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REVIEW

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A narrative literature review of remaining male reproductive health concerns as an aspect of persistent/late-onset complications of COVID-19

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Abstract

Background Although COVID-19 infection has dropped across the world and SARS-CoV-2 vaccines have been developed, global concerns remain about the disease's long-term health consequences. The purpose of this research was to review the consequences of SARS-CoV-2 on male health, particularly the reproductive system and the pathogenic mechanisms affecting male infertility. Improving knowledge on these issues may help in considering to which extent some of the remaining concerns should be addressed.

Results The primary target of this disease is the pulmonary system, but reproductive organs may be targeted by the virus. To enter host cells, the virus utilizes both ACE2 and TMPRSS2, which are differentially expressed in the spermatogonial stem, Leydig, and Sertoli cells, thereby providing possible testicular vulnerability. COVID-19-related stress and psychological distress may also affect aspects of male reproductive health.

Conclusions Since some pathological effects of COVID-19 infection and dysregulations are linked to infertility, more attention is needed to determine whether such dysregulations regress following infection decline.

Keywords Infertility, SARS-CoV-2, Male health, COVID-19

Introduction

In December 2019, a novel mutant strain of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was discovered in Wuhan, China, and was dubbed coronavirus disease of 2019 (COVID-19), and contagion spread quickly over the world, prompting the declaration of a global pandemic [1]. It is the largest family of beta-coronaviruses (β-CoV), which comprise single-stranded RNA-encoded viruses [2]. Infection is caused by the transport of the COVID-19 virus into host cells, which is mediated by a transmembrane serine protease-2 (TMPRSS2) [3]. COVID-19 crosses the cell membrane through angiotensin-converting enzyme 2 (ACE2) receptors, which are found in a variety of tissues including the lungs, cardiovascular system, gastrointestinal tract,

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neurological system, and testes [3]. Human spermatogenic cells (spermatogonia and spermatids), Leydig cells, and Sertoli cells express ACE2 receptors. As TMPRSS2 is found in the epididymis, seminal vesicles, and prostate, COVID-19 infections could progress and negatively affect male reproduction via testicular damage, impaired spermatogenesis, and accessory organs. Multiple other molecular components present in the male reproductive tract are also known to be effectors of COVID-19 infection, including TMPRSS variants 2, 4, 11A, 11D, and 11E; phosphatidylinositol 3-phosphate 5-kinase (PIKFYVE) involved in endocytosis, two-type pore channel 2 (TPCN2), cathepsin L (CTSL) and cathepsin B (CTSB) [4]. A report has shown that variant TMPRSS11D is required for SARS expression and has been found in seminal vesicles [5]. Thus, the testes and seminal vesicles co-express the ACE2 receptor and a protease, indicating that SARS-CoV-2 could infect all male reproductive tissues [5]. ACE2-positive spermatogonia express a higher number of spermatogenesis-related genes than ACE2-negative genes [5]. Direct damage to the testicles by the virus can eventually lead to spermatogonial necrosis. Orchitis, a complication of viral infection by SARS can have destructive effects on the testicles and impair male reproduction [5]. Alongside this widespread damage to the male reproductive tract, COVID-19–related stress and psychological distress have also complicated the disease [6], which may affect all aspects of male reproductive health. As time passes, our knowledge of this virus deepens and long-term health effects on COVID-19 survivors have been highlighted. It is not surprising that pathophysiological status contributes to male infertility, either by itself or in combination, and possibly worsened by COVID-19 infection. Since some pathological effects and dysregulations are linked to infertility, more attention is needed to determine whether the detected dysregulation persists following infection decline. This review aims to illustrate the consequences of SARS-CoV-2 on male health, particularly the reproductive system and pathogenic mechanisms affecting male infertility, and on other aspects of male health. Improving our understanding of these issues may aid in determining the extent to which some of the remaining concerns should be addressed.

