REVIEW

Is There Impact of the SARS-CoV-2 Pandemic on Steroidogenesis and Fertility?

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Summary

In December of 2019, several cases of unknown atypical respiratory diseases emerged in Wuhan, Hubei Province in China. After preliminary research, it was stated that the disease is transmittable between humans and was named COVID-19. Over the course of next months, it spread all over the world by air and sea transport and caused a global pandemic which affects life of everyone now-a-days. A large number of countries, have since been forced to take precautions such as curfews, lockdowns, wearing facemasks etc. Even with vaccines being produced in mass numbers, lack of targeted therapy continues to be a major problem. According to studies so far it seems that elderly people are more vulnerable to severe symptoms while children tend to by asymptomatic or have milder form the disease. In our review, we focused on gathering data about the virus itself, its characteristics, paths of transmission, and its effect on hormone production and secretion. In such, there is insufficient information in the literature worldwide, especially the ones that focus on the effect of COVID-19 on individual organs systems within the human body. Hence, the present evidence-based study focused on the possible effects of COVID-19 on adrenal gland and gonads i.e. on the process of steroidogenesis and fertility.

Key words

Adrenal gland • ACE2 • COVID-19 • Fertility • SARS-CoV-2 • Steroidogenesis • TMPRSS2

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Introduction

In Wuhan, Hubei Province, China, patients with an atypical type of pneumonia were diagnosed during the second week of December 2019. It was detected as a new coronavirus at this time, initially called nCoV-2019 (Ghaebi *et al.* 2020). In mid-January, with its specific description of "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), thus labeled as "Coronavirus disease 2019" (COVID-19), the genome of this pathogen was made public. This virus has spread rapidly worldwide and across mainland China, as of 10 August 2021, there have been 202 608 306 confirmed cases, including 4 293 591 deaths (WHO 2021c). The World Health Organization announced a pandemic state

for the entire world on March 11 (Bhagavathula *et al.* 2020, Silveira *et al.* 2021). SARS-CoV-2 is considered a public health issue as transmission rates are shown to be higher than other coronaviruses, primarily due to the risk of overloading intensive care units, thereby causing health systems to collapse (Silveira *et al.* 2021). In this review, we will focus on the virological features and pathogenesis of SARS-CoV-2, as well as diagnostic tools and, of course, possible impact on steroidogenesis.

Viral transmission

Viral infections are nowadays becoming an extremely serious issues to the public health. During last two decades, viral epidemics, including SARS-CoV (Severe Acute Respiratory Syndrome) which emerged in 2002-2003 with a case fatality rate (CFR) of 10 % (van Damme *et al.* 2020) and H1N1 influenza in 2009 have been recorded. MERS-CoV (Middle East Respiratory Syndrome coronavirus) has been the latest recorded epidemic, that emerged in Saudi Arabia (2012) (CFR 34 %) (Cascella *et al.* 2021, van Damme *et al.* 2020, WHO 2021b).

The First case of COVID-19 was detected in Wuhan, Hubei province, China on 31. December 2019. The etiology of this illness was attributed to a novel virus of coronavirus (CoV) family, SARS-CoV2 (Cascella *et al.* 2021). Soon after its identification, it became clear to the epidemiologists worldwide that its global spread was unstoppable. Stringent containment approaches including strict movement restrictions during the "lockdown", failed to restrict its spread. As a result, owing to its rapid uncontrolled outbreak in almost all countries within a few months, COVID-19 was declared a pandemic by the WHO (van Damme *et al.* 2020). Currently, entire world is afflicted by COVID-19 pandemic.

Infection spreading from bats, was the first marked as the possible origin of the disease (Fan *et al.* 2019), though to this day this has not been officially confirmed as the source of the first infection. No international preventive action was taken and the first details about the epidemic was released by National Health Commission of China in early 2020 (Lotfi *et al.* 2020).

COVID-19 occurs mainly in respiratory (nasal), fecal and blood samples of infected. Inhalation of droplets as well as contact with contaminated surfaces were discovered to be the main routes of transmission. It is expected to survive on various surfaces for extended periods of time. Similar as per influenza, wide expectations are that the virus will decrease with activity as the weather warms up during summer due to higher temperatures and increased exposure to UV rays (Esakandari *et al.* 2020).

Multiple precautions are currently in effect worldwide. Including global cure effort, lockdowns, curfews and use of disinfectants and face masks to prevent contact with face and respiratory tract are recommended.

