COVID-19 pandemic: what about the gonads?

Alev Selek 1 · Metin Güçlü 2 · Şinasi Erol Bolu 3

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Abstract
The novel SARS-CoV-2 has spread to virtually all countries of the world infecting millions of people, the medical burden of this disease obviously being enormous. The gonads of both sexes are among the organs that may be affected by COVID-19 and/or may affect the severity of the disease. The clinical spectrum of SARS-CoV-2 infection clearly differs between genders. The current evidence indicates that the underlying mechanism of such an interaction could be associated with genetic, hormonal, and immunological differences, as well as with gender differences in such habits as smoking and alcohol use. On the other hand, there are controversies as to how and to what extent the gonads could be affected by COVID-19, possibly impacting upon sex steroids, fertility, and other functions. This review underlines the possible mechanisms that could clarify these questions concerning COVID-19 and the gonads. In addition, reference is made to potential new treatment modalities presently under investigation, these supported by accumulating data published in the recent literature.

Keywords COVID-19 · Angiotensin-converting enzyme 2 · Transmembrane serine protease 2 · Androgen · Estrogen · Gonads

Introduction
The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has affected millions of people in virtually every country of the world, while ever greater awareness of the medical burden of the disease and knowledge about its management and treatment are constantly developing. Coronavirus disease 2019 (COVID-19) is a disease of multiorgan involvement, but emerging data point to the possible effects on organs and systems that have not until now been fully considered. The gonads of both males and females are among suspected organs which may be affected by and/or affect the severity of COVID-19. The SARS-CoV-2 pandemic may be called a sexually dimorphic disease, early Chinese reports [1, 2] and later global studies [3, 4] having suggested that women are less susceptible to COVID-19, and female patients exhibit a significantly lower mortality rate compared with males. There are a number of postulations regarding possible mechanisms driving this gender imbalance [5–7].

Angiotensin-converting enzyme 2 (ACE2) plays a key role in SARS-CoV-2 infection. It mediates viral infection but also exerts important regulatory effects on the immune system mainly during acute lung injury [8, 9]. The presence of ACE2 on almost all testicular cells, as documented in the literature [10, 11], raises important questions, among them whether male fertility and gonad functions are affected by SARS-CoV-2 infection. Meanwhile, it has also been shown that estrogen (E2) regulates the expression of SARS-CoV-2 receptor ACE2 in pulmonary epithelial cells [7]. Such emerging literature data also warrant investigation as to the pros and cons of estrogen therapy in COVID-19.

Estrogen and testosterone have different effects on the strength of immune responses, which may result in different disease courses and outcomes between males and females, with females exhibiting stronger immune responses than males [5, 12], this possibly being a reason for the better outcomes of females infected by COVID-19. The aim of this review is to clarify a number of issues regarding COVID-19
and the gonads of both sexes with the help of the emerging data published in the recent literature. We evaluate herein all studies on male and female reproductive functions associated with COVID-19 infection published in the English literature. A literature search was conducted in the PubMed, Scopus, Web of Science, ScienceDirect, Embase, and Google Scholar databases with search terms including “SARS-CoV-2,” “COVID-19,” “angiotensin-converting enzyme 2,” “transmembrane serine protease 2,” “androgen,” “estrogen,” “gonad,” “fertility,” “spermatogenesis,” “testosterone,” “male hypogonadism,” and “gender” until November, 2020. A total of 212 articles were found, of which 114 were included based on their relevance to this review and scope. Additional sources were identified from citations of the retrieved literature.

COVID-19 and the female gonads

Estrogen and ACE2

ACE2 is a transmembrane protein which mainly has protease functions, leading to cleavage of angiotensin I into inactive angiotensin [8, 13], thus counterbalancing the effects of the renin-angiotensin-aldosterone system (RAAS) [8, 14]. ACE2 additionally acts as a receptor for SARS-CoV-2 with high affinity and mediates the viral infection of cells, enabling easier human-to-human transmission [8, 15]. Transmembrane serine protease 2 (TMPRSS2) is also needed to allow fusion of the virus and host cell membranes [16].