Material and methods

We conducted a thorough search of the published literature available in the PubMed, Web of Sciences, and Scopus databases up to February 2023. We recovered and updated the data again as of this submission. Medical subject heading (MeSH) terms including: "SARS-CoV-2" OR "COVID-19" combined with "male reproductive system" OR "male infertility" OR "testis" OR "Seminal Plasma" OR "sperm" OR "semen" OR "testosterone" OR "Male health" OR "hypogonadism" were used which were adjusted for each database.

Effects of SARS-CoV-2 on semen quality and spermatozoa

Up to now, studies on the presence of the SARS-CoV-2 virus in spermatozoa have shown conflicting results, so the presence of SARS-CoV-2 in COVID-19 patients' testicular tissues and seminal fluid is still debatable. Yang and colleagues published evidence of the presence of SARS-CoV-2 in the testes of a COVID-19 patient of reproductive age by using reverse transcription polymerase chain reaction (RT-PCR) [7]. Feng et al. (2020) by an electron microscopical study of testicular tissues of COVID-19 patients revealed no evidence of the virus. Although these patients had viral orchitis, the reports found no SARS-CoV-2 in semen samples from 34 male patients around 29–36 days after clinical confirmation (symptoms including fever, cough, and respiratory distress) and viral positivity (qRT-PCR of pharyngeal swab samples) [8]. Furthermore, according to Holtmann et al. (2020), the virus was not present in semen samples and they concluded that mild COVID-19 infection was unlikely to affect testicular or epididymal function, although semen quality appeared to be affected following a moderate infection. In addition, SARS-CoV-2 RNA was not found in the spermatozoa of recovered patients or acute COVID-19-positive men [9]. Contrarily, in autopsy specimens and epididymides of patients who died of COVID-19, the presence of interstitial tissue edema, congestion, erythrocyte infiltration, and seminiferous tubular thinning was observed. The number of apoptotic cells increased significantly, as did CD3 + and CD68 + expression in testicular interstitial cells, and IgG in seminiferous tubules when compared to surgical samples from control-matched patients with prostate cancer. On the other hand, COVID-19 patients showed oligozoospermia in 39.1% (9 patients) with a significant increase in leukocytes in 60.9% when compared to 14 age-matched male healthy controls (for fathering the second child or infertility caused by his partner). In addition, decreased sperm concentration and increased seminal levels of IL-6, TNF-α, and MCP-1 were observed in comparison with those of control men [10]. Androgenic hormone levels are inversely related to the severity of COVID-19 infection [10]. The blood-testis barrier (BTB) controls viral infections by protecting the testicles from circulating immune pathogens, immune cells, and cytokines. However, high infection and inflammation can lead to changes in cytokine production and fertility problems by upsetting the balance of the immune system [11]. The overproduction of different pro-inflammatory cytokines, referred to as a cytokine storm, is a main feature of COVID-19 infection [12]. On the other hand, in patients with a history

of infertility, pro-inflammatory cytokines levels including IL-1 beta, IL-6, and TNF are higher in seminal plasma than in that fertile ones [13, 14], and show an inverse relationship with the motile sperm percentage [15]. Sertoli and spermatogenic cells regularly produce the cytokines IL-1, IL-6, TNF, and activin A during the cycles of the seminiferous epithelium, suggesting that cytokines regulate key testicular functions [16]. The hypothalamic-pituitary–testicular axis can be suppressed by cytokines, which reduce serum testosterone (T) [17]; IL-1 deactivates p450/c17 lyase, which reduces T and disrupts spermatogenesis by converting progestins to androgens [18]. In this context, patients with severe COVID-19 show significantly decreased serum testosterone [19]. While IL-6 levels in COVID-19 patient semen significantly increase together with high IL-6 expression in a systemic inflammatory milieu, the integrity of the BTB is compromised. It appears that IL-6 can help increase its permeability by lowering the expression of occluding adhesion proteins in rat testis. As a result, the virus may cross the BTB and damage testicular tissue [17, 20]. Induction of IL-6 mediated by hypoxia can also initiate inflammatory mechanisms in ischemia [21]. On the other hand, evidence suggests that IL-6 and chronic inflammation can alter DNA repair processes and contribute to apoptosis via reactive oxygen species-induced oxidative stress [22]. In a meta-analysis study of twelve articles, Xie et al. confirmed that different semen parameters including semen volume, sperm count, concentration, and motility were negatively affected by the SARS-CoV-2 infection [23]. As a result, exposure to SARS-CoV-2 may be related to an impairment in some sperm parameters and a decrease in reproductive potential.