Characteristics of SARS-CoV-2

The virus is single stranded 29.9 kb RNA β-coronavirus that is enveloped and positive-sense (Wu *et al.* 2020, Zhou *et al.* 2020). Further investigation of the viruses´ genome shown 88 % similarity with the bat-SL-CoVZC45 and bat-SL-CoVZXC21 sequences as well as over 96 % identity to bat CoV RaTG13 (Zhou *et al.* 2020). It has also been related to Malayan or Sunda pangolins in China (Lam *et al.* 2020). The protein-coding genes of COVID-19 have 79.5 % and 51 % similarities in sequence to SARS-CoV and MERS-CoV respectively (Lotfi *et al.* 2020). Similar to SARS-CoV, the virus employs Angiotensin-Converting Enzyme 2 (ACE2) receptor for cellular entry (Guo *et al.* 2020, Paces *et al.* 2020, Paraskevis *et al.* 2020, Zhou *et al.* 2020). This suggests that methods used to treat SARS-CoV and MERS-CoV might be also effective against COVID-19, although currently, there is no definite antiviral therapy developed for treating SARS-CoV-2 infection (Jha *et al.* 2021, Lotfi *et al.* 2020, Roychoudhury *et al.* 2021a). Given the frequent emergence of viral pandemics in the 21st century, proper understanding of their characteristics and modes of action are essential to address the immediate and long-term health consequences (Roychoudhury *et al.* 2020, Vašků 2020).

SARS-CoV-2 belongs to the beta coronavirus family as that of extremely pathogenic viruses such as SARS-CoV and MERS-CoV. It is a positive-sense single-stranded RNA (+ssRNA) and an enveloped virus. SARS-CoV-2 is regarded as a novel beta coronavirus infecting humans (Burrell *et al.* 2021, Jha *et al.* 2021). Although, the novel coronavirus has genetic features that are compatible with the family of coronaviruses it also has gene sequences different to already sequenced coronaviruses (He *et al.* 2020).

The most common symptoms of the disease are

fever, dry cough and tiredness. Less common symptoms are various aches and pains, sore throat, diarrhea, conjunctivitis, headache, loss of senses (taste, smell), skin rash or discoloration. It also causes serious symptoms such as difficulties in breathing or breath shortness, chest pain, loss of speech and movement (WHO 2021a).

Role of Angiotensin converting enzyme 2 and transmembrane protease, serine 2

Angiotensin converting enzyme 2 (ACE2) belongs to the dipeptidyl carboxydipeptidase family of angiotensin converting enzymes that are homologous to the human angiotensin 1 converting enzyme. Recently, it has been identified as a potent receptor for SARS-CoV, indicating connections of ACE2 with immunity, inflammation, and cardiovascular diseases (Gheblawi *et al.* 2020). The distribution of ACE2 expression was organ-specific, predominantly in the kidney, male testis, female breast, cardiovascular and gastrointestinal systems and adrenocortical cells in zona fasciculata and zona reticularis (Fu *et al.* 2020, Mao *et al.* 2021). Table 1 contains information on tissues showing ACE2 expression. A rank list of possible SARS-CoV-2 targets with lung AT2 cell (Alveolar Type II Cells) and macrophages as the top targets, followed by cardiomyocytes of heart, stromal cells in testis, ovary, adrenal, and thyroid glands. Among the above mentioned possible targets, the lung macrophages and the stromal cells in ovary and adrenal gland were identified for the first time, which could account for extreme clinical symptoms and rapid disease progression (Bost *et al.* 2020). The distribution of ACE2 expressions indicates that it may play a critical role in controlling cardiovascular and renal function, as well as fertility. Numerous studies have revealed the role of cell surface ACE2 as the cellular receptor for SARS-CoV and NL63 (Human coronavirus NL63) since the global outbreak of SARS in 2003. As 2019-nCoV is closely related to SARS-CoV, ACE2 has also been shown to be a major receptor of the novel 2019-nCoV (He *et al.* 2020, Li *et al.* 2007, Wu *et al.* 2009). The route of virus infection depends on the expression and distribution of the corresponding receptor as the virus reaches the cell by binding to cell surface receptors in order to complete intracellular replication, virus release, and other related cytotoxic activities (Fan *et al.* 2019, Jayawardena *et al.* 2019). SARS-spike CoV-2's glycoprotein (S protein) is necessary for binding to the host ACE2 receptor and membrane fusion. The conformational aspects of the interaction of the RBD (receptor-binding domain) of S protein with ACE2 have been elucidated by structural studies (Simmons *et al.* 2013, Walls *et al.* 2020, Wang *et al.* 2020a, Wang *et al.* 2020b). This binding triggers conformational changes in amino acids, which assist in the formation of salt bridges, the increase of van der Waals interactions, and the binding of ACE2 with a much higher affinity than SARS-CoV (Yan *et al.* 2020). Subunit S1 with the RBD that binds ACE2, membrane-fusion subunit S2, the transmembrane anchor, and the intracellular tail make up the S protein (Glowacka *et al.* 2011, Hoffmann *et al.* 2020, Wrapp *et al.* 2020). Recent studies have documented 10 to 20 fold higher binding affinity of the spike glycoprotein of the SARS-CoV-2 to ACE2 than that of SARS-CoV (Ni *et al.* 2020, Wrapp *et al.* 2020).

