EVALUATION STUDY OF ANGIOTENSIN CONVERTING ENZYME 2 ROLE IN INFERTILITY IN SARS-COV-2 PATIENTS

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Received: 22.06.2025 Accepted: 13.12. 2025

Abstract

Angiotensin converting enzyme 2 receptor is an entry point for COVID-19 infections into body cells. The review's primary objective is to provide readers with an in-depth comprehension of the potential impact of COVID-19 on the reproductive systems of both sexes. We have demonstrated that SARS-CoV-2 can impact on the urogenital tract as well. This indicates that it should be carefully considered while treating infected males who are of reproductive age. Two crucial physical barriers in males are the blood-epididymis (BEB) and the blood-testis barrier (BTB). Studies revealed that various viruses remain able to intrude through these defenses and then malfunction the testicles, even though they play a major role in male reproductive function. Consequently, this brief overview emphasizes the function of ACE2 receptors. Additionally, due to the indirect cytopathic consequences of viral replication and dissemination in the testis, coronaviruses may have a negative impact on male fertility. Most existing data indicate that SARS-CoV-2 has no impact on female reproduction. Cytokines and inflammation associated with nervous system injury could be a secondary mechanism by which the virus influences sex hormone levels. Angiotensin converting enzyme 2 down-regulation may be the cause of menstrual issues among infected women with SARS-CoV-2, irregular hormone levels, medications, and stress. The parameters have not changed significantly in vitro fertilization or the quality of ovarian follicles between the prior to and post-COVID-19 immunization groups.

Keywords: ACE2, COVID-19, reproductive system, SARS CoV-2.

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Introduction

A novel, highly contagious virus, the 7th member of coronavirus family employs wrapped RNA, surfaced in Wuhan, China in 2019. Typical clinical indications of COVID-19 include; dry cough, fever, besides in severe cases, damage to several organs. However, common symptoms include anorexia, myalgia, pharyngitis, rhinitis, and diarrhea (1). Previous research indicates that the pandemic has left the Chinese with a range of mental health issues, including suicidal thoughts and actions. In a research, one in four (25%) adult Americans stated they were very worried about getting sick (2). The spike protein's receptor-binding domain, which is found on angiotensin converting enzyme type 2, serves as where the virus binds (ACE2). Figure (1). The ACE2 receptor exists in vascular endothelial cells, myocytes, and alveolar cells because to COVID-19 has high affinity for it. It is also convenient for genital pathology, which includes the ovaries and testes. COVID-19 most likely has an impact on sperm formation and decreases its quantity. It also generates sex hormones and may lessen sexual desire (3). While COVID-19 principally infects the respiratory system, additional tissues have also been shown to sustain direct or indirect damage through the host-pathogen interacting, SARS Co-V2 virus is responsible for this. On the other hand, The least understood aspect of COVID-19 may be how it affects reproductive organs (4). The review includes discussion over the role of ACE2, the infiltration of COVD 19 and the epididymis/ testis blood barrier, as well as the recent studies on COVD-19 and testicular malfunction. The role of ACE2 on the ovaries and uterus of females will also be included in the review. The review's primary objective is to provide readers an in-depth

comprehension of the potential impact of COVID-19 on the reproductive systems of both sexes.

Angiotensin converting enzymes type 2 (ACE2)

Similar to human angiotensin1-converting enzyme, the angiotensin converting enzyme2 belongs to dipeptidyl carboxydipeptidases family.Figure(2). Distribution of ACE2 gene expression indicates that it may be important for controlling renal and cardiovascular health as well as fertility. Numerous investigations conducted since the 2003 global SARS outbreak have demonstrated that ACE2 on cell surface aids as a receptor used for SARS-CoV (9–11) and human coronavirus (HCoV-NL63). Due to their tight relationship to SARS-CoV, Additionally, evidence has shown that the new SARS CoV-2 binds to ACE2. When a specified receptor is expressed and distributed, the virus can enter the cell and bind to it to complete intracellular replication, release the virus, and cause cytotoxicity (6).