ACE2 is mainly expressed in the human heart, kidney, lungs, liver, intestine, and testis [17]. More recently, it was found that ACE2 is also expressed in human ovaries, oocytes, and endometrial tissue, although its functional role is still unclear [18–20]. Emerging studies in the last decade have suggested that ACE2 may regulate the production of estradiol and progesterone [21] and may enhance ovulation [22, 23] and the maturation of human oocytes [24]. Furthermore, ACE-2 is thought to have an effect on menstrual cycles by regulating the regeneration of endometrium and myometrium activity [20]. TMPRSS2 is more broadly expressed than is ACE2, and co-expression of ACE2 and TMPRSS2 has been shown in testicular, endometrial, and placental cells and in nonhuman primate ovarian cells in various studies [25–27]. The latter strongly suggests that endometrial tissue, oocytes, and ovaries are possible candidate sites for the SARS-CoV-2 infection. However, there have to date been no reports of the virus in the female reproductive tract. In addition, current data on other coronaviruses, especially SARS-CoV-1, indicate that the female reproductive system may be spared from viral infection [28].

On the other hand, unlike ACE2 actions, E2 might affect ACE2 expression. Kimberly et al. observed that high concentrations of E2-treatment reduced ACE2 mRNA expression in differentiated airway epithelial cells. Although they conclude that this reduction might not necessarily translate into a reduction of ACE2 protein on the cell surface, E2 can regulate the expression of ACE2 in differentiated airway epithelial cells [7].

Estrogen and sexual dimorphism in COVID-19

All reports, including the most recent, confirm that female patients exhibit a lower disease morbidity and mortality rate compared to male patients after COVID-19 infection [29, 30]. An Italian retrospective data reported that among 1591 consecutive severe COVID-19 patients referred for admission to intensive care, 1304 (82%) were men, this being similar for all age groups [31]. Moreover, large studies showed that the male-to-female mortality ratio was 2, particularly among patients over 70 years of age [26]. The question which is thus posed is why women are protected. In this regard, recent studies have postulated a number of mechanisms to account for this phenomenon, including ACE2 expression, smoking, social role, and presence of comorbidities [32, 33]. However, the immunomodulatory effects of sex hormones seem to be the most important factor explaining the lower mortality rates among women [5, 26, 34].

Estrogen is the main female sex hormone. To date, many different studies have shown that E2 regulates the strength of both innate and adaptive immunity [5, 12, 35–37]. E2 exerts its effects through estrogen receptors (ERs), which are expressed differently in the subsets of immune cells: ERα is highly expressed on T cells and ERβ on B cells [38]. During the innate immune response, ERs on monocytes, macrophages, and neutrophils are activated via estrogen, leading to release of proinflammatory cytokines, chemokine, and interferon [36]. Further activation of lymphocytes and alveolar macrophages leads to decreasing virus replication, resulting in a rapid defensive response [36, 37]. After this nonspecific first barrier targeting invaders and slowing infection, adaptive immunity comes into play. Estrogen stimulates the humoral response to viral infections by inducing higher levels of antibodies and activating antibody-producing cells. This elucidates why females have stronger cell-dependent and humoral responses to infection and also to vaccination than do males [39]. Additionally, it was confirmed that leukocyte function and macrophage phagocytosis are more efficient in females than are these processes in males; thus, pathogen elimination is more rapid in females [40].

However, regarding the immunomodulatory effects of estrogen, the immune response to pathological conditions other than infection is different, especially with respect to autoimmunity [26]. Female sex is disadvantageous for autoimmune, estrogen facilitating the development of immune-pathogenic effects. E2 acts through its peripheral metabolites in autoimmune rheumatic diseases, and the intracrine synthesis of active estrogen metabolites at the level of cells involved
in the immune response seems to be the common pathway for immunostimulatory activity [41].

COVID-19 and female reproduction

Since SARS-CoV-2 is a novel virus, data regarding its impact on human reproduction are as yet limited. To date, there have been no reports of the virus in the female reproductive tract, in vaginal secretions, in amniotic fluid, or in peritoneal fluid [25]. Although there is abundant expression of ACE2 in the ovaries and oocytes, no information at present exists as to possible ovarian dysfunction after COVID-19 infection. The evidence thus far therefore suggests that SARS-CoV-2 infection is unlikely to have long-term effects on female fertility [25, 27].