Effect of inflammation mediated by SARS-CoV-2 infection on male health and reproduction

Various testicular cell types produce factors that are fundamental for balancing innate immune activation and negative regulation, which maintains normal testicular function and immune privilege. Dampening mechanisms keep innate immune activation under precise control; otherwise, inflammatory conditions would be the cause of testicular damage associated with male reproductive disruption [24, 25].

An inflammatory cytokine storm is generated in COVID-19 situations, reducing viral infection of the cells and leading to an increase in leukocyte infiltration into the interstitial tissue, leading to orchitis and male infertility [5, 26]. While evidence for the presence of SARS-CoV-2 in spermatozoa is conflicting, COVID-19 may impair testicular function through pathways other than direct viral effects in the testes. The testicular tissues of patients suffering from COVID-19 are at risk of structural and functional dysfunction, owing to the chronic surplus levels of inflammatory cytokines [27, 28]. The activation of immune cell-derived pro-inflammatory cytokines may result in free-radical-mediated oxidative stress and cell apoptosis in several organs including the brain or testis [29, 30].

Post-mortem investigations of human testicular tissues reveal that SARS-CoV-2 infections cause testicular inflammation and spermatogenic cell loss, with CD3 + and CD68 + immune cells penetrating the testes [10]. In COVID-19 patients, T lymphocyte infiltration into the testicular parenchyma and injury to the seminiferous tubules might induce viral orchitis [7]. Histopathological studies of their testes demonstrate leukocyte infiltration and severe germ cell apoptosis, with thickening of the basement membrane [10]. In addition, ischemia-induced vasculitis produces segmental vascularisation of the testes as a result of enhanced coagulation, leading to tissue destruction [6].

The infiltration of CD68 + macrophages into testicular interstitial spaces can reduce testosterone synthesis [31]. Despite the absence of viral particles from the semen of eighteen men who recovered from COVID-19, a low sperm count and reduced sperm motility were detected [26]. It is uncertain whether viral RNA was present in spermatozoa during the early stages of the infection because the investigation was carried out 8–54 days after the onset of COVID-19 signs. Özveri et al. found acute swelling and pain in the groin and testicles of an asymptomatic COVID-19 patient [32].

Low testosterone levels in COVID-19 cases may cause aberrant spermatogenesis and impaired fertility in these patients [33]. The destruction of testicular biological components is mediated by proinflammatory cytokines and free radicals [34, 35]. Uncontrolled secretion of pro-inflammatory cytokines such as interferon-gamma (INF-δ), tumor necrosis factor (TNF-α), and various interleukins (IL-4, IL-6, and IL-12) can be caused by viral infection, and subsequently lead to oxidative stress and cell apoptosis [36, 37]. SARS-CoV-2 invasion of the testis, followed by oxidative stress and uncontrolled inflammation can result in spermatogenic failure, poor sperm motility, sperm DNA fragmentation, and male infertility [37].

Taken together, SARS-CoV-2 can provoke the inflammatory process, disturbances in immune regulation, and release free radicals, which can lead to male germ cell apoptosis, and destroy reproductive tissues, and subsequently semen parameters are considered the plausible targets for the virus. Therefore, investigation should be performed related to the common pathogenic mechanisms of COVID-19 and male infertility. In addition, pharmacologic agents should be selected or designed

aimed to target both COVID-19 infection and male infertility.

Endocrinological effects of COVID-19

Endocrine dysregulation is a significant clinical concern during the pandemic because it is linked to a variety of diseases such as hypothyroidism, adrenal insufficiency, hypogonadism, stress, depression, and anxiety, all of which are evident in COVID-19 subjects [27, 38–40].

