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REVIEW ARTICLE

COVID-19 Impacts on Reproductive Ability, Childbearing, and Sexual Health- Psychological well-being in the Human Population; a Narrative Review

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Abstract: The coronavirus was the causative agent of a global epidemic from 2019 to 2022. The viral effect on sexual health and hormonal profile plus the rate of healthy births are important issues in general health. In this review, we studied the effect of coronavirus on reproductive health using more than 70 articles to understand the interaction of the virus with the reproductive system.

High temperatures due to fever elevated ACE2 expression in both testis germ and somatic cells. Furthermore, they exhibit significantly elevated luteinizing hormone (LH) levels, but decreased testosterone, LH, and follicle-stimulating hormone (FSH)/LH ratios, which may indicate the possibility of hypogonadism and/or infertility. In contrast, women diagnosed with SARS-CoV infections during the first trimester of pregnancy are at a higher risk of spontaneous miscarriages, while infections occurring during pregnancy are more likely to result in preterm delivery.

The Coronavirus can theoretically and potentially affect men's fertility and sexual development, and possibly cause miscarriage in the first trimester of pregnancy with an unknown mechanism. The findings cannot affirm whether the hormonal alterations are due to a direct/indirect effect of the virus. Therefore, more studies are needed to answer related questions.

Keywords: Fertility; Reproductive health; COVID-19; SARS-CoV; Pregnancy

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1. Introduction

The Coronavirus, SARS-CoV-2, is a viral particle with terrible transmission and pathogenic character for the respiratory system which caused a worldwide pandemic during the past few years. The findings from the genomic analysis indicate that the virus is responsible for Severe Acute Respiratory Syndrome, acute lung injury, and acute respiratory distress syndrome, which ultimately leads to lung failure and death and is closely linked to bat viruses that share similar characteristics [1]. The gravity of the situation demands that preventive measures be taken to mitigate the impact of these viruses on public health. In the global context of the COVID-19 pandemic, researchers are actively investigating the pathophysiology of SARS-CoV-2 to elucidate its transmission, susceptibility, and potential treatments.

The virus, known for its high level of contagiousness, has been found in nasal secretions, sputum, feces, and infrequently in the blood (1%) of infected individuals. Moreover, cardiac, ophthalmic, and neurological indicators of COVID-

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19 have been conveyed, however, it has not been detected in the urine [2]. Furthermore, the reproductive consequences of coronavirus infection are yet to be known [3].

2. Male fertility and Covid-19

Owing to the great incidence of infection, disease, and mortality among male patients, it appears that there is a potential for genetic predisposition in men. Numerous researchers have recognized the principal gate for the coronavirus to enter the cell - through the viral spike protein (S) attached to the angiotensin-converting enzyme 2 (ACE2) and the use of cellular serine proteinase (TMPRSS2) for the S protein priming, the two have been identified in the testis. This is why there is concern about testicular infection and possible sexual transmission [3].

Transmembrane serine proteases type II like TMPRSS2 and HAT can split and stimulate the S for fusion to membrane and cleave the viral receptor carboxypeptidase ACE2 and augment virus-related infection [4].

It is known that the spike protein, which lends its crown to the COVID-19 virus, targets vastly expressed ACE2 by numerous types of cells in the testis, including Leydig cells, Sertoli cells, and the germline [5]. The significance of the ACE2 role has newly been emphasized by the MAS receptor detection on the human spermatozoa tail and the acrosomal domain of the sperm head in the same place as phosphoinositide 3-kinase (PI3K)[6]. disrupted PI3K activity leads to a truncated apoptotic cascade in spermatozoa, resulting in cytoplasmic vacuolization, oxidative DNA impairment, and possible infertility [7].

3. SARS-CoV-2 and the male genital system

Ma and colleagues [8] discovered that patients with potential hypogonadism and no evidence of a direct or indirect effect of SARS-CoV-2 on the testes had significantly elevated luteinizing hormone (LH) levels, but decreased testosterone/LH and follicle-stimulating hormone (FSH)/LH ratios. It is possible that the high fever associated with COVID-19, which is known to contribute to germ cell destruction [9], could indirectly affect testicular dysfunction. Additionally, it should be noted that LH release occurs in a pulsatile manner and follows a circadian rhythm [10].

It is suggested that there may be a biased sampling in the mentioned study, and therefore it is recommended that COVID-19-affected individuals and controls be tested simultaneously to avoid significant fluctuations in observed LH levels. Also, another study[11] discovered elevated ACE2 expression in both testis germ cells and somatic cells, which could indicate potential SARS-CoV-2 tropism in testicular tissues. Furthermore, the study demonstrated a correlation between the expression level of ACE2 and age, with the highest expression observed at 30 years of age [5]. These outcomes meet the intriguing research conducted by Liu and co-workers who analyzed scRNA-seq data from 2854 single cells and discovered that ACE2 is present in nearly all testicular cells, particularly in Sertoli cells, and these ACE2-positive cells exhibit high expression of stress response and immune activation genes [12]. However, to confirm this tropism, it is necessary to detect viral material in autopsied testicular specimens. Surprisingly, RT-PCR testing did not detect any positive results for SARS-CoV-2 in semen and testicular samples from COVID-19 patients despite the high expression of ACE2 [13]. Notably, SARS-CoV-2 genomes have been detected in urine specimens of several patients where the urinary and genital systems converge [14].