ACE2 is widely expressed in the human placenta and the umbilical cord [42]. Therefore, the potential for vertical transmission of SARS-CoV-2 and a consequent impact on early and late pregnancy outcomes is another area of uncertainty that needs to be explored. Most of the literature on pregnancy in patients with COVID-19 has covered women in labor or near term or else during the third trimester. In a large cohort of 3923 women admitted for delivery, only 0.43% of cases were SARS-CoV-2-positive, and most of them were asymptomatic; on the other hand, no neonates were positive for SARS-CoV-2 at 24 h of life [43]. However, studies conducted in pregnant women with COVID-19 report little increase in maternal morbidity, especially as concerns the respiratory system and preterm birth [44]. Nevertheless, pregnancy outcomes of women with severe COVID-19 infection do not appear to greatly differ from those of non-infected mothers [25, 45, 46]. Limited data concerning early pregnancy showed that miscarriage was rare [44, 45]. Most cases were asymptomatic and the pregnancy course did not differ from what was expected [47].

Vertical transmission is another concern. Although expression of ACE2 has been documented in the placenta, co-expression with TMPRSS2 has not been reported, suggesting that placental cells may act as a barrier to vertical SARS-CoV-2 transmission [27]. This is compatible with the current studies on newborns born to SARS-CoV-2 infected mothers. Most of the early clinical evidence suggests that vertical transmission of SARS-CoV-2 from mother to newborn does not occur [27, 45, 47].

Estrogen as a treatment for COVID-19

The immunomodulatory effects of estrogen are thought to be related to its levels. E2 fluctuations during menstruation are associated with differences in immune activities; this is also reported in patients using exogenous estrogen for contraception or hormone replacement therapy [34, 48]. In vitro studies have demonstrated that high concentrations of E2 treatment may reduce ACE2 mRNA expression, which suggests that immunomodulation is more robust with high levels [7]. On the other hand, it is known that estrogen has a protective role in endothelial function [49] by preventing or reducing lung and intestinal injuries after ischemic trauma [50, 51]. E2 also has anti-inflammatory effects similar to those of glucocorticoids [52]. In addition, estrogen exerts antiviral activity by increasing virus-specific CD8 cells, decreasing the transcription of virus genes and virus trafficking [5]. Emerging evidence from these experimental studies suggests that estrogens can modulate lung inflammation; furthermore, they may be effective in the prevention and treatment of COVID-19 [5, 26, 53, 54]. New trials with estrogen treatment for COVID-19 are ongoing [55]. Table 1 summarizes the evidence of a relationship between COVID-19 and the female gonads.

Table 1 Summary of the evidence of a relationship between COVID-19 and female

| ACE2/TMPRSS2 expression and estrogen |  |
|---|---|
| • ACE2 is expressed in human ovaries, oocytes, and endometrial tissue. |  |
| • TMPRSS2 is more broadly expressed and co-expression of ACE2, and TMPRSS2 has been shown in testicular, endometrial, and placental cells and in nonhuman primate ovarian cells. |  |
| • ACE2 may regulate the production of estradiol and progesterone, while it may enhance ovulation and the maturation of human oocytes and regulate the regeneration of endometrium and myometrium activity. |  |
| • E2 can regulate the expression of ACE2 in differentiated airway epithelial cells. |  |

Estrogen and sexual dimorphism in COVID-19

• Female patients exhibit a lower disease morbidity and mortality rate compared to male patients after COVID-19 infection.
• The immunomodulatory effects of sex hormones seem to be the most important factor for lower mortality rates among women.
• Females have stronger cell-dependent and humoral responses to infection and vaccination than males.
• Because leukocyte function and macrophage phagocytosis are more efficient, pathogen elimination is more rapid in females than in males.

COVID-19 and female reproduction

• Although there is abundant expression of ACE2 in the ovaries and oocytes, there is to date no evidence of ovarian dysfunction after COVID-19.
• Limited data concerning early pregnancy showed that miscarriage is rare.
• Pregnant women with COVID-19 show little increase in maternal morbidity, especially related to the respiratory system and preterm birth, while pregnancy outcomes of women with severe COVID-19 infection do not appear much different from those of non-infected mothers.
• Early clinical evidence suggests that vertical transmission of SARS-CoV-2 from mother to newborn does not occur.