COVID-19 pandemic

The coronavirus family of positive stranded RNA viruses is currently the most common, with thirty different species. They appear in nature, where they include unusual mammals and human illnesses. New coronaviruses have caused issues globally in recent times. For example, at 2012, the Middle East respiratory syndrome coronavirus or MERS-CoV was originally reported, and the severe acute respiratory syndrome coronavirus (SARS-CoV) first appeared in 2002. COVID-19, a disease caused by SARS CoV-2, has resulted in significant rates of morbidity and mortality worldwide. As we scramble find out more about how to prevent beta corona virus's spread, evolution, and aftereffects, it continues to mutate with ramifications for world health. The four basic structural proteins of the coronavirus are N (nucleocapsid), E (envelope), M (membrane), and S (spike) (8) figure(3).

ACE 2 expression in the testis

In 2004, it was found that adult human testicular Leydig and Sertoli cells expressed ACE2, however, precise mechanism underlying its expression in male reproductive function remains unclear. Out of 31 typical human tissue samples, the testis had maximum ACE2 mRNA expression level, followed by the heart, small intestine, kidney, and adipose tissue, has recently brought more attention to the presence of ACE2 expression in human tissues (9). The expression of the ACE2 receptor in the prostate has been identified by combining the bulk RNA-sequence profiles of two public databases. Additionally, testis and seminal vesicles have been found to have both RNA and protein levels of ACE2 expression among the top 10 highly expressed organs (10). Expression of ACE2 receptor found in testicles of median-aged men who tested positive for this virus, even at protein levels, according to a recent study from India, transmembrane-serine-protease2 (TMPRSS2) additionally performs significant role, thus it appears that virus entry and activation do not require ACE2 expression at the cell membrane (11). As an indicator of COVID-19 patients' impairment in male reproduction, we recommend measuring sperm DNA fragmentation index (DFI), in addition to other choices including sex hormones and analysis of semen. SARS CoV-2 attack Sertoli cells, spermatogonia, besides Leydig cells can cause gonadal dysfunction and alterations in sex hormones. Male infertility, aberrant sperm motility, inflammation, beside alterations in ACE2 signaling pathways, may result from an infection (12).

barrier between the blood and testes

In the mammalian body barrier, the blood-testis barrier (BTB) is one of the closely fitting blood tissue borders, often referred to as seminiferous epithelium barrier elements. The BTB is a physiological, anatomical, and immunological barrier. It is supported by resources from other cell phone kinds and is particularly generated using tight connections among the tiny capillaries endothelial cells. The BTB is especially complicated and unique because it contains many different components, such as desmosome hole junction, gap tight junction, basal ectoplasmic specialization basal, and others (13).

Infertility in male

A male genital tract coronavirus infection can shed light onto potential male reproductive impairment after infection with SARS CoV-2. The virus's detrimental effects in the testis demonstrate that it can infect the male reproductive tract and prevent male reproduction. Furthermore, the common clinical indications of the novel coronavirus support the theory that it may effectively infect the

reproductive system of males, including the testes. When the virus mixes with this metalloprotease, there is a substantial risk of testicular injury and disruption of spermatogenesis because only spermatogenic and somatic cells in the testes have ACE2 (14). In spermatogonia and spermatids, TMPRSS2 is extensively expressed as a necessary protease for viral infection. The combined expression of ACE2 as well as TMPRSS2 in both Leydig and spermatogonia cells indicated that the testis is an organ with a high risk of organ for SARS CoV-2 infection, which may cause male infertility and testicular degeneration. Based to a pervious study, individuals had substantially lower testosterone concentrations when infected than those with milder disease (15). It also suggests that testosterone synthesis may be inhibited by SARS CoV-2 replication in Leydig cells, which make testosterone. According to a new research study, individuals who have COVID-19 actually developed hypogonadotropic hypogonadism as their condition deteriorated, suggesting that the novel coronavirus may have an impact on Leydig cell secretory activity. Additionally, testis blood barrier may allow viruses to exploit the testes as a special reservoir to avoid antiviral drugs. In patients recuperating from COVID-19, testicular damage and endocrine problems could result from the virus's adaptive immune response, subsequently impairing spermatogenesis. Increased temperatures may have the potential to permanently damage germ cells in COVID-19 patients, as evidenced by the 100% positive incidence of IgG, particular antisperm antibodies, or antiphospholipid antibodies, may prevent fertilization. When treating infected patients who wish to procreate, medical professionals should also consider male fertility because the testes may serve as a harbor for the virus that spreads during sex (16).

