COVID-19 Infections in Gonads: Consequences on Fertility?

Authors
Nicole Bechmann[1] , Umberto Maccio[2], Reham Kotb[3], Rania Al Dweik[3], Michele Cherfane[3], Holger Moch[2], Stefan R. Bornstein[4, 5], Zsuzsanna Varga[2]

Affiliations
1 Institute of Clinical Chemistry and Laboratory Medicine, University Hospital Carl Gustav Carus Dresden, Technische Universität Dresden, Dresden, Germany
2 Department of Pathology and Molecular Pathology, University Hospital Zurich, Zurich, Switzerland
3 Department of Environmental and Public Health, College of Health Science, Abu Dhabi University, Abu Dhabi, United Arab Emirates
4 Department of Medicine III, University Hospital Carl Gustav Carus, Medical Faculty Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
5 Department of Diabetes, School of Life Course Science and Medicine, King's College London, London, UK

Correspondence
Dr. Nicole Bechmann
University Hospital Carl Gustav Carus Dresden, Technische Universität Dresden
Institute of Clinical Chemistry and Laboratory Medicine
Fetscherstraße 74
01307 Dresden
Germany
Tel.: + 4935145819687, Fax: + 493514587346
nicole.bechmann@uniklinikum-dresden.de

Abstract
COVID-19 may influence human fertility and sexuality in several ways. Different cell types in gonads show a constitutive expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine subtype 2 (TMPRSS2), which provide potential entry pathways for SARS-CoV-2. In addition to the biological effects of a COVID-19 infection on the gonads, the impact of the ongoing COVID-19 pandemic on mental health issues and sexual behavior may affect reproduction. This review summarizes the current knowledge on the influence of COVID-19 on the gonads and discusses possible consequences on human fertility. In this context, the close interaction between the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis in response to COVID-19-related stress is discussed. Some women noticed changes in their menstrual cycle during the COVID-19 pandemic, which could be due to psychological stress, for example. In addition, occasional cases of reduced oocyte quality and ovarian function are described after COVID-19 infection. In men, COVID-19 may cause a short-term decrease in fertility by damaging testicular tissue and/or impairing spermatogenesis. Moreover, decreased ratio testosterone/LH and FSH/LH in COVID-19 compared to aged-matched healthy men has been reported. Available data do not suggest any effect of the available SARS-CoV-2 vaccines on fertility. The effects of long COVID on human fertility have been reported and include cases with premature ovarian failure and oligomenorrhoea in women and erectile dysfunction in men. Despite the increasing knowledge about the effects of COVID-19 infections on human gonads and fertility, the long-term consequences of the COVID-19 pandemic cannot yet be assessed in this context.

Introduction

The first emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2019 has led to the COVID-19 pandemic with millions of infections and deaths worldwide. Even two years after the onset of the pandemic, the long-term consequences for the population and population development are still difficult to estimate. The potential effects of COVID-19 on reproduction are of particular interest in this context.

Endocrine, genetic, physiological, and psychological factors as well as social and lifestyle habits, such as smoking and alcohol consumption, influence human fertility. During the COVID-19 pandemic, several additional factors may affect fertility, including: (1) the biological effects of a COVID-19 infection on gonads; (2) the effects of COVID-19 on mental health; (3) the effects of the COVID-19 pandemic on sexual behaviour (▶ **Fig. 1**). The COVID-19 pandemic has also been associated with a decline in sexual satisfaction, reported by 44.5% of participants in a study (1314 responses of health professionals, mean age: 37 years), which included the following factors: lower libido, lack of nightlife, higher frequency of masturbation, and isolation from partner [1]. Polish women (n = 1644) reported a lower frequency of sexual activity and a lower libido during the pandemic than before [2]. However, another study showed that the average frequency of sexual intercourse was significantly increased during the pandemic compared to 6–12 months before [3]. There are also claims that the ongoing pandemic might result in a "baby boom", since couples spend more time with each other [4].