Transmembrane serine protease 2 (TMPRSS2) is a cell surface protein primarily expressed by endothelial cells of the respiratory and digestive tract. As a serine protease, it is involved in cleaving peptide bonds of proteins that have serine as the nucleophilic amino acid within the active site (Hoffmann *et al.* 2020). The cellular transmembrane protease serine S1 member 2 (TMPRSS2) is needed to cleave S2 protein from S1 and assist in membrane fusion in order for the receptor binding domain (RBD) of S1 to attach to the host ACE2 receptor. SARS-CoV-214 has a 10- to 20-fold higher receptor-binding ability than SARS-CoV and MERS-CoV due to certain special features of the S1 protein (Wrapp *et al.* 2020). TMPRSS2 serine protease was co-localized in adrenocortical cells in zona fasciculata and zona reticularis Mao *et al.* 2021, in certain testicle cells – stem germ cells, Leydig and Sertoli cells (Navarra *et al.* 2020), in kidney, lungs, stomach, liver and pancreas (Lü *et al.* 2020). Table 1 contains information on tissues showing TMPRSS2 expression. TMPRSS2 gene has a pivotal role also in prostate cancer development and progression (Mollica *et al.* 2020). In a recent study based on gene co-expression of ACE2 and TMPRSS2 in 24,519 human prostate cells, it was found that the 0.61 % of club cells and the 0.40 % of hillock cells showed co-expressions for TMPRSS2 and ACE2 (Song *et al.* 2020). The authors also reported higher TMPRSS2 and ACE2 co-expression in males pneumocytes I/II compared with female cells, representing an interesting evidence which could play a role in gender 'pattern' of COVID-19.

In another recent study, Prostate cancer patients receiving androgen deprivation therapy (ADT) had

a significantly lower risk of SARS-CoV-2 infection compared with patients who did not receive ADT (odds ratio: 4.05; 95 % CI: 1.55-10.59). This study sets the scenario for further studies assessing the role of antiandrogens commonly used for prostate cancer patients to prevent or treat COVID-19 (Montopoli *et al.* 2020).

Table 1. Pathophysiology of SARS-CoV-2 infection on the male reproductive system, female reproductive system and adrenal gland.

Tissues showing receptor expression	**ACE2**	Ovary, oocytes, uterus, placenta, seminiferous tubule, Leydig cells, Sertoli cells, spermatozoa, adrenal gland	Dutta and Sengupta 2020, Jing *et al.* 2020, Lü *et al.* 2020, Stanley *et al.* 2020
	TMPRSS2	Ovary, epididymis, prostate gland, seminal vesicles, adrenal gland	Dutta and Sengupta 2020, Jing *et al.* 2020, Lü *et al.* 2020, Stanley *et al.* 2020
Possible effect on adrenal gland		Adrenal lesions, necrosis, cortical lipid degeneration, hemorrhage, unspecific focal adrenalitis	Freire Santana *et al.* 2020
Possible effect on male reproductive system		Pathological changes in testes, reduction of Leydig cells, orchitis, affected semen parameters (such as sperm function and motility), lipid peroxidation; and DNA damage due to oxidative stress	Duarte-Neto *et al.* 2020, Dutta and Sengupta 2021, Holtmann *et al.* 2020, Yang *et al.* 2020
Possible effect on female reproductive system		Menstrual cycle changes, ovarian tissue damage, decrease in ovarian function and oocyte quality	Lü *et al.* 2020, Singh *et al.* 2020

SARS CoV-2 effect in the adrenal gland

SARS-key CoV's, just like the influenza virus, uses immunoinvasive tactics to knock down the cortisol stress response of the host. The SARS-CoV expression of certain amino acid sequences, which are molecular mimics of the host adrenocorticotropic hormone (ACTH), is a very fascinating hypothesis that has been suggested. The stress-induced increase in cortisol can also blunt this type of molecular mimicry, as antibodies produced against the viral particles will inadvertently kill the circulating ACTH, and so limiting the host's stress response (Wheatland 2004). The fact that most SARS-CoV-2 proteins are extremely homologous (95-100 %) to the original SARS-CoV proteins makes us wonder if SARS-CoV-2 might also use the same molecular mimicry strategy (Pal and Banerjee 2020, Xu *et al.* 2020). Patients with extreme COVID-19 could also be more likely to experience critical corticosteroid-related disease insufficiency (CIRCI). However, data on the dynamics of cortisol in patients with COVID-19 is not yet available (Akbas and Akbas 2021, Pal and Banerjee 2020). Information from the SARS outbreak indicates that the hypothalamic-pituitary-adrenal (HPA) axis could be affected by this disease (possibly also COVID-19) (Akbas and Akbas 2021).

Hypothalamic tissues and pituitary tissues express ACE2, allowing SARS-CoV-2 to target these tissues. While we do not have adequate evidence for now, given the neurological symptoms, it can be thought that COVID-19 directly or immune-mediated hypothalamus and pituitary are affected (Akbas and Akbas 2021, Pal and Banerjee 2020). Degeneration and necrosis of adrenal cortical cells were shown by autopsy findings in patients who died from SARS, suggesting a direct cytopathic effect of the virus. Besides, in the adrenal glands, viral antigens and the genomic sequence of SARS-CoV have been demonstrated. Therefore, cortisol dynamics are likely to be altered in patients with SARS (and probably

also with COVID-19) (Ding *et al.* 2003, Gu and Korteweg 2007). Therefore, cortisol dynamics are likely to be altered in patients with SARS (and possibly also patients with the occurrence of COVID-19). Similarly, 46 % of patients in whom adrenal insufficiency was not found had microscopic lesions in the adrenal glands detected in 28 autopsies with reported SARS-CoV-2 infection. The microscopic findings reported in these cases are unspecific focal adrenalitis, necrosis, lipid degeneration, vascular thrombosis, hemorrhage, and focal inflammation (Freire Santana *et al.* 2020).

