authors do not have conflicts of interest/disclosures to declare.

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