The hypothalamic-pituitary-gonadal (HPG) axis is mediated by the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus as response to diminished levels of circulating sex hormones, oestrogens in females and testosterone in males (▶ **Fig. 1**) [5]. GnRH stimulates the production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in the anterior pituitary. In males, LH targets Leydig cells and FSH acts on the Sertoli cells in the testis causing the synthesis of testosterone responsible for spermatogenesis [6]. In females, FSH stimulates follicle development and oestrogen production, while LH causes ovulation and further stimulates progesterone and oestrogen production [7]. Impairment of the HPG axis thus has direct consequences for fertility in males and females (▶ **Fig. 1**). The interaction between the hypothalamic-pituitary-adrenal (HPA) axis, which integrates internal and external stress response, and the HPG axis may also contribute to possible effects of COVID-19 infections on human fertility (▶ **Fig. 1**). In response to stress, the adrenal glands secrete glucocorticoids such as cortisol that diminish LH release in the pituitary and sex hormone production in the gonads [8]. This is particularly important, as glucocorticoids such as dexamethasone are the most commonly used therapeutic approach to limit the progression of severe COVID-19 and inflammation [9, 10] and exogenous glucocorticoid administration is well known to cause temporary impairment of fertility [11].

In the present review, we examine possible entry pathways of SARS-CoV-2 virus into human gonads and the current knowledge of subsequent COVID-19 infection and its short- and possible long-term effects on human fertility.

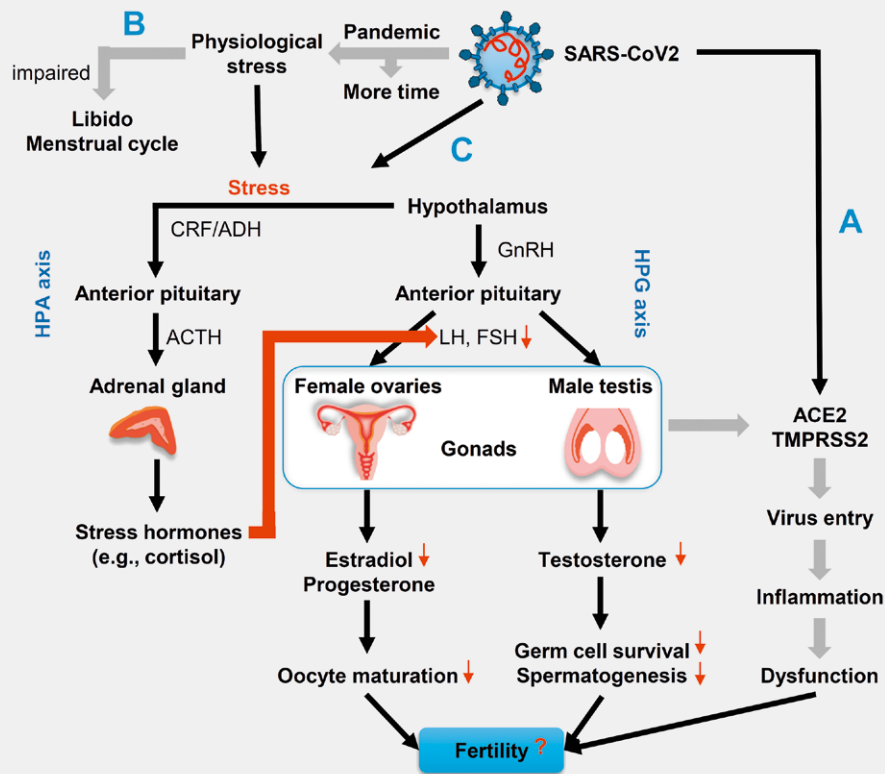## ACE2 and TMPRSS2 expression in testis and ovaries

SARS-CoV-2 virus entry is highly dependent on the co-expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine subtype 2 (TMPRSS2) on the surface of the target cell [12]. In addition to an age- and sex-dependent expression of both enzymes, the expression is dependent on the respective tissue and is thus directly involved in the virus vulnerability of specific tissues [13, 14].

The testis is one of the organs with high constitutive expression of ACE2 due to its physiological functions in Leydig cells, including the regulation of testosterone production and balancing the local vascular regulatory system by the modulation of Angiotensin II to Angiotensin I conversion [15–17]. ACE2 and TMPRSS2 proteins are predominantly expressed in the cytoplasm and membrane of spermatocytes, spermatids, and Sertoli cells; increased levels of ACE2 and TMPRSS2 have been observed in testicular tubules in elder patients with COVID-19 [18]. Testicular mRNA levels of *ACE2* and *TMPRSS2* also increase in COVID-19 patients [18]. Another study including also younger men (32–88 years) confirmed expression of *ACE2* in Sertoli cells, spermatogonia, fibroblasts, and Leydig cells [19]. Our own data showed an equally strong ACE2 expression in the testicular tubuli and interstitium (▶ **Fig. 2**). Single-cell RNA sequencing indicates that *ACE2* is predominantly enriched in spermatogonia and Leydig and Sertoli cells [20]. Gene Ontology (GO) categories associated with viral reproduction and transmission are highly enriched in *ACE2*-positive spermatogonia, while male gamete generation-related terms are downregulated [20]. ACE2 expression in normal testis cells decreased with increasing age [21]. Male gonads constitute a potential target tissue for SARS-CoV-2.