Estrogen as a treatment for COVID-19

• Emerging evidence suggests that estrogens can modulate lung inflammation; furthermore, they may be effective in the prevention and treatment of COVID-19.
• New trials with estrogen treatment for COVID-19 are ongoing.
COVID-19 and the male gonadal axis

Factors determining higher COVID-19 prevalence and mortality in men

Sexual dimorphism and comorbid diseases

COVID-19 disease primarily affects vulnerable individuals with preexisting conditions, among whom it has caused more than 600,000 deaths [2, 56]. Although advanced age is the main determinant of the severity of COVID-19 disease course and related mortality in both sexes, men have worse clinical outcomes independent of age [3]. It is reported that worse results are seen in men at all stages of the disease, such as admission to intensive care units and need for ventilation support [4]. Sexual dimorphism in prevalence and severity of numerous diseases is not limited to viral diseases, also being observed in cardiovascular, lung, and autoimmune diseases. Generally speaking, unhealthy lifestyle habits such as smoking and alcohol consumption, often leading to cardiovascular diseases, hypertension, and diabetes, are more common in men, and all of these occur at younger ages than in women [57, 58]. It has moreover been determined that these comorbidities are the most common conditions related to increased COVID-19 mortality. In many studies, hypertension was the most common comorbidity, followed by diabetes and coronary heart disease [59]. Studies have demonstrated similar sexual differences during past coronavirus infections such as SARS-CoV-1 and MERS-CoV [60]. In a study by Channappanavar et al., female and male mice of different age groups were analyzed for their susceptibility to infection by infection with SARS-CoV-1. They observed that male mice were more susceptible to SARS-CoV-1 than female mice, and the significance was more prominent with advancing age [36]. Sexual selectivity has attracted considerable attention, and male gender has been shown to be the most important independent risk factor for COVID-19 in a study from China. This trend was still obvious when comorbidities were excluded [61, 62].

Androgen levels

Although androgen levels were proposed as a critical factor in determining male susceptibility to COVID-19, the effect of androgen levels has not, in fact, been demonstrated in many research studies. While males show similarly low testosterone levels both before puberty and at advanced ages, boys are less susceptible to COVID-19 infection than older male adults. In contrast, despite the high testosterone levels of male neonates and post-pubertal boys, the COVID-19 infection rate was not increased in babies at the 6th to 8th week after delivery [29], while COVID-19-related mortality is not particularly high among adult men, who display the highest testosterone levels among adult males [63, 64]. All these results indicate that age and comorbid diseases are more important factors than testosterone levels in the spread and severity of COVID-19 disease among men [65]. A large German cohort study reported that the majority of the male patients with COVID-19 who were transferred to intensive care units have had low testosterone levels [66]. Rastrelli et al. also reported that poor prognosis and high mortality rates were associated with lower total and free testosterone levels in SARS-CoV-2 infected men when they were admitted to respiratory intensive care units [67]. To conclude, according to emerging data, gender disparity in COVID-19 disease severity cannot be explained by androgen levels alone.

Could the use of cigarettes affect the frequency and severity of the disease?

Unhealthy habits like smoking and alcohol consumption are more common in men than in women. Initially, these habits were thought to be possible determinants of sexual disparity in COVID-19 disease severity: some of the studies indicated that cigarette smoking induces elevated ACE2 expression in the respiratory tract and that smokers have a higher susceptibility to COVID-19 than nonsmokers [57, 68, 69]. Of interest, the high risk of smoking during disease activity was also demonstrated during previous MERS-CoV infections [70]. In contrast, however, a study from Italy pointed out that 84.4% of patients with COVID-19-related pneumonia had never smoked and 20 (15.2%) were former smokers [71]. Another study from New York City and a meta-analysis written by Lippi et al. have also reported that current smoking rates among COVID-19 patients were below those of their respective general populations [72, 73]. Nonetheless, although no direct relationship can be demonstrated between current smoking and COVID-19 disease activity, SARS-CoV-2 infection is seen to be more severe in smokers [74].