There are accumulative pieces of evidence suggesting that male reproductive systems are susceptible to viral infections [15]. Unlike bacterial infections, which typically target accessory glands and the epididymis, circulating viruses in the bloodstream primarily attack the testes [8].

Notable viruses that can cause orchitis and potentially result in male infertility include human immunodeficiency virus (HIV), Zika virus, mumps virus, influenza, and Coxsackie virus [16]. Moreover, viruses such as Ebola [17], and Hepatitis viruses B/C can be sexually transmitted through semen [8]. The impact of these viruses is observed through damage to spermatozoa, abnormal sex hormone secretion, and dysregulated inflammatory cytokine regulation. For instance, a study conducted on rams demonstrated that endothelial cells in the peritubular areas of the testes can serve as suitable hosts for the replication of the bluetongue virus. This replication leads to an enhanced type-I interferon response, reduced testosterone synthesis by Leydig cells, and the destruction of Sertoli cells [18]. Orchitis has also been reported as a consequence of SARS infection, a virus similar to SARS-CoV-2 [9]. In light of these findings, it is plausible to hypothesize that the testes may likewise encounter an abnormal possibility of impairment and dysregulation in the occurrence of COVID-19 [8].

While spermatogenesis and androgen secretion are the main responsibilities of the testes, sex-related steroids evaluation could show the condition of the male gland, where, serum testosterone (T) levels do not statistically alter, serum LH increases and serum T/LH decreases in COVID-19 patients [8]. The basal level of T between populations differs extensively. Hence the ratio of T/LH or T/E2 hormones is considered to be a superior parameter for the assessment of male gonad function [19, 20]. A recent study displayed that COVID-19-infected patients experience a significant increase in serum prolactin (PRL) levels. This increase in PRL levels can subsequently lead to pituitary suppression and a decrease in gonadotropins [21]. Therefore, the raised LH and declined T/LH ratio are more probable to be instigated by the dysfunction of testes, for example, the feasible damage of Leydig cells [8] (Fig 1).

4. Susceptibility of the endometrium to infection and SARS-CoV-2 potential damage

Fertility, particularly the successful implantation of embryos, is influenced by changes in the expression of genes in the endometrium during the menstrual cycle [22]. Gene expression varies between different phases of the menstrual cycle to accommodate physiological changes [23].
These variations in gene expression between phases create a dynamic environment for viral infections, which in turn affect their expression patterns throughout the menstrual cycle. This establishes a cyclical pattern of susceptibility to viral infections [24]. Previous reports from the Human Protein Atlas (HPA) have indicated that ACE2, the receptor responsible for SARS-CoV-2 cell entry, is expressed at low levels in the endometrium [25]. ACE2 levels are also mitigated in critical tissues e.g. the lungs [26]. However, it cannot be suggested that low levels of ACE2 expression imply no viral influence on the tissue [24].
Various potential mechanisms of SARS-CoV-2 cell entrance have been anticipated [27, 28]. TMPRSS2, alongside ACE2, has shown moderate endometrial expression [24]. But, there is no relationship concerning TMPRSS2, ACE2, and the other studied genes [24]. Based on the findings, it can be inferred that the endometrium is likely protected from SARS-CoV-2 through TMPRSS2. Nevertheless, the presence of other proteases linked to S protein degradation suggests an alternative mechanism for endometrial involvement [24]. TMPRSS4 significantly changes through the menstrual cycle and shows a significant upsurge in the mid-secretory phase [24]. It also shows an interesting correlation with other genes including ACE2 in the early secretory phase [24]. Because S proteins are targeted by TMPRSS4 which increases infection in intestinal epithelial cells, it is supposed that endometrial vulnerability to infection by SARS-CoV-2 is mediated by TMPRSS4 [28, 29]. TMPRSS4 regulation was found to be associated with CTSL and CTSB at all stages except the initial secretory stage [27]. It was observed that cell infection by SARS-CoV-2 occurred in TMRPSS2- cell lines expressing both CTSL and CTSB, suggesting a potential role for these proteins in cleaving viral S protein. The positive correlation between protease FURIN and TMPRSS4 in the late secretory phase indicates their potential involvement in splitting S protein [24, 30-32]. Furthermore, during the mid-secretory phase, TMPRSS4 shows a positive correlation with MX1, which actively participates in SARS-CoV-2 infections by attracting neutrophils to infected tissue and engaging their elastases to cleave S protein along with TMPRSS2 [24, 33]. The statistically significant expression alterations of TMPRSS4, CTSB, CTSL, FURIN, and MX1 during the cycle suggest a susceptible environment for infection in the early secretory and mid-secretory phases [24, 25] (Fig 2).