The ovaries are the core of the female reproduction system, and cell damage, for example, caused by SARS-CoV-2 infection, or pathologies such as endometriosis can lead to infertility. A co-expression of ACE2 and TMPRSS2 was observed predominantly in oocytes and partially in granulosa cells [22]. Our research revealed a dominant ACE2 expression in ovarian hilus and minimal expression in ovarian cortex (▶ **Fig. 2**). No differences in the expression of *ACE2* and *TMPRSS2* in the ovaries were found in dependence on age [22]. The abundant expression of ACE2 in the female reproductive system is associated with the generation of angiotensin (1–7) which stimulates ovarian follicle growth, oocyte maturation and ovulation [23]. In rats, ACE2 expression and activity are increased during pregnancy, in particular in the placenta and the uterus [24]. However, ACE2 expression appears to be lower in the human ovaries than in the testis (▶ **Fig. 2**), which may indicate a higher susceptibility of the male gonads for SARS-CoV-2 than the female gonads.

Dipeptidyl peptidase-4 (DPP4) expression in the gonads

In addition to ACE2 and TMPRSS2, there is emerging evidence that SARS-CoV-2 uses DPP4 (also known as cluster of differentiation 26) as co-receptor during host cell entry [25, 26]. Single-cell RNA sequencing reveals expression of *DPP4* in the human testis (spermatogonia and spermatogonial stem cell) and ovaries (predominantly endothelial cells) [27]. Besides *ACE2* and *TMPRSS2*, *DPP4* is also expressed in the human placenta [28]. DPP4 expression also plays an important role in polycystic ovary syndrome (PCOS), which is a common hormonal dysfunction among women of reproductive

▶ **Fig. 1** Potential factors that may affect fertility in females and males during the COVID-19 pandemic: **a**: SARS-CoV-2 virus entry is highly dependent on the expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine subtype 2 (TMPRSS2) and a simultaneous expression in human gonads could cause local inflammation after virus entry leading to tissue dysfunction. **b**: Physiological stress during the ongoing pandemic may also have an impact on the libido and the menstrual cycle. **c**: The interaction between the hypothalamic-pituitary-gonadal (HPG) axis and the hypothalamic-pituitary-adrenal (HPA) axis plays a crucial role in human fertility, and a possible imbalance caused by SARS-CoV-2 infection could affect fertility in the short and/or long term. ADH: Antidiuretic hormone; ACTH: Adrenocorticotropic hormone; CRH: Corticotropin-releasing hormone; FSH: Follicle-stimulating hormone; GnRH: Gonadotropin-releasing hormone; LH: Luteinizing hormone.
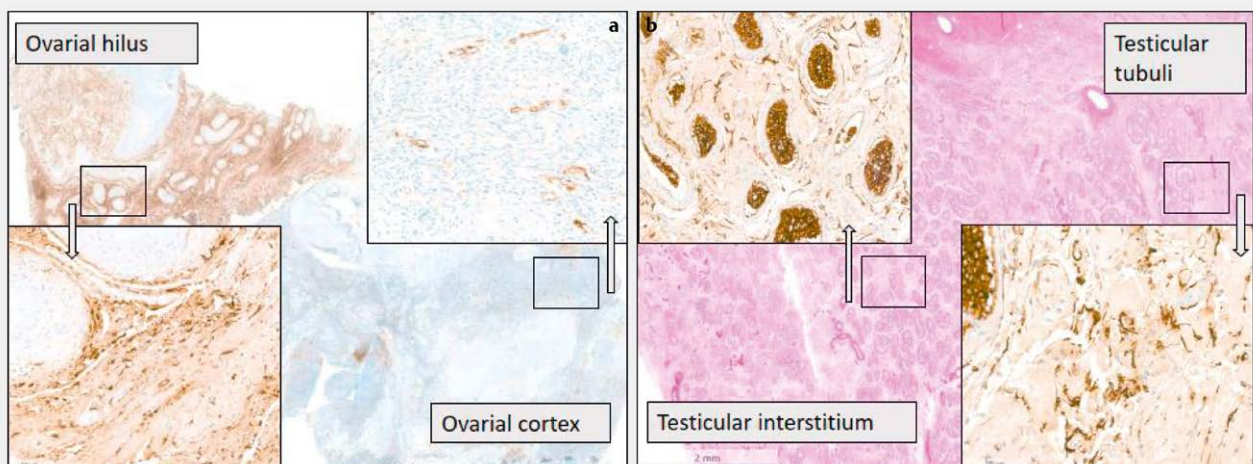
▶ **Fig. 2** Differential ACE2 expression in ovary and testis: **a**: Representative histology from the ovary of an 87-year-old patient who died from SARS-CoV-2 infection and revealed detectable SARS-CoV-2-RNA (not shown) in post-mortem ovarian tissue at autopsy. Immunostaining for ACE2 shows a prominent expression in ovarian stromal cells of hilus (left side of the image) and a weak expression in some cortical stromal cells (right side of the image). **b**: Representative histology from the testis of a 56-year-old patient who died from SARS-CoV-2 infection. The background shows a conventional HE-stain of the autopsy sample. Immunostaining for ACE2 demonstrates a strong expression in all cellular elements of the tubuli (Sertoli and spermatogonia, left side of the image) and a middle-strong expression in the Leydig cells in the testicular interstitium (right side of the image).