It is commonly known that viruses like the mumps, human immunodeficiency virus, and viral orchitis can be caused by the hepatitis B virus infiltrating testicular cells. In addition, male infertility and testicular tumors may arise from virus-induced damage to the testicles in certain instances. SARS CoV-2 is just like the “cousin” of SARS CoV-2 and shares the receptor ACE2 with SARS CoV-2. Previous research has studied the probable impairment of the testis in SARS patients and the impact of SARS CoV-2 on spermatogenesis. Their findings revealed that orchitis is a consequence of SARS and that spermatogenesis could be altered following infection (6).

Mechanistic pathways

Covid-19 infections of blood- testis and blood- epididymis barriers

The blood-epididymis barrier (BEB) and the blood-testis barrier (BTB) are constricted barriers in male reproductive organs that help in decline immune reaction and testicular inflammation (17). Testicular aberration may be caused by the presence of ACE2, a powerful receptor that the virus can use to enter the testes, as well as by a reduction in BTB's capacity to protect the testis from viral entrance. Express viral multiplication following entry may encourage immune cell pyroptosis and endothelial cell apoptosis in the testes, result in increased the inflammatory biomolecules such as chemokines, cytokines, and adhesion molecules. Examples of inflammatory cytokines that may affect the integrity of BTB and induce oxidative stress in Sertoli cells are TNF-α and IL-1β. This is caused by the important function that cytokines play in changing the essential proteins at the BTB, which encourages the breakdown of desmosomes, gap junctions, and tight junction fibrils in Sertoli cells. During viral infection, particularly COVID-19 infection, there has been a strong correlation shown between a marked rise in cellular inflammation and the death of cells and damage to many organs. In the end, these routes destabilize cell adhesion molecules, interfere with BTB, besides encourage malfunction of the testicles (18).

Direct viral damage to the testicles

Replication of viruses in cells directly contributes to lesions seen under a microscope, which in effect results in spermatogonia necrosis, which exhibits damage to the testicular parenchyma and death of Sertoli cells as a result of cytopathic effects of viral replication. The key factor influencing coronavirus infection and ACE2 follows viral replication. At the single-cell transcriptome level, that was found that the pattern of ACE2 expression in the human testis of adults was mostly concentrated in Leydig and Sertoli cells, which are capable of mediating SARS CoV-2's cell entrance (15). A significant drop in Leydig cells was observed in certain patients' interstitium, which ultimately resulted in ultrastructural lesions and a fall in Leydig cell

counts. Leydig cells, which produce the majority of androgens in males, are grouped between seminiferous tubules and blood vessels. Testosterone production in Leydig cells may be hampered by viral replication. According to a recent study, Leydig cell secretory activity may be impaired and hypogonadotropic hypogonadism was observed in COVID-19 patients. For spermatogenesis, blood testis -barrier, and fertility to remain intact, men require testosterone. Male fertility may be negatively impacted by modifications in sex hormone concentrations brought on via SARS (CoV-2) (19).

Virus-caused Direct damage to the epididymis

The formation of epididymal stones is one of the primary symptoms of an infection by the coronavirus in animal models. The capacity of the virus to replicate in the testes significant cellular micropathological damage, which over time may give rise to the development of epididymal stones. When this area is dysfunctional, sperm motility, DNA damage, and membrane lipids are altered, which can further affect sperm quality and impede sperm maturation. ultimately leading to the seminiferous tubules collapsing and spermatogenesis stopping (20)

Damage to male fertility caused by indirect immunological mechanisms

The testicle has unique immunity due to the testis blood barrier, which protects the testes from pathogen invasion. As they control leukocyte distribution and growth, the immune system's response to viral infections depends critically on cytokines. However, infections and inflammatory processes may cause the body's immune system out of balance because they can either over activate or produce immunological deficiencies, which could have fatal consequences for people. When a virus injures the BTB, immunological pathology linked to an unchecked immune response may result in the loss of the testicular parenchyma, and any ensuing functional impairment may cause infertility in males (21).