Immunohistochemical staining of ACE2 in human adrenal gland sections showed no obvious immunoreactivity in the zona glomerulosa, which is the unique source of the mineralocorticoid aldosterone. In contrast, ACE2 was widely distributed in the zona fasciculata/reticularis, which produces glucocorticoids and androgens. Transmembrane Serine Protease 2 (TMPRSS2) appears to prime the viral spike (S) protein to enhance ACE2-mediated SARS-CoV-2 entry. TMPRSS2 was widely expressed in all three zones of the adrenal cortex (Hoffmann *et al.* 2020, Mao *et al.* 2021, Yang *et al.* 2020). This finding was further confirmed by the co-localization of ACE2 or TMPRSS2 with CYP11B1, a marker for the functional differentiation of cells in the zona fasciculata and reticularis. These results suggest that SARS-CoV-2 may potentially directly target zona fasciculata/reticularis of the adrenal cortex, thereby influencing circulating glucocorticoid levels (Mao *et al.* 2021). Vanderriele *et al.* (2018) strongly demonstrated the presence of ACE, and ACE2 in H295R and HAC15 cells, therefore these cells may be considered as a useful in vitro model for the investigation of effects on steroid hormone synthesis, specifically the production of 17β-estradiol and testosterone.

Although data on COVID-19-mediated modulations in cortisol dynamics are yet not available, the glucocorticoid insufficiency (specifically cortisol) may disrupt the HPA-HPT crosstalk during stress-loaded situations and will not affect testosterone and LH production (Sengupta and Dutta 2021). Thus, it also suggests HPT-independent testosterone downregulation by SARS-CoV-2 infection (Dutta and Sengupta 2020).

As per recent findings, the possibility of venous thrombo-embolism in COVID-19 patients have been indicated and its favorable treatment by heparin in some of them. Thus, it can be assumed that an acute adrenal insufficiency in COVID-19 patients may also be due to a thrombotic event at the adrenal level. This could result in impaired hormone production with consequent shock and worsening of the possibility of reacting to severe respiratory distress (Bellastella *et al.* 2020).

Furthermore, patients with chronic glucocorticoid (GC) excess may be at high risk of developing COVID-19 infection with a severe clinical course (Guarnotta *et al.* 2020). Table 1 and Figure 1 provide additional information on the possible effects of SARS-CoV-2 on the adrenal gland.

SARS-CoV-2 effect in the testis

In addition to respiratory symptoms, COVID-19 patients have been reported to have multi-system complications, such as cardiovascular and digestive system problems. One potential mechanism may be that the pathogen that causes COVID-19, severe acute respiratory syndrome coronavirus (SARS-CoV-2), enters cells through its receptor, angiotensin-converting enzyme-2 (ACE2), this virus may therefore invade organs with a high expression of ACE2 (Guan *et al.* 2020, Hoffmann *et al.* 2020, Zhang *et al.* 2020a, Zhang *et al.* 2020b). In adult male Leydig testis cells, ACE2 has been reported to be highly expressed, and male COVID-19 patients have been reported to have abnormal sex hormone concentrations compared to healthy men (Douglas *et al.* 2004, Ma *et al.* 2020), indicating that viral infection may injure male reproductive endocrine function.

In the male reproductive system, the testis, primarily due to its elevated ACE2 expression levels, should probably be the organ most vulnerable to SARS-CoV-2 infection. In spermatogonia, seminiferous tubules, Sertoli and Leydig cells, ACE2 receptors are present (Chen *et al.* 2020, Fan *et al.* 2021). Over damage to the testis, spermatozoa, abnormal sex hormone expression, and inflammatory cytokine dysregulation are the deleterious consequences of viruses (Gupta *et al.* 2021, Puggioni *et al.* 2018). It has been shown that testicular expression of ACE2 is age-related. The highest level of expression has been identified in patients aged 30 and older than 20, whereas those aged 60 have the lowest level of expression (Shen *et al.* 2020). That may suggest that, because of COVID-19, young male patients are more likely to experience a testicular injury than older patients. This also indicates the profound pathophysiological role of different hormonal environments in male infection with SARS-CoV-2 (Dutta and Sengupta 2020, Roychoudhury *et al.* 2021a).