Androgen receptors, CAG repeats, and androgen sensitivity

Different theories have been proposed to explain sexual dimorphism in COVID-19, such as variability in androgen sensitivity, androgen receptor action, and even gene polymorphism [75]. However, there are contradictions among many of the proposed ideas. Androgenetic alopecia (AGA), also known as male pattern hair loss, may be a symptom of hyperandrogenism. This was first observed in Spain where there were very high rates of patient mortality: the finding was named the Gabrin sign. Goren et al. noted the presence of the bilateral pneumonia accompanied by AGA in 71% of men diagnosed with COVID-19 [75]. It is well known that androgen sensitivity is associated with CAG repeat length and polymorphisms on the androgen receptor gene. Male sex steroids exert their effects through the androgen receptor in both
men and women. Hyperandrogenic findings such as oily skin, acne, and androgenetic alopecia have been shown to be associated with short CAG repeat length [61]. Interestingly, short CAG repeats cause different metabolic consequences in males and females. While high androgen levels in men are associated with favourable health status, such as increased insulin sensitivity and lean body mass, they can lead to abdominal obesity and insulin resistance in women [76, 77]. Similarly, in women diagnosed with PCOS, it is believed that shorter CAG repeats in the androgen receptor gene may cause negative effects [78]. Therefore, it is thought that worse outcomes of COVID-19 in men may be associated with CAG repeat length on the androgen receptor gene.

**Androgens and immune modulation**

As demonstrated in previous reports, immune response might be modulated by androgens, and testosterone can suppress innate immune responses. Ultimately, a less robust immune response is generated in males than in women, as well as a decrease in antibody response to viral infection [58, 79]. It has been hypothesized that this is one of the possible mechanisms that may weaken immune defense against SARS-CoV-2 [57]. The effect of androgens on immune modulation is not limited only to antibody response: it can also increase the number and function of circulating neutrophils. In this way, androgens can increase the production of growth factors and interleukins such as IL-1b, IL-10, and IL-2. It is hypothesized that this could be one of the possible mechanisms that may alter antiviral immune response to SARS-CoV-2 [80].

**Viral entry facilitated by androgens and effects of X chromosomes**

Endocytosis and fusion of the viral membrane with the membrane of the target cell have been defined as entryways of SARS-CoV-2 into the airways [81]. ACE2 plays a role as a receptor protein, while TMPRSS2 functions as a protease that cleaves the viral spike protein. Therefore, both ACE2 and TMPRSS2, regulated by the androgen receptor, are essential for viral activity and hosting of SARS-CoV-2 in pneumocystis [82, 83]. Gene expression of TMPRSS2 and ACE has been observed in many tissues, such as the pancreas, kidney, lungs, and both male and female gonads. The TMPRSS2 gene encodes TMPRSS2 as an enzyme, and it has been reported that expression of this gene was upregulated by androgenic hormones mainly in prostate cancer cells. Additional studies also showed that ACE2 and TMPRSS2 gene expression can be increased in all tissues by androgens [81, 84–86]. Both androgen receptor and ACE2 genes, and most of the genes regulating immune responses are located on the X chromosome. Some of these genes may play a role as disease-susceptibility genes in both sexes. The fact that males have only one copy of the X chromosome may play a part in male vulnerability during severe viral infections. Therefore, androgen sensitivity and production of the sex-specific steroids may be important factors for disease severity in men who are more susceptible to these effects [36, 87].

**Androgens and lungs**

The effect of androgens on the pulmonary system might also explain why males are more vulnerable to viral attacks. Viral infections may show opposite effects between aged males and pre-pubertal children [88, 89]. In a study by Channappanavar et al., male mice infected with SARS-CoV-2 displayed higher virus titers and increased inflammatory cell infiltration in their lungs. In addition, it was noted that male mice had increased pulmonary vascular permeability and alveolar edema in their lungs compared to age-matched infected female mice [36]. It is well known from other mouse studies that male neonates are more prone to developing neonatal respiratory distress syndrome than female. Moreover, during fetal development, the lungs of male fetuses develop more slowly, while they have a smaller number of types II pneumocystis and a smaller amount of surfactant, which plays an important protective role for the lungs and facilitates respiration. Surfactant synthesis is influenced by the androgen receptor. In addition, androgen receptor gene expression has been shown throughout the respiratory tract predominantly in the bronchial epithelium and PTII cells [90, 91]. These findings show that male selectivity of the lung pathologies might start from the mother’s womb and is multifactorial.