5. Fertility preservation techniques in cancer patients

Consolidated anti-cancer therapies are effective in producing better responses by increasing the survival rate, thus allowing many patients to have a family after the cancer has healed [34]. As a result, for the aforementioned patients, public health services should be able to implement fertility preservation (FP) measures and simultaneous cancer treatment services, even in COVID-19 health emergencies [34]. The International guidelines [34-37] for FP in individuals with cancer, as outlined in various international publications, stress that counseling about reproductive options should be offered soon after diagnosis and staging of the disease, to enable the identification of appropriate strategies for ensuring reproductive safety based on the type of tumor and its prognosis. The cryopreservation of mature oocytes and embryos for women with adequate ovarian reserve and induce multiple follicular growths (MFG) subsequent controlled ovarian stimulation (COS) is recommended by both the American Society of Clinical Oncology and the European Society for Medical Oncology [34, 38]. It has been suggested that cryopreservation of immature oocytes after their ovarian retrieval may be a viable alternative to avoid hormonal stimuli. This is because the oocytes are less prone to damage caused by freezing, and are also free of metaphase spindle [39]. When the COS-induced MGF is not attainable the ovarian tissue cryopreservation can be proposed as an alternative procedure [40]. Laparoscopic surgery is necessary to sample the ovarian tissue, after which the cortical parts are frozen until orthotopic or heterotopic re-implantation on the remaining ovary or in the peritoneal pocket [34]. Instead, gonad shielding throughout radiation therapy, together with ovarian temporary clampdown of gonadotropin-releasing hormone (GnRH) agonists [40] and further accessible techniques to reserve ovarian role, are likewise contemplated operative.
Regarding the controversial use of GnRHa before anticancer therapies, numerous scientists explain this way as an appropriate method in breast cancer patients demanding insistent chemotherapy procedures [40], although it emerges wrongly in patients with lymphoproliferative diseases [41, 42]. About male patients, semen cryopreservation is a largely adopted FP procedure that, if properly programmed, does not imply any delay in starting anti-cancer treatments [43]. However,

at present, several groups are interested in the optimization of testicular tissue reimplantation previously cryopreserved, although this procedure has not yet been tested in humans [42].
The British Royal College of Obstetricians & Gynecologists and the American College of Obstetrics and Gynecology have offered merely a small number of recommendations for pregnant COVID-19+ patients established on the inadequate data described in the literature (https://www.rcog.org.uk/coronavirus-pregnancy). Contempt the increased possibility of infectivity in addition to the potential complications and potential perinatal consequences in infected pregnant women, little scientific information is available today about the precautions that should be taken for assisted reproductive technology (ART) procedures in cancer patients [44, 45], In young cancer patients undertaking immediate chemotherapy or gonadotoxic radiotherapy procedures, FP plans need an ethical primacy and should not be delayed or suspended because of an amplified risk of infection [46]. Therefore, to convince these patients to receive FP techniques and perform their parental project after cancer recovery, it is necessary to consult with oncologists and oncofertility specialists to assess the true risk of COVID-19 infection in individual cases to prevent viral disease [46].
During the COVID-19 pandemic, the European Society of Reproduction and Embryology recommends that entirely healthy and fertile women who intend to have a normal pregnancy, even in the nonexistence of COVID-19 infection, should evade pregnancy during this period, while infertile patients under ART care, it is desirable to suspend childbearing plan according to egg or embryo freezing. Moreover, the American Society for Reproductive Medicine also recommends that assisted reproductive therapies, such as gamete preservation and fetal transplantation, and elective surgery for healthy individuals be stopped while the process of gamete preservation for cancer patients is ongoing. [47].

6. ART and COVID-19

The COVID-19 pandemic is an unprecedented global situation. Pregnant women and would-be mothers' situation should be monitored to achieve new evidence that helps them [48]. Infertile oncology patients require immediate collection of oocytes. Women who are of advanced maternal age and/or have reduced ovarian reserve cannot delay the retrieval of oocytes indefinitely [48].
To ensure that ART treatments can continue without interruption, it is recommended to avoid treating patients who have a higher risk of COVID-19 infection due to pre-existing clinical conditions. Emergency plans should be in place to address accidental exposure of staff members to the risk of COVID-19 infection. Additionally, it is important to provide honest counseling to couples regarding the unknown effects of COVID-19 on potential pregnancies to support them. These measures aim to reduce both the time required for oocyte retrieval and the risk of dropouts in patients with time-sensitive fertility issues. [49].