Physiologically circulating levels of testosterone regulate the hypothalamus-pituitary-gland axis and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in response to the pulsatile hypothalamic release of gonadotrophin-releasing hormone (GnRH), via negative feedback; however, in testicular pathogenesis, a decrease in testosterone levels may result in dysregulation of GnRH production, followed by abnormal LH and FSH secretion [41]. The abnormal circulating levels of LH and FSH seen in COVID-19 cases [33, 42] may be attributable to early inflammatory responses activating gonadotrophin-producing cells [27]. On the other hand, SARS-CoV-2 obtains cellular access through ACE2 receptors in a process requiring the TMPRSS2 protein. Human endocrine glands, including the thyroid, pancreas, ovaries, testes, and pituitary, express ACE2 or TMPRSS2 [28]. Therefore, central hypogonadism can also be expected, since the hypothalamus is affected by SARS-CoV-2 actions on the central nervous system [43].

In a prospective cohort study, the serum T level of male COVID-19 patients ($n=358$) was found to be significantly lower than that of the negative COVID-19 patients ($n=92$). Furthermore, serum T levels were significantly lower in severe COVID-19 patients compared to mild-moderate COVID-19 patients, in COVID-19 patients requiring intensive care compared to COVID-19 patients who did not require intensive care, and in COVID-19 patients who died versus survivors [44]. In COVID-19 patients, low testosterone levels might contribute to spermatogenic abnormalities, erectile dysfunction, and infertility [27]. In a 12-month cohort study, Salonia et al. reported that following the recovery of confirmed COVID-19 patients, nearly 30% of men had low levels of circulating testosterone [45]. In addition, male hypogonadism and low T levels were risk factors for hospitalization for COVID-19 [46]. A systematic review of 2092 patients and 1138 matched- controls with an average follow-up of 24.3 ± 18.9 days, indicated that COVID-19 can result in short-term impaired sperm production and T level [47].

A meta-analysis of 35 articles containing 2092 patients and 1138 controls showed short-term impaired andrological effects. Reduced normal sperm parameters and unbalanced endocrine parameters (T levels) were observed in the acute phase of the disease [47]. Central hypogonadism, altered levels of gonadotropins, and testicular atrophy also is evident in this pathogenesis [27].

Therefore, there are two possible theories for the function of T, in the pathogenesis of SARS-CoV-2: First, the effects of T on immune system modulation; second, its effects on viral penetration into cells. These, with other causes of unbalanced endocrine parameters, central hypogonadism, and testicular atrophy give credence to the idea that COVID-19 patients and survivors may be at a high risk of infertility-related issues and should be carefully tracked in order to rule out hormone and sperm parameter aberrations.

Effects of hypoxia in COVID-19 on the male reproductive system

Hypoxia can cause alterations in blood flow and oxygen delivery, and elevations of body temperature, all of which are detrimental to Leydig cell activity and spermatogenesis, and which may cause male infertility. Testicular hypoxia induces germ cell death and germ cell DNA integrity damage in mouse models [48, 49] and activation of systemic, tissue, and cellular mechanisms causing neovascularization and angiogenesis influenced by VEGF (vascular endothelial growth factor) [50]. Hypoxia-inducible factor 1 (HIF-1) increases VEGF secretion and expression of their receptors (VEGFR) in animals exposed to systemic hypoxia [51, 52]. In the testes of hypoxia-exposed mice (6% oxygen for 6 h), the expression of HIF-1α is induced in the pachytene spermatocytes, spermatids, and luminal spermatozoa of seminiferous tubules compared with adult male mice under normoxic conditions [53]. VEGF is expressed in Sertoli and Leydig cells of the mouse testis [54]. Common features of hypoxia are increased testicular temperature and reactive oxygen species (ROS) production, which may partly explain decreases in sperm count, and normal sperm morphology in animal models exposed to hypoxia or with impaired systemic blood flow [55, 56]. Chronic and intermittent hypoxia decreases epididymal sperm count and motility in male rats [57, 58]. In rodent models, hypoxia causes vacuolation of Sertoli cells, increased pycnosis of germ cells, dilation of testicular blood vessels, reduced number of Leydig cells, and changes in testosterone levels [56, 59]. In rats exposed to hypobaric hypoxia, there is a reduced haploid/diploid cell ratio, increased apoptotic germ cells (particularly spermatogonia and spermatocytes), reduced cellularity of the seminiferous epithelium, and sporadic degeneration of seminiferous epithelial cells [60]. In healthy men, chronic hypoxia contributes to reversible oligozoospermia, reflecting the effect of hypoxia on male infertility [61]. Chronic hypoxia in male rats induces germinal epithelial degeneration,