Infertility mediated by cytokines

It indicates that SARS CoV-2 affects several organs throughout the body, along with immune-pathological reactions and elevated cytokine storms. Elevated concentrations of COVID-19 patients' plasma contained cytokines, since a cytokine attack could exacerbate these patient's infections (22). Sexual dysfunction may arise as a result of elevated cytokine levels. Therefore, abnormalities in cytokine production may result in infertility. The pituitary-hypothalamic-testicular axis by cytokines could compromise the integrity of the blood-testis barrier, which may lower serum testosterone and consequently lower testosterone and sperm production. The virus may directly harm testicular tissue through blood-testis spread (23).

Infertility caused by inflammation

The blood-testicular barrier under conditions of local or systemic inflammation, might not offer a viral barrier that is impermeable. Leukocyte infiltration in the testicular interstitial tissue, a characteristic of human testicular orchitis, can induce inflammation that results in male infertility, which attracts leukocytes for defense against the viral infection due to an inflammatory cytokine storm. Patients infected with SARS CoV-2 are actually at a significant risk to develop a condition similar to orchitis, which is characterized by a severe seminiferous tubule damage and T lymphocyte infiltration into the testicular tissue. All testes exhibit thicker basement membranes, extensive germ cell degradation, and a high degree of leukocyte infiltration. These findings lend credence to the hypothesis that testicular injury development and its subsequent consequences on fertility may be significantly influenced by the adaptive immune response brought on by the coronavirus. Direct SARS CoV-2 infection of endothelial cells and diffuse endothelial inflammation have been observed in one investigation. It is possible that endothelial dysfunction following organ ischemia served as the impetus for a study that detailed ischemia-related priapism in COVID-19 patients. The research suggests that the development of testicular damage brought on by a SARS CoV-2 infection may be significantly influenced by vasculitis orchitis, and suggests that a change in the hormonal profile has an increasingly significant pathophysiological impact in COVID-19 by increasing vulnerability to SARS CoV-2 infection (24).

Effects on female reproductive system

As of at present, no confirmed infections of the virus in the amniotic fluid, peritoneal fluid, vaginal secretions, or

female reproductive tract have been reported. Even though the ovaries and oocytes both have high levels of ACE2, there is currently no information about the possibility of ovarian dysfunction following COVID-19 infection. Therefore, it appears from the data available that female fertility is unlikely to be permanently impacted by SARS CoV-2 infection (25). By interacting to ACE2, COVID-19 may invade target cells and have an effect on female reproductive system (angiotensin-converting enzyme I. In order for it to exert its particular function, that typically manifests in the placenta, ovaries, uterus, and vagina, ACE2 typically maintains angiotensin II levels and angiotensin-1–7. The ovarian reserve, which influences ovulation by lowering egg quality when depleted, is the cause of female fertility. Several viruses, including the RNA viruses Zika and hepatitis C, have previously been separated from vaginal fluid. Finding out whether SARS CoV-2 is present in vaginal fluid can provide important details regarding the virus's mode of transmission and the best way to administer it (26). Numerous investigations that have examined vaginal samples from COVID-19-positive women of reproductive age, both pregnant and non-pregnant, have not been able to recognize the virus. Furthermore, the virus was not detected at postmenopausal vaginal fluid in patients who had severe respiratory symptoms (27).

Therefore, the main observational indicator of COVID-19's impact on female fertility is ovarian reserve function. Age, the kind of fertility loss, subgroup analysis, and sensitivity studies must all be considered in order to investigate heterogeneity. Around the age of thirteen, a woman becomes fertile, and at forty-nine, she starts to become infertile (28).