7. Fetal placenta, a barrier against the virus COVID-19

SARS-CoV-2 vertical transmission and consequence possible pregnancy problems like miscarriage, fetal abnormalities, fetal growth retardation, and/or stillbirth, are the most common distresses for COVID-19 pregnant women [50]. Consistent with clinical evidence, the occurrence of vertical transmission of SARS-CoV-2 is restricted [51]. Despite testing negative for SARS-CoV-2, neonates born to COVID-19-positive mothers often exhibit abnormal findings related to fetal and maternal vascular malperfusion [52]. Maternal-fetal interface cells, including syncytiotrophoblasts, cytotrophoblasts, endothelial cells, and vascular smooth muscle cells, express high levels of ACE2 [53].
Syncytiotrophoblasts are commonly infected with SARS-CoV-2, indicating the presence of a placental barrier that may not be completely effective. [54]. As the mechanisms of vertical intrauterine transmission of SARS-CoV-2 remain unknown, thorough clinical examinations with regular ultrasounds and fetal heart rate monitoring are strongly recommended for infected pregnant women. [50]. There were no cases of vertical transmission identified among pregnant women with SARS-CoV infection [55-58]. Nevertheless, the outcome of SARS on motherly effects appears to be related to the pregnancy stage while the commencement of SARS-CoV happens [59, 60]. Wong et al. [59] discovered that the SARS-CoV infections existent through the first trimester of pregnancy were extra likely to produce spontaneous miscarriages, whereas infections present afterward 24 weeks of pregnancy progressed into delivered preterm [61].
Because of the possibility of transmitting the virus at birth, most infected mothers apply for a cesarean section, while infants of such women have been diagnosed with the early-onset virus [62]. By distinction, there were COVID-19 patients who implemented vaginal delivery and all their infants were negative for SARS-CoV-2 [45, 62, 63]. The samples of vaginal mucosa and shedding in birth canals are imperative in representing whether SARS-CoV-2 is communicated throughout vaginal delivery [61]. Several studies showed that gathered vaginal secretion (1/80) or infant blood (12/80) were SARS-CoV-2 negatives [44]. Further, as exposed by HPA, vaginal secretion expresses virtually no ACE2 [64], entailing that SARS-CoV-2 may not infect the tissue [61]. Taken together, the risk of SARS-CoV-2 transmission by vaginal delivery looks low, though more ultimate verification is essential

[61].

Ultimately, to specify the possible transmission of SARS-CoV-2 through lactation, several studies analyzed collected breast milk samples (7.63) from infected patients with COVID-19 pneumonia after the first lactation [44, 65]. However, these samples tested negative for SARS-CoV-2, signifying no evidence accompanying the breastfeeding transmission of SARS-CoV-2 [44]. These results resembled pregnancies with SARS-CoV infection. No viral RNA was perceived in the specimens of umbilical cord blood, amniotic fluid, and breast milk from those pregnant while infected with SARS-CoV [66-68]. Indeed, the SARS-CoV antibody can be obtained from the umbilical cord and breast milk [54-56]. Based on such understandings, the pregnancy antibody may pass through the placental barrier to guide antiviral protection in the fetus to fight SARS-CoV-2 [61] (Fig 3).

8. Ovarian tissue and SARS-COV2

The lack of SARS-CoV replication in ovarian tissue, as documented in previous studies [27], indicates that the tissue is susceptible to SARS-CoV-2 infection [13]. However, there is currently no evidence to describe SARS-Cov-2 replication in the reproductive system of COVID-19 patients at the time of death [69]. Instead, infected tissues from the lungs and heart have been recognized to be the primary cause of patient death [70, 71]. Additionally, it is important to note that the existing data on pathology primarily focuses on samples from postmenopausal women, which limits our understanding of how SARS-CoV-2 may affect mature oocytes [69]. Additional experimental data is needed to verify whether female germ cells can be infected by COVID-19 in the ovarian tissue of reproductive-aged women. Moreover, it should be acknowledged that the presence of ACE2 and TMPRSS2 mRNA transcripts in mature oocytes may not necessarily indicate the active synthesis of the corresponding proteins [69]. During oocyte maturation, mRNA translation gradually diminishes, resulting in the accumulation of substantial amounts of RNA transcript, which plays a crucial role in supporting the embryo before genome activation [72].

The impact of SARS-CoV-2 on the early stages of pregnancy is not well understood. There is a concern about the possibility of viral infection in adult eggs due to the presence of ACE2 and TMPRSS2. Consequently, there are hesitations about initiating a pregnancy during the COVID-19 pandemic. However, the findings presented in this study suggest that procedures involving fertilization outside of the female reproductive tract are unlikely to pose significant risks and may even reduce or eliminate exposure to susceptible cell types. The risk of infection for primordial follicles, which determine ovarian reserve, seems to be low. This indicates that any potential effects of COVID-19 on fertility may only be temporary [69].