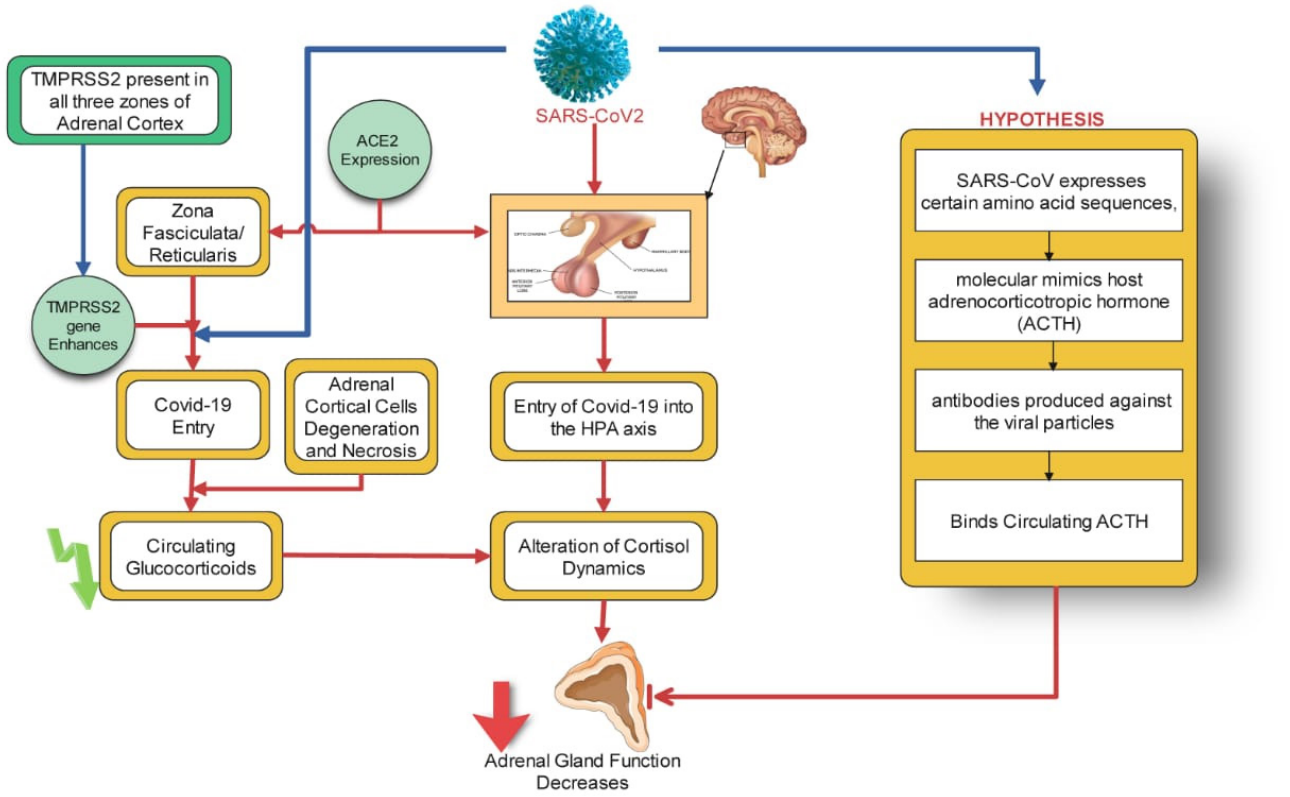

Fig. 1. Possible effect of SARS-CoV-2 on adrenal gland. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TMPRSS2: transmembrane protease/serine subfamily member 2; ACE2: angiotensin-converting enzyme 2; ACTH: Adrenocorticotropic hormone; HPA axis: hypothalamic-pituitary-adrenal axis.

Steroidogenesis is one of the main functions of the testes. As a result, monitoring sex hormone levels could be used to determine gonadal function in COVID-19 patients (Madjunkov *et al.* 2020). In a study comparing the hormone levels of 119 infected men with 273 age-matched control subjects, the effect of SARS-CoV-2 infection on testicular hormonal function was evaluated. In the infected group, the authors found a significant increase in the levels of luteinizing hormone (LH) and a concomitant decrease in the ratio of serum total testosterone/luteinizing hormone (T/LH). C-reactive protein and white blood cell count were negatively correlated with the T/LH ratio, likely by injury to Leydig cells, meaning an early transient hypogonadism stage (Ma *et al.* 2020). Nonetheless, COVID-19 may have temporary or permanent detrimental effects on male reproduction. It may involve endocrine alterations in LH and testosterone (Wang *et al.* 2020, Wang *et al.* 2020). In men with COVID-19, elevated serum LH negates the possibility of hypothalamic-pituitary-testicular axis suppression and hints of primary damage to Leydig cells. It is to be noted that orchitis was also a recognized complication of SARS (Xu *et al.* 2006). Rastrelli *et al.* (2021) investigated hormone levels in male patients admitted to the respiratory intensive care unit (ICU) with SARS-CoV-2. Worsening of clinical status was coupled with a progressive reduction in T levels and increase in LH levels. However, these results should be interpreted with caution, since the sex hormone baseline in these patients before infection was not available. Besides, SARS-CoV infection was shown to significantly reduce serum testosterone in male mice (Channappanavar *et al.* 2017). Although more research is required to determine the reasons and underlying mechanisms, findings show irregular sex hormone secretion in COVID-19 patients, implying that reproductive function should be evaluated during follow-up (Ma *et al.* 2020).