age (prevalence of 5–20% in women) characterised by abnormal androgen levels associated with the appearance of numerous small cysts formed in the ovaries [29]. PCOS is associated with infertility and increased risk for type 2 diabetes, venous thromboembolism, cerebrovascular and cardiovascular events, and endometrial cancer [29]. Young age and female sex are normally associated with a lower risk of severe or even fatal COVID-19 [30], but female patients with PCOS present a distinct subgroup of women with a potentially higher risk for adverse COVID-19 outcomes [31]. A population-based cohort study revealed an increased COVID-19 infection rate in women with PCOS compared with age and general practice matched control women [32]. Androgens regulate transcription of *TMPRSS2* and *DPP4* [33], which may contribute to the higher SARS-CoV-2 infection rates in women with PCOS. In addition, the increased rates of comorbidities including type 2 diabetes and cardiovascular disease may contribute to the severity in these patients. DPP4 inhibitors, commonly used in people with diabetes, diminish levels of free androgens in patients with PCOS and affect innate immune response [34, 35], which may also be beneficial in the context of COVID-19, especially in patients with PCOS.

DPP4 expression was detected in several testicular peritubular cells and cells of the interstitial space indicating a potential impact on spermatogenesis [36]. In rats, DPP4 inhibitors vildagliptin, and sitagliptin showed promise in protecting against testicular torsion/detorsion-induced injury through an anti-inflammatory effect augmented by nitric oxide synthase inhibition [37]. The expression of DPP4 in human gonads, which may be increased by various medical conditions such as PCOS, provides further evidence that the gonads may be a potential target for SARS-CoV-2.

Female gonads, fertility, and COVID-19

Viral diseases such as hepatitis B and Zika virus infection have already been linked to impaired fertility in women [38]. There is also indirect evidence that SARS-CoV-2 might affect female fertility by engaging ovarian tissue and granulosa cells, thereby diminishing oocyte quality and ovarian function [39]. However, a cohort autopsy study failed to detect SARS-CoV-2 in the ovaries (n = 7) [40]. Endometrial epithelial cells might also be infected due to the expression of ACE2, which might affect early embryo implantation [41]. In an observational, single-centre study including 78 females of reproductive age, ovarian injury, including declined ovarian reserve and reproductive endocrine disorder, was observed in women infected with COVID-19 [42]. Another retrospective cohort study found no evidence that a history of SARS-CoV-2 infection in females may negatively affect female fertility, embryo laboratory outcomes, or clinical outcomes in assisted reproductive technology treatments [43]. Long-term sequelae of COVID-19 infection affecting female fertility have been described in a few isolated cases (see long COVID section). Not only COVID-19 infection itself can affect female fertility, but psychological stress during the pandemic may also have consequences. In a survey study (1031 females), 46% of the participants reported a change in their menstrual cycle, and 53% reported worsening of premenstrual symptoms since the onset of the COVID-19 pandemic [44]. Menstrual disorders seem to be generally more common during the pandemic than before [3]. Female fertility is affected by a variety of factors, and current data do not provide sufficient evidence to determine whether infection with SARS-CoV-2 can temporarily or even permanently impair female fertility.