9. COVID-19 and its psychological effects

The COVID-19 pandemic is expected to result in higher rates of post-traumatic stress disorder (PTSD), depression, and anxiety, both in the general population and particularly among COVID-19 survivors [73-76]. Similar to past events such as the 9/11 attacks [77] or earthquakes [78], there are psychological consequences associated with COVID-19, and it is important to implement appropriate treatment strategies for both short-term and long-term care. While only a small number of individuals may be more susceptible to psychological trauma, it is undeniable that most people will experience some level of emotional distress due to factors such as isolation, social distancing, loss of loved ones, challenges in accessing medications, and the economic impact of lockdown measures [79]. Additionally, the coronavirus pandemic has resulted in a decrease in sexual desire among couples, which can be attributed to the connection between sexual activity and psychological well-being [80-83]. Moreover, the hypogonadal state induced by COVID-19 can significantly worsen sexual desire and mood [84-100] (Table 1.)

10. Conclusions

The Coronavirus can theoretically and potentially affect hormonal profile and fertility and possibly cause miscarriage in the first trimester of pregnancy, where several studies confirm this, but the exact mechanism and details need further investigation. Alterations in sex hormone levels in men suggest potential hypogonadism. Also, elevated ACE2 expression in testis germ and somatic cells suggests potential tropism of SARS-CoV-2 to testicular tissues. SARS-CoV infections during the first trimester of pregnancy could trigger spontaneous miscarriages, while infections after 24 weeks of pregnancy develop into preterm delivery. There also is no evidence proving SARS-CoV-2 breastfeeding transmission. Due to the unknown effects of SARS-CoV-2 on early pregnancy stages and the theoretical possibility of viral infection of adult eggs, initiating a pregnancy during the COVID-19 epidemic has been a concern. Countries around the world should try to raise public awareness for recognition of the virus and its function, provide training courses for couples who intend to have children to learn about insurance medical services that support COVID-19-related disease and how to prevent and manage the disease, reduce the stress and costs of managing families before, during, and after pregnancy.

Table 1: Comparison of clinical and demographic features between two groups

Psychological Status	Study Type	Final Sample Size	Test (s)	Major Outcomes	Ref.
Depression	Descriptive cross-sectional design	1115	Beck Depression Inventor	Of the individuals included in the study, almost half (47%) exhibited symptoms of depression at a minimal level. A quarter (25.7%) had mild symptoms, while over one-fifth (22.3%) displayed moderate-level depression symptoms. Only 5% showed severe depression symptoms. Statistical analysis showed that female and single participants had significantly higher levels of depression compared to other participants (p<0.05).	[84]
Anxiety, depression, and PTSD*		57984 (Mage=14.8, SD=1.6, range: 11–20 years)	7-item Generalized Anxiety Disorder (GAD-7) and the 9-item Patient Health Questionnaire (PHQ-9)	In this study, the rates of anxiety, depression, and PTSD symptoms were found to be 7.1%, 12.8%, and 16.9%, respectively. These mental health outcomes were significantly associated with COVID-19-related exposure (all p < 0.001). Family relationships and social support emerged as significant predictors for these outcomes (all p < 0.001).	[85]
Generalized anxiety and depressive symptoms	Cross-sectional design	502 (234 females; Mage = 39.3 years, SD = 11.8; range 20 to 77 years)	questionnaires: Big Five Inventory-10 (BFI-10), Whitley Index 7 (WI-7), Coronavirus Anxiety Scale (CAS), COVID-19 Anxiety Syndrome Scale (C19-ASS), and PHQ Anxiety and Depression Scale (PHQ-ADS)	The study revealed a negative correlation between extraversion, agreeableness, conscientiousness, and openness with generalized anxiety and depressive symptoms. In contrast, neuroticism, health anxiety, and both measures of COVID-19 psychological distress showed a positive correlation with generalized anxiety and depressive symptoms.	[86]
Generalized anxiety and depressive symptoms	Online survey	1115 (aged 18–85)	Online questionnaire: The PHQ-9, GAD-7, a Scale of Perceived Health and Life Risk of COVID-19, a Social Support Scale, and a Scale of Pandemic-Related Difficulties	The prevalence of depressive and generalized anxiety symptoms was observed to be higher among younger age cohorts, particularly those aged 18-29 and 30-44, in comparison to older adults belonging to the age groups of 45-59 and 60-85 years.	[87]
Psychological distress (including general anxiety, depression, and health anxiety)	Cross-sectional design	641 (Mage = 20.1, SD = 2.11)	Self-report questionnaire Depression Anxiety Stress Scale (DASS-21)	Approximately 50% of the individuals surveyed indicated experiencing increased levels of psychological distress, specifically in the areas of health anxiety, general anxiety, and depression. A greater likelihood of experiencing psychological distress was observed among female participants, those with a confirmed case of COVID-19 in their immediate social network, individuals with underlying medical vulnerabilities, and those who recently experienced three or more viral symptoms.	[90]
Psychiatric symptoms (PTSD, major depression, anxiety, insomnia, and obsessive-compulsive disorder (OCD))	Prospective cohort study	402 (265 male, Mage = 57.8, range 18 to 87 years)	Self-report questionnaire: Impact of Events Scale-Revised (IES-R), PTSD Checklist for DSM-5 (PCL-5), Zung Self-Rating Depression Scale (ZSDS), 13-item Beck's Depression Inventory (BDI-13), State-Trait Anxiety Inventory form Y (STAI-Y), Medical Outcomes Study Sleep Scale (MOS-SS), Women's Health Initiative Insomnia Rating Scale (WHIIRS), and Obsessive-Compulsive Inventory (OCI)	In the sample population, a considerable percentage of patients exhibited psychopathological symptoms, with 28% reporting symptoms of PTSD, 31% experiencing depression, 42% exhibiting anxiety, 20% presenting with OC symptoms, and 40% reporting insomnia. In total, 56% of the patients scored within the pathological range for at least one clinical dimension. Interestingly, despite having lower levels of baseline inflammatory markers, female patients experienced higher levels of anxiety and depression than male patients.	[88]
Depression, anxiety, and stress	-	2766 (71.7% females, Mage =32.94, range 18–90 years	DASS-21	Higher levels of depression, anxiety, and stress were observed in individuals who exhibited characteristics such as female gender, negative affect, and detachment.	[90]