There are conflicting reports SARS-CoV-2 infection in male specimens contributes to acute stage hypogonadism and it is suggested that even fatal consequences can result from a decrease in androgenic action. Several human and animal studies have related hypogonadism to increased levels of pro-inflammatory cytokines, primarily IL-1β, IL-6, and TNF-α, which are essential inflammatory mediators in the pathogenesis of SARS-CoV-2. Nonetheless, as in the case of COVID-19,

an acute critical inflammatory condition can suppress hypothalamic-pituitary-testicular (HPT) axis activity, resulting in reduced levels of low luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone (Dutta and Sengupta 2020, Ma *et al.* 2020, Maggio *et al.* 2005, Mohamad *et al.* 2019, Pozzilli and Lenzi 2020). However, this theoretical perception does not correlate to a study conducted in 81 male COVID-19 patients that recorded lower serum testosterone levels, higher LH levels, and lower T:LH ratios compared to control subjects matched by age. These findings can indicate direct effects of SARS-CoV-2 infection rather than through the HPT axis in testicular cells (Ma *et al.* 2020). Therefore, the interactions of male SARS-CoV-2 infection and sex hormone regulation are significant missing links that await in-depth investigation (Dutta and Sengupta 2020). Besides the direct relation of SARS-CoV-2 infection and oxidative stress (OS), treatment of COVID-19 includes antiviral drugs like ribavirin which is associated with induction of OS, reduced testosterone level, impaired spermatogenesis, and sperm abnormalities in animal studies (Almasry *et al.* 2017, Narayana *et al.* 2002).

Sengupta and Dutta (2021) explained possible mechanisms of SARS-CoV-2 infection mediated testosterone depletion. Androgen receptor and ACE2 are located in chromosome-X, while androgen receptor activation is needed to trigger TMPRSS2 gene transcription, aiding SARS-CoV-2 entry into host cells. SARS-CoV-2 infection triggers inflammatory responses and oxidative stress-mediated disruptions of Leydig cell functions. Advanced age, psychological, and other co-morbidities associated with COVID-19 may also lead to oxidative stress. Viral amino acids may mimic ACTH molecules and stimulate production of antibodies against host ACTH, thereby reducing glucocorticoid levels and suppressing host response to combat stress. Hypothalamic-pituitary-testicular (HPT) axis may not be affected by SARS-CoV-2 infection, thus due to low testosterone level, LH level remains high in COVID-19 patients (Sengupta and Dutta, 2021). COVID-19 is a worry for couples trying to conceive. After binding with ACE2-positive cells, SARS-CoV-2 penetrate within the testes that could become a viral reservoir (Barbagallo *et al.* 2020, Cardona Maya *et al.* 2020). Table 1 and Figure 3 provide additional information on the possible effects of SARS-CoV-2 on the male reproductive system.

SARS-CoV-2 effect on the ovary

Females are less vulnerable to COVID-19. Epidemiological studies have shown that males account for most COVID-19 casualties, but only marginally more likely to be infected than females (Zhang *et al.* 2020a, Zhang *et al.* 2020b). In the largest survey of 72,314 suspected or confirmed cases of COVID-19 in China (men, 63.8 % of cases; women, 36.2 % of cases), the case-fatality ratio was higher among men (2.8 %) than among women (1.7 %) (Griffith *et al.* 2020). Furthermore, compared to men without comorbidities, male patients with comorbidities have a higher risk of having critically ill status, although there is no such correlation in women (Meng *et al.* 2020). The female reproductive hormones, estrogen, and progesterone, down-regulate ACE. Some evidence also supports the notion that through direct antiviral activity and immune-mediated mechanisms, estrogens and progesterone could exert a protective effect on women, thereby explaining the greater severity of COVID-19 in post-menopausal women (Cattrini *et al.* 2020). As previously mentioned, not only an exacerbated inflammatory reaction but also a hypercoagulable condition characterizes COVID-19 pathophysiology. Estrogen has been shown to decrease platelet aggregation and thrombus formation in animal models, while androgens improve them. This also tends to apply in humans under conditions of normal levels of estrogen exposure since the risk of thromboembolism is higher in males during the life cycle, while the risk of females throughout their fertile years is lowest, steadily increasing throughout menopause (Pivonello *et al.* 2020).

ACE2 expression was recorded in ovarian granulosa cells in a previous animal study (Honorato-Sampaio *et al.* 2012), which suggests that the ovary may also become a target of SARS-CoV-2. Li *et al.* (2021) detected serum testosterone, oestradiol, progesterone, LH, FSH, and AMH by electrochemiluminescent immunoassays. According to their research, average sex hormone concentrations and ovarian reserve did not change significantly in COVID-19 women of child-bearing age in comparison with those of age-matched controls. No previous study has evaluated the impact of COVID-19 on female sex hormones, therefore this is thought to be the first study focusing on clinical and laboratory findings, and especially sex hormones. A further study of sex hormone changes was conducted in 91 patients during the illness. The results revealed no statistically significant variations between the COVID-19

patients and the controls in all the sex hormone concentrations. However, some patients experienced abnormal changes in their levels of sex hormones, such as inappropriately high FSH and LH levels during the early follicular period, which may imply ovarian suppression in these patients (Li *et al.* 2021). In females, a severe acute COVID-19 illness can disrupt the hypothalamic-pituitary-gonadal (HPG) axis, lowering endogenous estrogens and progesterone production (Mauvais-Jarvis *et al.* 2020).