**Effects of COVID-19 on the hypothalamic-pituitary-testicular and male reproductive axes**

The hypothalamic-pituitary-testicular (HPT) axis is primarily responsible for regulating reproductive activity and orchestrating the release of both centrally and peripherally produced sex hormones. This is a very dynamic axis, and its activity lasts a lifetime; however, it may easily be altered by external factors. The hypothalamic-pituitary-adrenal, thyroid, and gonad axes can all be rapidly affected by viral infections such as COVID-19 [92, 93]. This effect can be exerted either directly via viral infiltration or indirectly as a consequence of systemic responses. During severe infection caused by SARS-CoV-2, many factors might affect this axis, such as the virus itself, medications used for treatment, environmental disinfectants, and psychological effects of the disease. Essentially, both the brain and the testicles are well protected against external influences via the mechanism called the blood-brain and blood-testicular barrier, respectively [94, 95]. Some of the viruses
can pass these barriers directly or owing to damaged barriers caused by the effects of systemic or local inflammation.

In the Endocrine Society Guidelines, hypogonadism is defined as “failure of the testes to produce physiological concentrations of testosterone and/or a normal number of spermatozoa due to pathology at one or more levels of the HPT axis.” Hypogonadism may be primary, due to testicular dysfunction, or secondary, due to the hypothalamic/pituitary diseases, and in some instances, the two may occur together. The cause of hypogonadism may be organic, or else, it can be due to congenital, structural, or destructive pathology that results in permanent hypogonadism, or functional caused by potentially reversible conditions that suppress gonadotropin and T concentrations [96]. All types of hypogonadism described above can be seen during SARS-CoV-2 infection. Concerning the hypogonadism patient with COVID-19, he or she may be affected by a wide spectrum of the disease [96–98].

It has been shown that ACE2, which is the primary entry route of SARS-CoV-1 to the target cells, is also expressed in hypothalamic and pituitary tissues [99], though to date, there are few data showing that the virus directly affects these tissues. In an autopsy series of patients who had died due to SARS-CoV-1, viral genomes have been identified in hypothalamic tissues, along with infarct, edema, and neuronal degeneration [100]. Many of the patients had described neurologic symptoms, anosmia, and ageusia during COVID-19 infection, symptoms that may be linked to a central cause and reflect the role of the hypothalamus and related organs [101]. Compared with healthy controls, in previous SARS virus attacks, serum prolactin, FSH, and LH levels were increased, and estradiol and progesterone levels were decreased, reflecting primary hypogonadism. By contrast, in cases of SARS-CoV-1, secondary hypothyroidism and adrenal insufficiency have frequently been observed, these possibly reflecting hypophysitis or direct hypothalamic involvements [92]. However, there have been conflicting findings during the current SARS-CoV-2 infection. In men with COVID-19, Ma et al. reported high levels of PRL and LH vs. low testosterone and follicle-stimulating hormone levels, reflecting primary testicular damage during active disease [102]. It is well known that testosterone levels in patients with COVID-19 are not a reliable marker of testicular function, as acute and severe infection can suppress the HPT axis and decrease circulating testosterone [96].

Almost all the testicular cells including seminiferous duct cells, spermatagonia, Leydig cells, and Sertoli cells express very high levels of ACE2 mRNA [103, 104]. This causes all tissues of the testicle to be affected by COVID-19 infection. As a result, the disease can easily spread to all testicular tissue and may affect male reproductive function. ACE2 expression on adult Leydig cells may play a crucial role in regulating steroidogenesis, whereas on Sertoli cells, it could affect sperm production. Orchitis, which can lead to germ cell apoptosis and disruption in spermatogenesis, was documented during the outbreak of SARS-CoV-1 in 2002 [105]. Additionally, orchitis has been revealed in testis autopsy specimens obtained from six patients who died of SARS-CoV-1 [106]. Not only SARS-CoV-1 but also many viruses such as HIV, hepatitis B and C, mumps, Epstein-Barr, and papilloma virus have been reported to affect the testicles. Although the testicles have a highly selective blood-testis barrier, it is well known that the male reproductive system is vulnerable to many viral infections [107, 108]. Holtmann et al. reported that, after a mean of 43 days following a positive SARS-CoV-2 result, the virus was not detected in the semen of recovered or acutely infected men with SARS-CoV-2 [109]. In contrast, about 15% of the semen samples from COVID-19 patients were reported positive for SARS-CoV-2 in another study. There are conflicting reports about the presence of SARS-CoV-2 in the semen of patients who were previously diagnosed with COVID-19. On the other hand, sexual transmission of the virus has not been shown to date [110–113].