Table 1: Comparison of clinical and demographic features between two groups (continue)

Psychological Status	**Study Type**	**Final Sample Size**	**Test (s)**	**Major Outcomes**	**Ref.**
Psychological distress	Longitudinal surveys	1854	The Japanese version of the Kessler psychological distress scale (K6)	Between December 2019 and July 2020, there was an observed rise in the psychological distress of young people, particularly females, which subsequently declined by December 2020. The initial level of psychological distress was influenced by the individual's health status and psychological traits, but not by their subsequent change. Gender did not appear to affect the initial level of distress but was linked with an increase in psychological distress over time.	[89]
Depression and anxiety	-	500 (Mage = 47.26 years, SD= 15.82), 54.8% females)	A structured questionnaire, including the PHQ-9, GAD-7, the global rating of change scale, and items related to COVID-19	According to the study, 19% of participants exhibited symptoms of depression while 14% experienced anxiety. Additionally, a significant proportion of individuals (25.4%) reported a decline in their mental health since the onset of the pandemic.	[91]
Anxiety and depression	Observational study	28 to 35 participants completed each survey tool	Patient Health Questionnaire (PHQ-2), Generalized Anxiety Disorder (GAD-2), a novel coronavirus-specific survey, and the Kessler Psychological Distress Scale (K10+)	The pandemic resulted in worsened anxiety levels for 48.57% of participants and depression levels for 45.71% of participants, according to the findings.	[92]
Psycholo- gical distress	Cross-sectional study	473	A web-based survey including a novel Self-Learning and Related Activities survey, PHQ-9, GAD-7	Approximately 29.8% (141 out of 473) of students expressed apprehension regarding the transition to online education. Following the lifting of the state of emergency, there was a significant decline in the subjective mental health status of the participants, as indicated by a P-value lower than 0.001.	[93]
Psycholo- gical flexibility, coping, mental health, and wellbeing	Online survey	555 (72% female, Mage = 39.2, range 18 to 86 years)	Online questionnaire-based study: CompACT-8, Short Warwick-Edinburgh Mental Well-Being Scale (SWEMWBS), PHQ-9, GAD-7, Impact of Event Scale-6 (IES-6), Brief COPE	The study found a significant positive correlation between psychological flexibility and overall well-being, as well as a negative correlation with anxiety, depression, and distress related to the COVID-19 pandemic.	[94]
PTSD and depression	Online survey	5792	An online questionnaire including questions on personal information, quarantine-related knowledge, items of the Impact of Event Scale-Revised (IES-R) and the Center for Epidemiologic Studies–Depression (CES-D) scale	Among the individuals who underwent institutional quarantine, a majority of males (n=1392, 75.7%) exhibited the highest incidence of PTSD symptoms. A significant proportion of females (n=920, 72.8%) who reported an income exceeding 75000 takas in Bangladeshi currency displayed elevated levels of depression symptoms.	[95]
Psychopathological symptoms and psychological well-being	Longitudinal study	1258 (Mage=23.43, SD = 6.45; 75.4% female) at T0. Of these, 712 also completed the T1 survey, and 369 also completed the T2 survey.	Three-wave, longitudinal, web-based survey including Beck Anxiety Inventory (BAI), Beck Depression Inventory-II (BDI-II), Dimensional Obsessive-Compulsive Scale (DOCS), Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5) and 5-item World Health Organization Five Well-Being Index (WHO-5). Collected in March 2020 (T0, the lockdown phase), in May 2020 (T1, the end of the lockdown phase), and in November 2020 (T2, the second wave of COVID-19 infection).	There was a noteworthy decline in symptoms related to anxiety, depression, PTSD, and obsessive-compulsive disorder, along with a significant improvement in psychological well-being between T0 and T1. Conversely, there was a significant increase in psychopathological symptoms and a decrease in psychological well-being observed between T1 and T2.	[96]

Table 1: Comparison of clinical and demographic features between two groups (continue)