Furthermore, the treatment procedure affects the female hypothalamic-gonadal axis (Kao *et al.* 2019). In certain conditions, glucocorticoid therapy can be effective if its effect on the reproductive and endocrine system in women of reproductive age is not yet understood. There is currently no clinical evidence available regarding the effects of COVID-19 on the ovarian function of women of reproductive age. Female reproductive health has become increasingly important over the last decade, and there has been a global need to pay attention to the impact of COVID-19 on the reproductive system. Clinical research is therefore urgently needed to confirm whether COVID-19 viral infection causes endocrine disorders and damage to the ovaries in women of childbearing age (Li *et al.* 2021).

Women with Polycystic Ovary Syndrome (PCOS) are considered to typically belong to an age and sex group which is at lower risk for severe COVID-19. However, current evidences link the risk of severe COVID-19 with certain factors such as hyper-inflammation, ethnicity predisposition, low vitamin D levels, and hyperandrogenism, all of which have known direct associations with PCOS. This strong overlap of risk factors for both worse PCOS cardio-metabolic manifestations and severe COVID-19 should be highlighted for proper management of PCOS patients (Kyrou *et al.* 2020). Table 1 and Figure 2 provide additional information on the possible effects of SARS-CoV-2 on the female reproductive system.

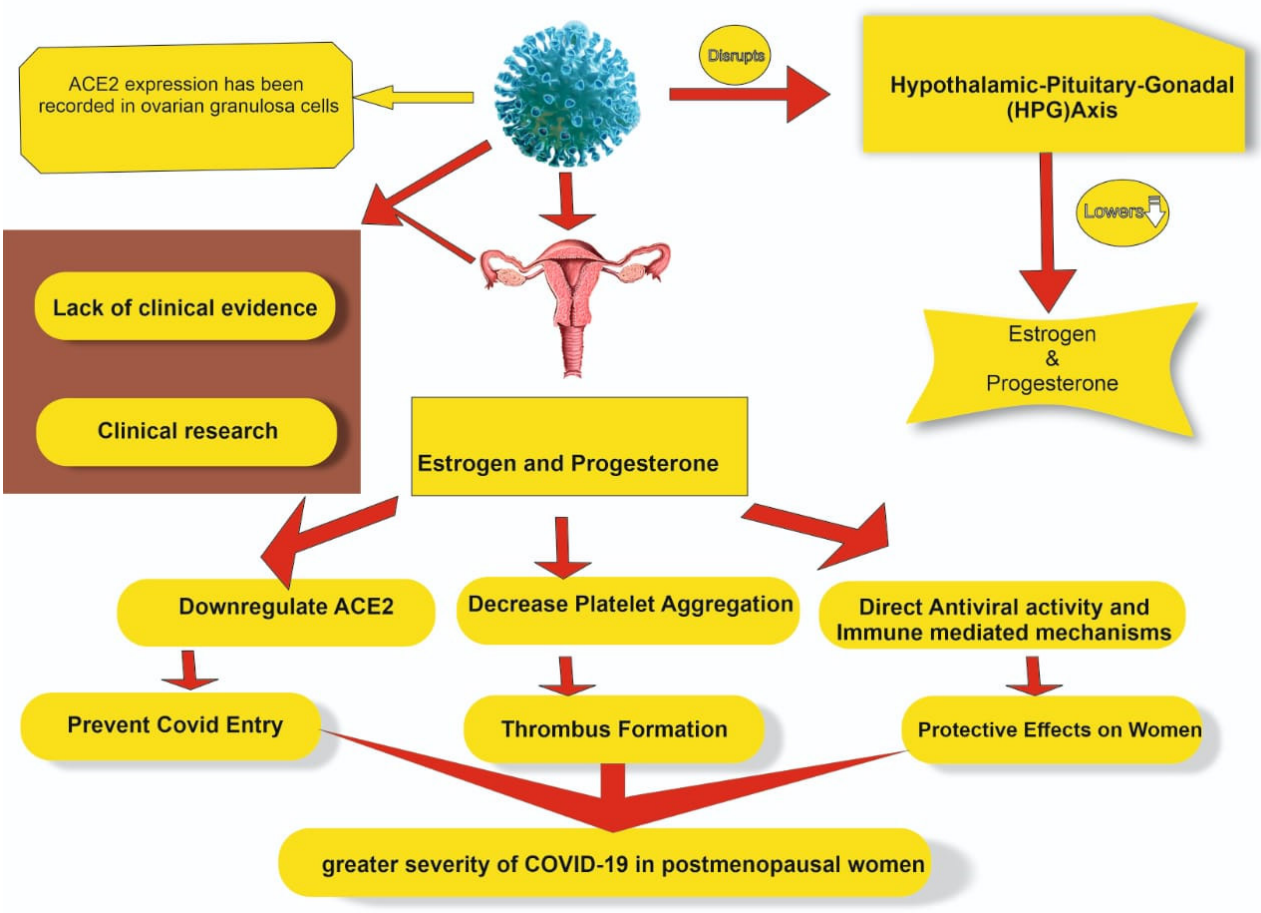