destruction of germ cells and their detachment from the basement membrane, and enhanced lipoperoxidation. Further localized changes seen in the testes include increased vascularisation, increased testicular temperature, decreased testicular size, and increased interstitial space [62].

Hypoxia is produced by a lack of oxygen (O2) as an electron recipient, which results in reduced electron transmission across the electron transport chain at the mitochondria and an increase in the creation of ROS [63]. Increased testicular or seminal ROS is most likely the mechanism by which a permanent decrease in oxygen delivery impairs germ cell development, irreversible cellular damage, or death [64]. Although these molecules serve physiological functions in spermiogenesis, abnormally high quantities have deleterious consequences for germ cell survival and differentiation [65, 66].

After a COVID patient has fully recovered, a sustained increase in testicular temperature induces morphological abnormalities in spermatozoa owing to impaired spermiogenesis and meiosis, primarily via immunological and inflammatory processes [67]. However, in a longitudinal study, these perturbations are correlated with significant impairments in semen volume, sperm concentration, normal morphology, progressive motility, and sperm count, which tend to persist over time [68]. Given the possibility that recovered patients may experience transient infertility, similar to that in oligoastheno-teratozoospermia, it has been recommended that the reproductive function of patients recovering from the disease be carefully monitored and assessed, in order to identify and prevent more serious reproductive issues [68, 69].

Therefore, hypoxia in COVID-19 patients is another element supporting the impact of SARS-CoV-2 on male gonadal function, which can significantly raise the risk of unfavorable COVID-19-related outcomes.

Fever as an indirect mechanism underlying SARS-CoV-2-mediated alterations in male fertility

Alterations in male fertility caused by SARS-CoV-2 may be to some extent explained by fever, as a primary manifestation of COVID-19. In a cohort study, Holtmann et al. classified SARS-CoV-2-infected patients according to the presence or absence of fever. They reported that total count of motile sperm and semen volume were significantly lower and the number of immotile sperm was significantly higher in patients with a reported fever. Furthermore, there was a trend toward decreased sperm concentration and sperm count values in individuals who reported having a fever, but these results were not statistically significant [70]. Gacci et al. also concluded that the impact of fever on sperm quality is insignificant [71]. In contrast, Cakir et al. (2023) reported that semen parameters were adversely affected by fever throughout the active infection phase, with sperm concentration being the parameter most severely affected [72]. Fever can have a reversible deleterious impact on sperm parameters and DNA integrity up to one cycle (74 days) of spermatogenesis. In addition to raising the testicular temperature, hyperthermia can induce vascular issues. These alterations initiate the inflammation process in testicular tissue. After the patient has fully recovered, SARS-CoV-2 may cause immunological or inflammatory responses that might have long-term negative consequences on the testicles [67, 73]. Therefore, since the inflammatory condition persists within the male genitourinary tract after healing and temperature normalization, these results suggest that the abnormalities made by the virus are not a mere reaction to the onset of the fever but have long-term adverse effects on gonads and also persist over time [67].

Possible overlap factors between COVID-19 and varicocele

Varicocele, which is regarded as one of the leading causes of male infertility (accounting for up to 35–44% of males assessed for infertility), has multiple pathophysiological pathways altering spermatogenesis [74]. Recent investigation has implicated oxidative stress and antioxidant deficiency, hyperthermia, hypoxia, hormone dysfunction, and chronic inflammation as significant contributing factors in varicocele pathophysiology [75, 76]. Some evidence suggested that there is an overlap between common symptoms of varicocele and known risk factors of severe COVID-19, for instance, hypoxia, hyperthermia, and oxidative stress. Therefore, maintaining a high level of medical attention for patients who struggle with a pre-existing disease, such as varicocele, and offering suitable practical recommendations for effective treatment of the COVID-19 disease should be prioritized [77].