Psychological Status	Study Type	Final Sample Size	Test (s)	Major Outcomes	Ref.
PTSD	Longitudinal study	The study was conducted in two phases: from May to June 2020 (T1) and June 2021 (T2), with 317 and 403 eligible responses respectively. A total of 74 Health Care Workers (HCWs) completed the survey at both T1 and T2.	An online survey including the PTSD checklist for DSM-5 (PCL-5) and the risk perception questionnaire	The prevalence rate of PTSD in healthcare workers (HCWs) increased from 10.73% at T1 to 20.84% at T2, with a cut-off score of 33. There was a significant increase in PTSD scores among HCWs at T2 compared to T1 ($p < 0.001$). Furthermore, a positive correlation was observed between risk perception and PTSD ($p < 0.001$). Additionally, the presence of PTSD at T1 was found to be a significant predictor of PTSD at T2 (= 2.812, $p < 0.01$).	[97]

* Post-traumatic stress disorder (PTSD).

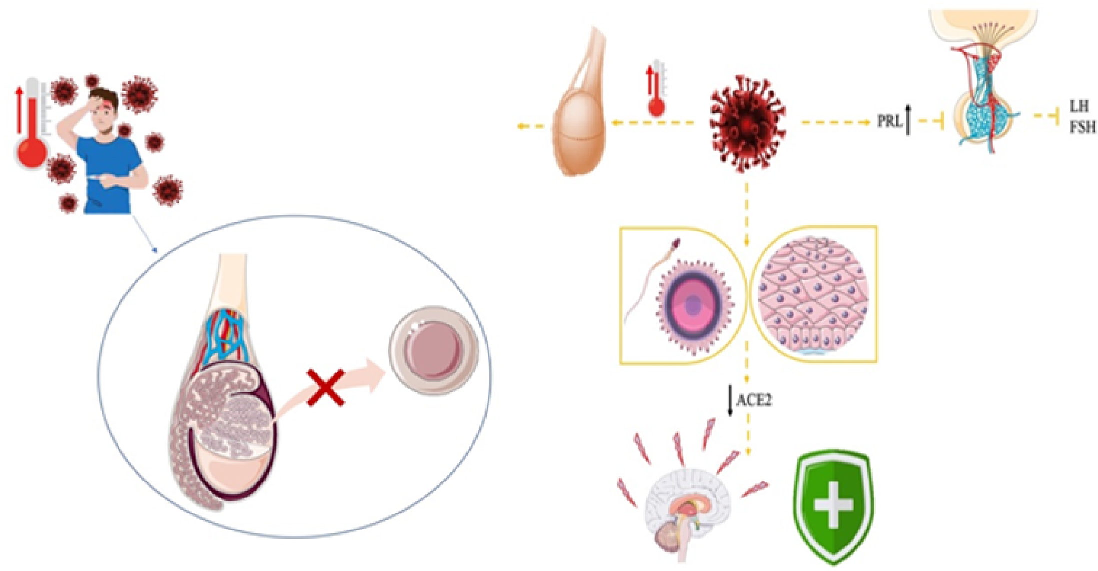

Figure 1: SARS-CoV-2 and male genital system. Patients with covid-19 experience a significant increase in serum prolactin (PRL) level which can subsequently lead to the suppression of the pituitary gland and the reduction of gonadotropins. Therefore, LH surge and decreased T/LH ratio are most likely caused by testicular dysfunction such as Leydig cell damage.

11. Appendix

11.1. Acknowledgment

None.

11.2. Conflict of Interest

None.

11.3. Funding and supports

None.

11.4. Authors contributions

None.