Male gonads, spermatogenesis, fertility, and COVID-19

Various viruses including Ebola virus, Zika virus and cytomegalovirus have been reported in human semen, among these some can affect male fertility [45, 46]. Moreover, viruses such as HIV, mumps, hepatitis B and C, papilloma-family (HPV) and Epstein–Barr (EBV) as well as SARS-CoV (2002) are described to cause viral orchitis [47]. The testis is among the few organs with immune privilege, which allows them to remain intact and unaffected by host response to antigen introduction [48]. This may explain why proteome analysis in testes of COVID-19 patients revealed only a small number of differentially expressed proteins compared with non-infected samples, whereas other organ types showed much more changes when infected with SARS-CoV-2 [49]. All of the identified proteins were downregulated compared with the non-COVID-19 infected controls (*ACLY*, *FASN*, *SQLE*, *FDFT1*, *INSL3*, *FAM83F*, *RNF216*, *DRC7*, *TM7SF2*, *SARAF*) [49].

Theoretically, SARS-CoV-2 may affect the male reproductive system in a number of ways by altering: (a) testicular architecture; (b) reproductive hormone profile; (c) spermatogenesis (ejaculate quality); (d) sperm function; (e) sexual/erectile function; (f) a combination of the former [50]. A prospective cohort study indicates that COVID-19 infection may be accompanied by a short-term decline in fertility in men [51]. Histopathological examinations on testicular and epididymal specimens of COVID-19 patients revealed the presence of interstitial edema, congestion, red blood cell exudation in testes, and epididymides [52]. The number of apoptotic cells within seminiferous tubules was significantly increased and the concentration of CD3$^+$ or CD68$^+$ interstitial cells of the testicular tissue was enhanced in sections of COVID-19 patients compared to control cases [52]. Nevertheless, CD3$^+$ and CD68$^+$ positive cells are also present in epididymides under physiological conditions and play there a role in phagocytosis [53]. An autopsy-based study on COVID-19 positive patients demonstrated the presence of SARS-CoV-2 RNA in 47% of examined testicles [54]. In another study, infection with SARS-CoV-2 has been detected post-mortem in 3 of 12 testicular specimens [40]. Hematoxylin and eosin staining revealed a normal spermatogenesis in three COVID-19 positive men, whereas spermatogenesis was impaired in three COVID-19 positive men with elevated ACE2 levels [55].

These data suggest an impairment of spermatogenesis in COVID-19 patients, which might be explained in part by an enhanced immune response in the testes. A prospective cohort study including 120 Belgian men who had recovered from COVID-19 showed that semen were not infectious with SARS-CoV-2 one week or more (mean 53 days) after infection, but the sperm quality was partly suboptimal [56]. This is in contrast to another group that detected SARS-CoV-2 in semen of COVID-19 patients (6 out of 38), including recovered patients (2 out of 23) [57]. In another study, eight out of 12 patients infected with COVID-19 had normal semen quality [58]. A study comparing 81 reproductive-aged men with SARS-CoV-2 infection found that serum LH was significantly increased, but the ratio of testosterone to LH and the ratio of FSH to LH were dramatically decreased compared to age-matched healthy

men (n = 100) [59]. The authors also confirmed these findings in a larger cohort [58], which may also have implications for the fertility of men infected with SARS-CoV-2. Fever, a symptom observed in many patients infected with COVID-19, can induce oligozoospermia and apoptosis, which may also alter sperm parameters even in absence of an enhanced immune response in the testes [60, 61]. Potential confounding factors, such as the age of the male infected with SARS-CoV-2, could have an additional effect on sperm quality [62], which were only partially considered in the present studies. The ability to detect SARS-CoV-2 in seminal fluid is further of great importance for reproductive medicine, particularly for reproductive technology and sperm cryopreservation [63], since viruses stored in liquid nitrogen could retain their pathogenic potential [64]. The exact mechanism and full extent of how SARS-CoV-2 may affect male fertility remain unclear and extensive prospective studies are needed to fully address these questions.