In order to enter host cells, the SARS CoV-2 binds to ACE2 receptors. Positive single-stranded RNA encapsulates the spherically encased viruses known as coronaviruses. There will be an interaction between N protein, a nucleocapsid's essential component and the RNA of virus, despite the fact that the viral's envelope incorporate the 1st three proteins. The (SARS CoV-2) viral S protein exhibits a strong connection to ACE2, just like that of (SARS CoV-1). The two domains (S1 and S2) are the viral S proteins' 2 portions. S1 domain directly interacts with receptors of host cell, while S2 domain enables the union of the host cell membranes and viral. Viral S proteins are cleaved and activated via this process is further assisted by the cytoplasmic serine 2 transmembrane protease. After then, the genomic RNA of the virus is discharged into the cytoplasm of the target cell, where it uses the organelles of the host cell to proliferate. to produce new virion. It has been shown that SARS CoV-2 infection decreases ACE2 activity and expression, which raises Ang-II recruitment and decreases bloodstream synthesis of Ang-1–7 This helps to explain the inflammatory responses observed in COVID-19 patients (29).

Effects of COVID-19 on ovaries

Studies revealed that postmenopausal females might be at hazard of contracting the virus SARS CoV-2 because to the elevated ACE2 expression mRNA transcripts in their ovaries to confirm that ACE2 expression was extremely low in the ovarian cortex's stromal and perivascular cells, and that distinct ovarian cell types did not express TMPRSS2.To find out how TMPRSS2 and ACE2 are expressed in the ovarian cells of human , several groups used single cell sequencing. For the surface of the S protein to enter the host cells, protease TMPRSS2 or CTSB/L must co-express with ACE2. fewer than 5% of secretory and ciliated cells expressed ACE2.

The biological function of Ang-II results in steroids production, the maturation of oocytes, the follicles formation, the regulation of ovulation, and the maintenance of corpus luteum progression. Angiotensin-1–7 primarily functions to induce ovulation and stimulate the production of progesterone and estradiol. Certain characteristics of COVID-19, such as hyper-inflammation, hyperandrogenism, ethnic predilection, and extremely low vitamin D levels, are recognized to have a direct correlation with Polycystic ovary syndrome PCOS. Additionally, a notably high proportion of female patient populations have several cardio-metabolic illnesses, such as diabetes type 2, hypertension and obesity, which may raise the likelihood of unfavorable COVID-19 outcomes (5).

Ovarian reserve appears not to be impacted by the SARS CoV-2 virus, based on the findings of a study by Madendag et., al., 2022, and other research by PUCA & PUCA 2022

on the disease's impact on ovarian reserve. On the other hand, Significant immunological reaction and inflammation, as well as psychological stress and anxiety resulting from the COVID-19 infection, may be associated with changes in menstruation status. Additionally, most menstrual status changes are transient and go away a few months after the COVID-19 infection (30). Patients with COVID-19 require extended follow-up, and doctors should be alert to monthly irregularities, particularly in younger female patients. Further data from epidemiologic, clinical, and to completely understand the impact of this infection on the human ovary, especially in fertile women, long-term follow-up studies are necessary (31).

Effects of COVID-19 on the uterus

Endometrial ACE-transcript levels were low and they were not expressed as proteins, per a study utilizing the human-protein map (HPA). Furin RNA, a protease that cleaves S protein, and TMPRSS4 expression were both low, whereas the protein level was moderate, TMPRSS4 improves viral infectivity. Nevertheless, a number of findings showed that TMPRSS4 was strongly expressed during the entire endometrial cycle, cleaving S protein at several locations to boost infectiousness. Expression of TMPRSS4 was seen throughout every menstrual cycle., while it was most prevalent during menstruation, despite the low expression of ACE2. By cleaving the S protein, TMPRSS4 facilitates the attachment of CoV-2 to the infected cells and ACE2. Specifically, between the proliferative and middle secretory phases of the endometrium, Diaz-Gimeno's study found that ACE2 and age were positively correlated, particularly early during the secretory phase. It also suggests that older women might be more susceptible to SARS (CoV-2) (17).