Fig. 2. Possible effect of SARS-CoV-2 on the female reproductive system. ACE2: angiotensin-converting enzyme 2; HPG axis: hypothalamic-pituitary-gonadal axis.

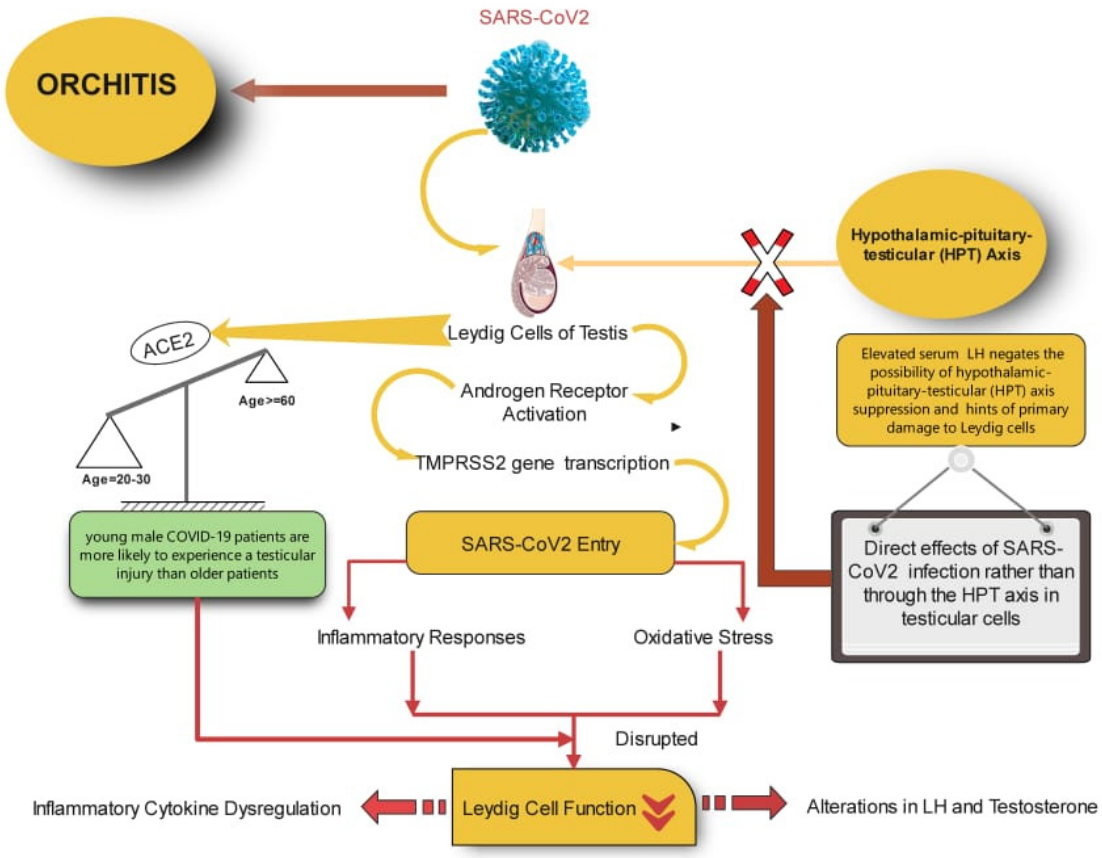

Fig. 3. Possible effect of SARS-CoV-2 on the male reproductive system. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TMPRSS2: transmembrane protease/serine subfamily member 2; ACE2: angiotensin-converting enzyme 2; HPT axis: hypothalamic-pituitary-testicular axis; LH: luteinizing hormone.

Conclusions

Endocrine activity with COVID-19 remains largely unexplored despite the continuing pandemic. At this point in time, the above data pertaining to COVID-19 and the endocrine system and steroidogenesis is mostly conjectural and factual, though, this study focuses on shedding some light into the problematic. Validated conclusions must not be drawn on the basis of the data provided, as many of the results are based on previous SARS experience and recent literature from small-scale studies. In this pandemic situation, it is crucial to ensure that rigorous and adequate clinical trials are performed to clarify the exact underlying mechanisms how COVID-19 is associated with steroidogenesis and fertility. The knowledge does, however, provide sufficient space for future study. Endocrinologists in clinical practice will need to pay more attention to these possibilities, as premature as it may sound, particularly while dealing with COVID-19 survivors.

Conflict of Interest

There is no conflict of interest.

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