Human fertility and SARS-CoV-2 vaccines

COVID-19 vaccines are the most effective tool to protect against severe COVID-19 infections and to combat the current pandemic, but some individuals of reproductive age remain unvaccinated against SARS-CoV-2 due to concerns about potential adverse effects on fertility. Clinical trials for COVID-19 vaccines approved in the UK (Pfizer/BioNTech, Moderna, AstraZeneca) revealed no difference in the rate of unintended pregnancies in the vaccinated groups compared with the non-vaccinated groups, which indicates that the vaccines do not prevent pregnancies [65]. A small study showed that neither SARS-CoV-2 infections nor BNT162b2 mRNA vaccine (Pfizer/BioNTech) altered ovarian follicular function compared with uninfected and unvaccinated women [66]. Moreover, mRNA based SARS-CoV-2 vaccines do not appear to induce differences in ovarian stimulation and embryological variables between in vitro fertilisation cycle [39]. Some studies report menstrual cycle changes, including small changes in cycle length in some individuals after COVID-19 vaccinations [67–69], but these changes normalised rapidly after vaccination. Moreover, a study in rats found no adverse effects of BNT162b2 on female fertility or reproduction [70].

Two studies investigated the effects of BNT162b2 and mRNA-1273 (Moderna) vaccination on sperm parameters and found no differences in the sperm concentration, semen volume, sperm motility, and total number of motile sperm [71, 72]. A prospective cohort study suggests that SRAS-CoV-2 infection may be associated with a short-term decline in fertility in men, whereas no differences were observed in women or after COVID-19 vaccination in either sex [51]. Available data do not indicate adverse effect of currently available vaccines on female and male fertility, thus providing a safe route out of the current COVID-19 pandemic.

Long COVID and reproduction

A substantial proportion of patients who have recovered from COVID-19 continue to suffer from various complications known as long COVID or post-COVID-19 syndrome. Nonspecific, persistent symptoms that were associated with long COVID include chronic fatigue, muscle weakness, weakness, sleep disturbances, anxiety, and depression [73, 74], but only little is known about potential long-term effects on reproduction after overcoming a SARS-CoV-2 infection. A case report described a 34-year-old woman who had already given birth to one child and now presented with infertility 12 months after her COVID-19 infection as a long COVID consequence [75]. In another case, a 34-year-old woman suffered from premature ovarian insufficiency with high gonadotropin levels and a very low progesterone level of 0.3 nmol/l after COVID-19 infection [76]. After her SARS-CoV-2 infection, she was referred to a long-COVID clinic due to persistent fatigue and continuing myalgia. Moreover, her menstrual cycle became irregular with oligomenorrhea and she began to have regular hot flashes and night sweats [76]. In males, an immunohistochemical study demonstrated the presence of COVID-19 virus particles in in the penis long after the infection [77]. Moreover, expression of endothelial nitric oxide synthase, a marker of endothelial function was decreased in men previously infected with COVID-19 compared to non-infected control men [77]. As a consequence erectile dysfunction may occur and is further favoured by other factors that may be associated with long COVID, such as endocrine and cardiovascular complications, stress and potential side effects of treatments [78]. Even six months after recovery from an acute COVID-19 infection, malformed sperms were still detected in one patient [79]. A prospective longitudinal cohort study including 84 males with confirmed COVID-19 and 105 healthy controls found significant impairment in sperm morphology, sperm concentration, semen volume and the number of spermatozoa in COVID-19 patients up to 60 days post-infection [80]. As a further long-term consequence after COVID-19 anorgasmia was described in two male patients [81]. In terms of long COVID, not only organ-dependent influences on reproduction should be considered, but also psychological factors, such as depression and sleep disturbance [82, 83], which may have adverse effects on sexuality.

Conclusion

Despite an increasing number of studies addressing the impact of COVID-19 infections on human gonads and reproduction, the long-term consequences of the COVID-19 pandemic cannot be completely assessed at this point. Prospective long-term and mechanistic studies are needed to understand possible effects of COVID-19 on human reproduction and to use these findings for potential new therapeutic approaches. At this stage, the available data suggest that if there are any changes in fertility due to COVID-19, they appear to be temporary, except in very rare cases.

Conflict of Interest

The authors declare that they have no conflict of interest.

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