SARS (Coronavirus 2) infection possibly linked with various pregnancy and neonatal problems, and it creates a risk to both the mother and the embryo. Decreased ACE2 levels in gravid as a result of the condition cause an increase in the levels of Ang-II in placenta, which encourages placental vasoconstriction and expands the hazards of gestational hypertension, which in turn leads to premature delivery and embryonic development limitation. According to a recent thorough assessment,COVID-19-infected pregnant women are most probably for dying or birthing prior to their due date, and their infants are more likely to end up in the neonatal unit. Although there is currently not sufficient proof linking COVID-19 to placental malfunction, more obstetricians and gravids are apparently favoring caesarean sections in order to reduce potential obstetric complications. Furthermore, COVID-19-associated severe kidney damage is rather common because to the renal's elevated levels of ACE2, In particular for critically ill patients, renal insufficiency is a risk factor of hospitalized patient mortality. Pregnant mice's kidneys revealed elevated ACE2 concentrations and the cells of renal tubules that infected by a virus, according to a prior study. Thus, we should pay attention to the maternal kidney function of infected women throughout pregnancy (32).

Discussion

International research clearly shows that the severity and lethality of COVID-19 virus are higher in males than in females. Moreover, infection -with SARS CoV-2 was more common at the reproductive age group. Therefore, due to COVID-19's male susceptibility, Males' reproductive system is highly vulnerable.

There are just two studies that examined The existence of SARS CoV-2 in semen sample, their results are not in agreement. Therefore, in order to identify whether the virus is present in semen samples and, thus, probability of viral sexually transmission . These investigations did not state if the virus had been investigated in clean semen samples, seminal plasma, or washed spermatozoa. Examination of washed sperm is still a compelling suggestion Given that the latter can direct how semen samples are utilized

in assisted reproduction, it is assumed that it was conducted using clean semen samples. Although Research has not yet looked into how SARS CoV-2 affects the testis, understanding potential impacts on the male fertility requires knowledge of past coronavirus outbreaks. One investigation using testicular samples revealed that the SARS coronaviruses seriously impacted the reproductive system. In a study, researchers compared the pathological changes in the testicles of six died SARS patients with controls. The findings showed that SARS caused orchitis. Along with extensive loss of germ cells and the testis also showed notable leucocyte infiltration and macrophage staining, indicating the influence of the immune system's

reaction on the testis, in addition to the little or the absence of spermatozoa from the seminiferous testicular tubules.

Nevertheless, absence of Sequences of the SARS genome in the testis that impacted provides additional evidence on the testicular damages that was caused by the immunological response. Even if SARS Coronaviruses are either absent from semen samples or are unable to penetrate the seminiferous tubules, this study unequivocally shown that they cause orchitis and may result in infertility. SARS CoV-2 is reported to penetrate the cells via exploiting the abilities of angiotensin converting enzyme 2 receptor (33).

While entering into the body via the respiratory system, the coronavirus may spread to other cells that express ACE2, which could be responsible for its influence across multiple organ systems. According to single-cell transcriptome studies, ACE2 receptor is broadly expressed by Sertoli, spermatogonia, and Leydig cells, which makes them extremely predisposed to coronavirus infection. Thus SARS CoV-2 was found to poses a significant risk for damaging testicular cells.

There was no complete genitourinary examination performed. In a Chinese investigation, 34 COVID-19 patients ' semen samples did not contain the virus Following an average of 31 days despite the fact that Six of the thirty-four patients (19%) experienced scrotal pain, which was considered a sign of viral infectious orchitis

(34), (17). According to an original study, SARS CoV-2 induced prostatic discharge was absent in 18 cases. There is not any more evidence to suggest that the prostate is affected. In a 2022 investigation, Ghosh and colleagues evaluated semen parameters for the COVID-19-recovered group as well as the control group

, included motility, semen volume, pH, sperm morphology and count(35). The recovered cohort exhibited a substantial reduction in sperm concentration, with a p-value of 0.013, from 42.5 (17−78) million/mL in the control group to 24 (1−72) million/mL. Sperm motility revealed a similar trend, with controls demonstrating 50% motile sperms; however, in the recovered group, the sperm motility was considerably decreased at 10% (0–65). Additionally, a significant difference in sperm morphology ($p<0.005$) was seen between the covered group (2.5%), and control group (8.5%). Semen volume and pH did not significantly differ across the groups (36).