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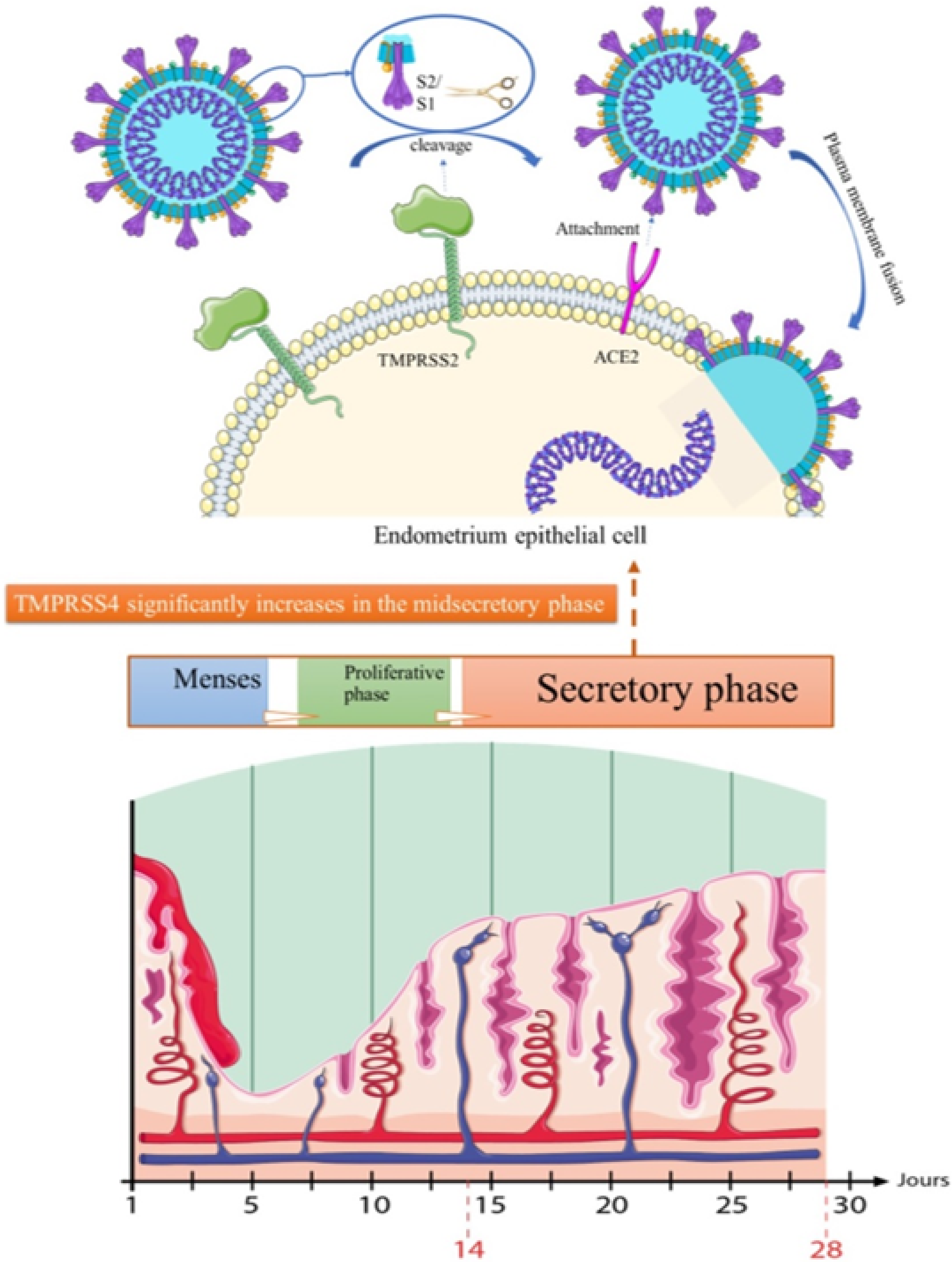

Figure 2: The uterus endometrial and fertility.

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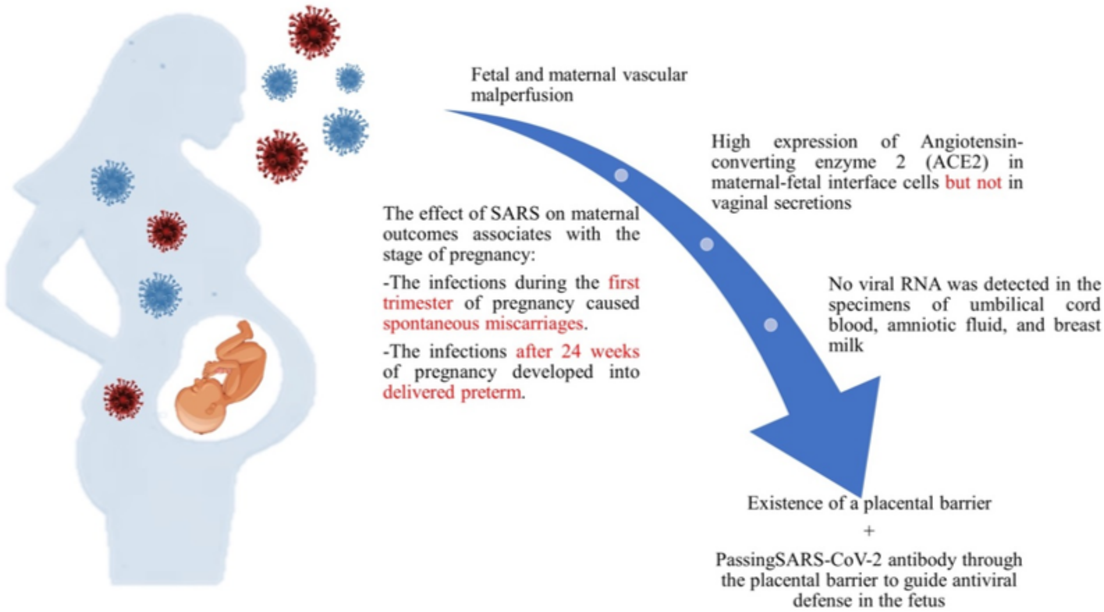

Figure 3: The fetal placenta is a barrier against the virus COVID-19.

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