Gender difference in SARS-CoV-2 infectivity: men are more susceptible

There are several reports that androgens, particularly T levels cause the gender predisposition to the severity of the disease symptoms in COVID-19-infected patients; however, which one affects the other?

The effect of T on the development of the condition and severe immunological activation in COVID-19-positive men was confirmed during the pandemic [78]. With rather low T levels and more immune stimulation in hospitalized men with COVID-19, there is an elevated risk of their admission into intensive care units (ICU) or mortality, as well as severe clinical symptoms. Although the fundamental causes of developing severe COVID-19 and the predisposition of one gender are yet unknown, they may include inflammation-mediated cholesterol

reduction, infection-driven hypogonadism, and reduced testosterone synthesis. Late-onset hypogonadism may be a factor in older individuals' lower testosterone levels [78, 79]. However, from the involvement of androgens in the immune response and the fluctuation in androgen levels during male life, testosterone may play a dual role in the clinical course of COVID-19 infection. In the early stages, its immunosuppressive impact could explain why men are more susceptible to infection than women of all ages. When the infection is established, decreased testosterone levels in elderly males may result in reduced immunosuppressive function and hence a more strong cytokine secretion [78]. Hypogonadism may therefore have a protective function in the early stages of COVID-19 infection; however, it may also make a patient's clinical course more severe [80]. Men with reduced T levels are more prone to have endothelial dysfunction, increased platelet activity, poor cardiovascular health status, hemostasis, and thrombosis homeostasis, predisposing them to atherosclerosis and cardiovascular diseases, immune system dysfunction and systemic inflammation, all of which may contribute to worsening the clinical course of the diseases and general parameters [78, 81].

Low serum T levels and co-regulated expression of ACE2 and TMPRSS2 by androgen receptors in human prostate and lung cells, on the other hand, may enhance SARS-CoV-2 internalization, promote endothelial dysfunction, thrombosis, and a faulty immunological response, resulting in both poor virus clearance and systemic inflammation [82, 83]. Considering these data, low serum T levels may worsen the clinical outcome of advanced COVID-19 infection by exacerbating or activating the cytokine storm. T may predispose men to a prevalent COVID-19 infection, which is thought to characterize the hormonal milieu in those critically ill. Generally, men who are of reproductive age and want to become parents should be advised to delay starting infertility treatments for a minimum of 3 months (the length of the spermatogenesis process) in order to obtain healthy spermatozoa that have not been exposed to the virus during their development. They should also be warned that the quality of their sperm after contracting the COVID-19 infection may not be optimal.

The overview of the SARS-CoV-2 effects on male reproductive health is shown in Fig. 1.

Limits of the study

As COVID-19 has late-onset consequences, the change or stability measurement of longitudinal effects over time has yet to be investigated. Therefore, it requires an excessive amount of time to complete the literature review and gather and interpret the results. In addition, this review has been performed within a snapshot in time and it has not been designed as a systematic review, so it is