The Sertoli cell is the type of testicular cell that exhibits inflammation in SARS patients., where ACE2 expression is common. The ACE2 positive rate was greater within the testicles of infertile men compared to those of healthy males, suggesting that SARS CoV-2 might disrupt reproduction by aberrantly activating the ACE2 pathway. According to one study, several patients had SARS (CoV-2) in their semen sample, which suggests that the testis is an additional entry point for infection (37).

The findings demonstrated that ACE2 expression is significantly elevated in testicular cells, particularly Leydig cell and Sertoli cell. Additionally, in vitro experiments showed that Sertoli cells bind to SARS Cov-2. So, one possible direct method that this virus causes harm to the testicles via attaching and entering such ACE2-positive cells. Considering that a significant portion patients that has been infected with COVID-19 are children or young adults, testicular injury from virus may develop as a secondary consequence after the fact, according to current clinical data. The breakdown of the BTB is another possible indirect route. The blood-testis barrier functions as a fortress, which is reducing or stopping the immune response to create the perfect conditions for germ cell survival, as is widely known. Rather than penetrating testis tissues directly and initiating leukocyte infiltration, as well a case with SARS, SARS Cov-2 might bind ACE2, infected Sertoli cells, and compromise the BTB. A study on SARS revealed orchitis in testicular tissues without SARS-Cov positive (6).

In spite of the fact that considers on extra tissues have not been done, lifted ACE2 expression has been illustrated to contribute to COVID-19 dreariness and mortality patterns and to improve viral disease. Besides, COVID-19 has an expanded expression of the ACE2 receptor quality. Human testicles had the most noteworthy sum of ACE2 quality expression, which may demonstrate their high defenseless to impacts an infection with SARS- CoV-2.. Most COVID-19 patients at first show respiratory indications, but small is known approximately the infection's urogenital manifestations.

The organic capacities of ACE2 in Leydig cells incorporate controlling the era of testosterone and controlling the neighborhood vascular frameworks to keep up the appropriate interstitial liquid volume via the conversion of AT2 into AT1. Pathogenesis and disease caused by SARS CoV-2 are largely determined by receptor recognition. Cells with increased ACE2 expression have a greater official liking for SARS CoV-2, which supports more efficient cellular passage. Intercession techniques can as it were be moved forward by understanding SARS CoV-2 cell passage instruments (38). Estrogen's immunomodulatory effects are correlated with its concentrations. Contrasts in immunological activity correlate to changes in estrogen during menstruation; this is also observed in women receiving exogenous estrogen for hormone replacement therapy or contraception. Studies conducted in vitro have demonstrated that higher estrogen therapy concentrations diminish the expression of ACE2 mRNA, suggesting the immunomodulation becomes more sturdy at elevated quantities, also estrogen is known to play a protection role for endothelial action by preventing or lessening intestine and pulmonary damage following ischemia stress. The anti-inflammatory effects of estrogen are similar to those of glucocorticoids. As well, by that viral infection and trafficking gene transcription are decreased, whereas virus-specific CD8 cells are raised., estrogen has antiviral effects. Developing data from exploratory researches, pulmonary inflammation can be minimized via estrogens.; moreover, these might being convincing for preventing as well as treating COVID-19 (25).

ACE2 may improve oocytes maturity and ovulation, as well as control the synthesis of progesterone and estradiol. Moreover, ACE2 may influence menstrual periods by controlling myometrial activity and endometrial regeneration. Coronavirus (COVID-19) virus may possibly infects the placenta as well as result in various histological defects like villitis/intervillositis, fetal vascular malperfusion, maternal vascular malperfusion, and villous fibrin deposition. Still up for discussion, however, are COVID-19's effects on the fertility of female, the ramifications to newborns, also the possibility that SARS CoV-2 can transmit through sexual activity, vertical movement, and lactation.. Furthermore, COVID-19's effects on fertility of female, the potential of SARS CoV-2 transmission through breastfeeding, vertical contact, and sexual contact, and the consequences for infants are all topics of continuous discussion. Additionally, there is no evidence that vaccinations have a negative impact on a woman's ability for conception or bear children. Considering all of this, several uncertainties remain regarding COVID-19's impact on female reproduction. To further understand this important problem, more thorough and prolonged studies utilizing organoid, explant, organs-on-chips, and animal patterns of illness were needed. In therapeutic practice, females that suffered with or have recently been afflicted with COVID-19 are intended to receive extra attention from clinicians. It is our aim that physicians will be able to gather, compile, and submit patient data in order to aid researchers in gaining a more thorough understanding of COVID-19's impact. Given that COVID-19 is still present, policymakers should enhance laws and regulations, especially in light of the hardships that women endure in order to offer (32).