Very recently, a study published by Li et al. demonstrated that histopathological testis and epididymal tissues were abnormal in male patients with COVID-19 [114].

Table 2 Summary of the factors associating the higher prevalence and mortality rate in males and effects of SARS-CoV-2 on the male reproductive system

Aging and comorbid diseases

- Progressive decline in testosterone levels with aging
- Higher prevalence of comorbid diseases, such as DM, HT, and CVD
- COPD is more common in men and has a more severe course.

Sexual selectivity and genetic factors

- ACE2, which is the primary entry route of SARS-CoV to the target cells, is more highly expressed in males than in females.
- Both androgen receptor and ACE2 genes, genes involved in inflammation, are located on the X chromosome.
- Androgen receptor sensitivity for testosterone is different between males and females, which leads to reverse metabolic consequences.
- Testosterone has an impact on immune modulation.
- The lungs of males are more prone to disease development.

Behavioral and social differences, and other factors

- Males have a higher rate of smoking and alcohol consumption.
- Women are more vigilant concerning hand hygiene and more likely to seek preventive care.
- Males have more personal contact in business and travel settings.

SARS-CoV-2-related factors

- Male subjects have delayed viral clearance of SARS-CoV-2.
- Higher ACE2 expression levels have been demonstrated in the lungs of males.
- High ACE2 and TMPRSS2 expression in Leydig cells of the testis leads to further decrease in testosterone levels, which causes additional morbidity during acute illness.
- SARS-CoV-2 may affect the hypothalamic-pituitary-testicular axis, leading to decreased testosterone levels.
affected by COVID-19. Researchers have shown that the involvement is not limited to the testicular parenchyma but is also associated with increased apoptosis in germ cell lines. They detected a high ratio of CD3+ and CD68+ in interstitial cells, supporting the increased immune response against testicular tissue. In addition to decreased sperm concentration, increased seminal levels of IL-6, TNF-α, and MCP-1 were observed. These results showed that COVID-19 disease may have a greater impact on male fertility than expected [114]. Factors associating the higher prevalence and mortality in males and effects of SARS-CoV-2 on the male reproductive system are summarized in Table 2.

Conclusion

SARS-CoV-2 needs ACE2 and TMPRSS2 expression for viral activity, while androgens increase ACE2 and TMPRSS2 gene expression regardless of the levels. By contrast, estrogen might reduce ACE2 mRNA expression in differentiated airway epithelial cells. Therefore, viral entry seems to be easier in males, which may explain the gender difference in susceptibility to COVID-19. Females have stronger cell-dependent and humoral responses to infection, and pathogen elimination is more rapid in females than in males. Immunomodulatory effects of sex hormones may explain the sexual difference in COVID-19 disease severity and mortality. On the other hand, data concerning the effect of SARS-CoV-2 on the gonads, especially in males, are increasing. Both reproduction and sex steroid synthesis of males are found to be diminished by SARS-CoV-2 infection in some studies. Therefore, follow-up of patients to monitor for gonad function and even fertility should be encouraged after COVID-19. Lastly, sex steroids, mainly estrogen, can modulate inflammation and may therefore be effective in the prevention and treatment of COVID-19. Even androgen-modulating drugs could be evaluated as a potential treatment for COVID-19.

Authors’ contributions AS and SEB conceived the idea for the article and drafted it; AS and MG performed the literature search, data analysis, and writing process; and AS[D1] and SEB critically revised the work.

Declarations

Ethical approval This study was granted exemption from requirement of ethics approval since there is no ethical approval requirement for review articles in the Kocaeli University local ethics committee.

Conflict of interest The authors declare that they have no conflict of interest.

Consent to participate All authors give full consent for publication of this manuscript.

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