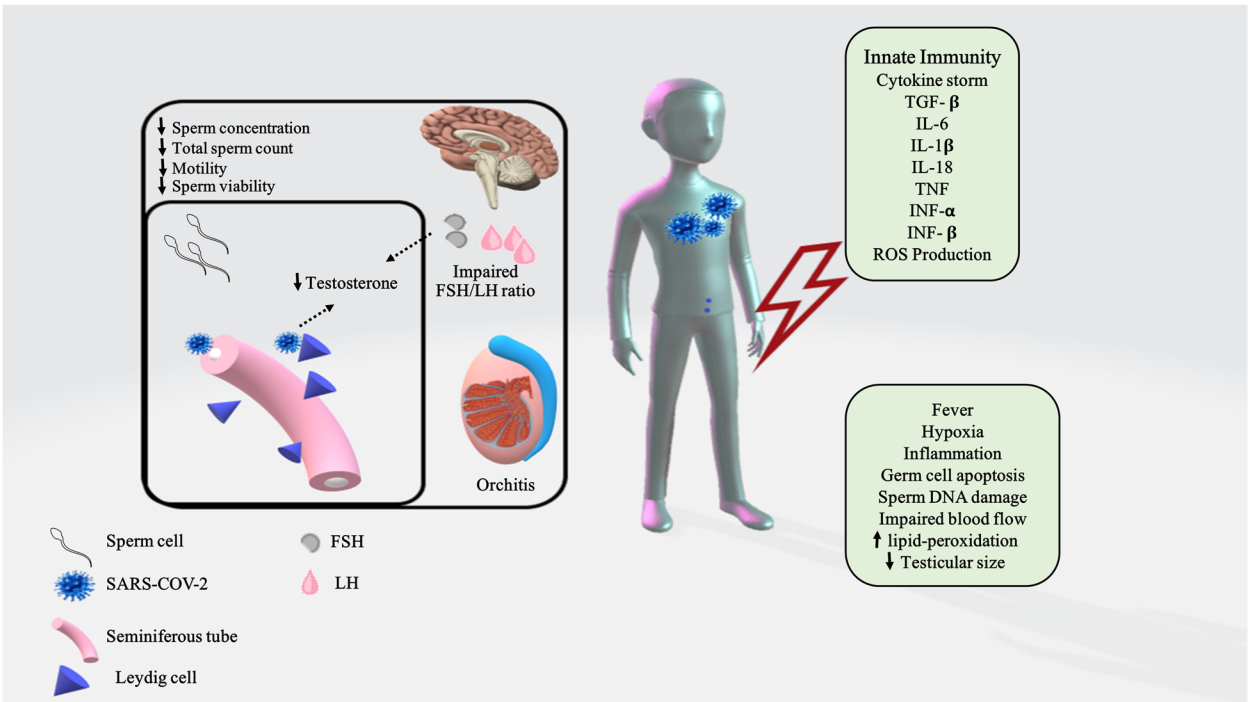

Fig. 1 The SARS-CoV-2 effects on male reproductive health

possible that not all of the relevant literature was taken into account.

Conclusion

Different mechanisms may play a role in male health and infertility in COVID-19 infection. With time the knowledge of SARS-CoV-2 has deepened and long-term health consequences on survivors have been increasingly highlighted. Inflammation, hyperthermia, endocrinological dysfunction, hypoxia, oxidative stress, anxiety, and stress have been found to be major drivers of unhealthy males during the pandemic, some of which persist post-infection. It is not surprising that the pathophysiological status that contributes to male infertility, either alone or in combination, may maybe made worse by COVID-19 infection. Improving knowledge on this issue may help in considering to which extent some of the remaining concerns should be addressed.

Abbreviations

SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
COVID-19	Coronavirus disease of 2019
β-CoV	Beta-coronaviruses
TMPRSS2	Transmembrane serine protease-2
ACE2	Angiotensin-converting enzyme 2
PIKFYVE	Phosphatidylinositol 3-phosphate 5-kinase
TPCN2	Two type pore channel 2
CTSL	Cathepsin L
RT-PCR	Reverse transcription polymerase chain reaction
LH	Luteinizing hormone
FSH	Follicle-stimulating hormone
INF-δ	Interferon-gamma
TNF-α	Tumor necrosis factor
GnRH	Gonadotropin-releasing hormone
BTB	Blood-testis barrier
HIF-1	Hypoxia-inducible factor 1
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
T	Testosterone
ICU	Intensive care unit

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Authors' contributions

Conceptualization: Azra Allahveisi, Elham Hosseini; literature search: Parivash Afradiasbagharani, Mahshid Bazrafkan, Raheleh Kafaeinezhad, Elham Hosseini; manuscript draft: Azra Allahveisi; critically revised the work: Elham Hosseini. All authors read and approved the final manuscript.

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