Conclusion

In addition to representing considerable hazards to a person's general health, infection with this new virus may result in male infertility. Reproductive doctors and biologists can benefit from research on the proteome examination of COVID-19-recovered patients' semen understand effects of this virus on male reproducti, they also, developed plans aid in reduction or prevention its negative effects. The majority of the information now available suggests that the female reproductive system is not infected by the (SARS CoV-2)virus. Still, there might be the more covert approach for the virus to influence the level of sex hormone. There is a significant probability of emerging infection with (SARS CoV-2) in reproductive system, making it a possible target. It is inconceivable to ignore the later impacts on female and fertility, which need for more research.{Lippi, 2020 #105}

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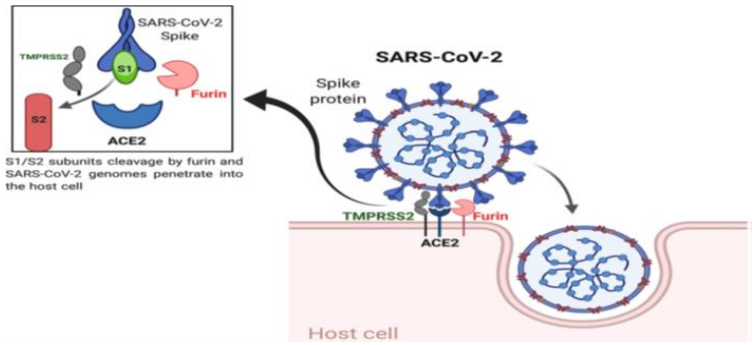
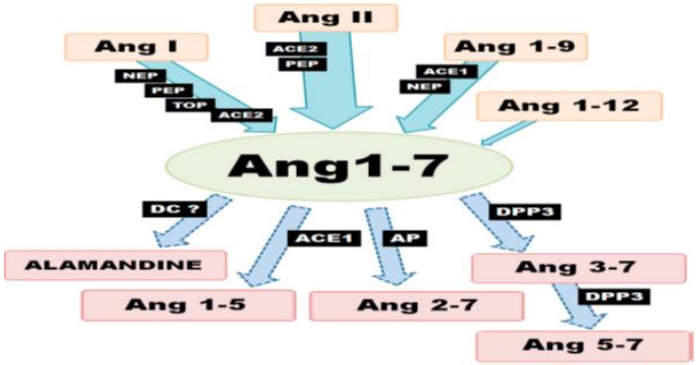
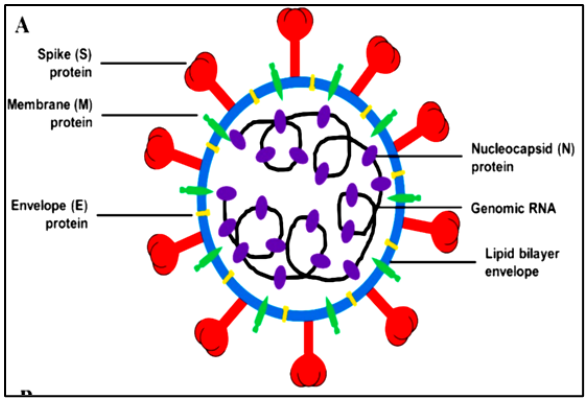


Figure (1) Possible molecular connections of SARS-CoV-2's spike protein with ACE2 receptor of the host cell. (5)



Figure(2): The creation and degradation pathways for Ang-(1–7) by enzymes. (7)



Figure(3): Diagrammatic structure of coronavirus. (3)