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Angiotensin Converting Enzyme 2 (ACE2) - A macromolecule and its impact on human reproduction during COVID-19 pandemic

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ABSTRACT

Coronavirus disease 2019 (COVID 19) is caused by severe acute respiratory syndrome novel coronavirus 2 (SARS-nCoV-2). It has been declared a pandemic by the World Health Organization (WHO) on March 11, 2020. Since then, several researchers have worked/ are working on this virus by a multifactorial approach to finding out the mechanism of entry, transmission route, post-infection replication process, survival, and post-recovery utilities. As we know, SARS, MERS, and Zika viruses have affected human reproductive potentials, consequently, COVID 19 also can affect both men's and women's reproductive potential through ACE2 macromolecule. This study aimed to summarize the role of ACE2- macromolecule in COVID 19 entry and further processes in the reproductive path of both men and women. Research articles were searched in NCBI-NLM, Google Scholar, and Scopus databases. We searched based on the phrase “COVID 19”, “ACE2”, “ACE2 in testes”, “ACE2 in the female reproductive tract”, “ACE2 during pregnancy”, “ACE2 during early embryo”, “COVID 19 and impact in human reproduction” and selected the articles for summarizing this article. Most recent articles and the mechanism of COVID 19 were selected for our understanding. The results of the study revealed that COVID 19 impacts the reproductive potential of both men and women. Testes are the most vulnerable organ prone to infection in men, and vaginal fluid and the uterus could be the choice of infection in the female. Till now, COVID 19 has not been directly detected in semen samples and vaginal fluid. Results of the study can be concluded that ACE2 plays a major role in COVID 19 infection, ACE2 expression could

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be more in the testes, ovary, uterus, and vagina. COVID 19 could impact more on human reproduction and lead to a loss of fertility status for a while. All antiviral treatments could pose a negative impact on human reproduction. Further research should be carried out on the already existing theoretical hypothesis of SARS-Co-V-2 on human reproduction.

1 Introduction

Severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-Co V-2) was first identified in 2019, December in Wuhan, China (Huntley et al. 2020). Since then, the viral infection has spread across the entire globe victimizing people from more than 150 countries (Ali and Alharbi 2020). This novel coronavirus causes acute respiratory syndrome in patients. World health organization (WHO) declared the infection a pandemic in March 2020 (Jebril 2020) and named this disease COVID 19 (Coronavirus disease 2019). As per the world data, the virus has infected 25.3 million people worldwide and has been the cause of 848 thousand deaths, as of August 2020 end. SARS-CoV and SARS-CoV-2 share 76% sequence similarity and SARS-CoV-2 utilizes almost the same mechanism as SARS before infecting the host (Rabaan et al. 2020). This infection shows very mild symptoms such as cold, cough, and fever in nearly 80% of the infected population (Mohapatra et al. 2020). While people with good immune systems remained asymptomatic on contracting the virus, 20 % of the infected population showed severe symptoms leading to hospitalization (Long et al. 2020). Of the symptomatic 20% cases, only 4% developed acute respiratory distress syndrome (ARDS) and need ventilator support for artificial breathing during treatment (Ma et al. 2020; Granados-Bolivar et al. 2022; Tran et al. 2022; Matin et al. 2022; Mirsaliyev et al. 2022).

Also, COVID 19 shows gender differences and it affects men more widely than women, the phenomenon of occurrence of which is still unknown (Blaskó et al. 2020; Islam et al. 2022; Rabiul Islam et al. 2022). This gender disparity is extended to the fatality rate with higher fatalities in men compared to women (Blaskó et al. 2020). ACE 2 (angiotensin converting enzyme 2) plays a major role in SARS-CoV-2 pathogenesis, it aids in direct host cell damage (Yan et al.2020). Until today, it remains very unclear how COVID 19 disrupts the innate immune system of the hosts. Immune deregulation termed as “cytokine storm” is highly associated with acute respiratory problems (Rabaan et al. 2021; Chau et al. 2021). Many researchers have confirmed the presence of proinflammatory cytokines in the COVID 19 patients. Various research has also confirmed the innate immune response against COVID 19 from the presence of inflammatory chemockines in the bronchoalveolar fluid of COVID patients (Merad and Martin 2020; Feys et al. 2022; Margiana et al. 2022). Other research suggests a significant upregulation of genes of interferon, those directly involved in the antiviral activity (Holzinger et al. 2007). These could be due to the innate immune response against COVID 19 in mildly symptomatic patients. COVID 19 infection results in the upregulation of various chemokines associated with an increase in several inflammatory cytokines like IL-6 (Interleukin-6), leading to the damage of tissue (Azkur et al. 2020; Karimabad et al. 2022). Another mechanism COVID 19 triggered various IFN (interferons) responses, which leads to the upregulation of proinflammatory genes in the lungs (Zhou et al. 2020; Chakraborty et al. 2022).

The binding of COVID 19 to the ACE2 receptor mediates the viral entry and replication process. Tissues with higher ACE 2 expression levels serve as the potential target for SARS-CoV-2 infection (Zhang et al. 2020a). When compared to other body tissues, testes are found to have more expression of ACE2 that might be prone to infection. The expression of ACE2 could be found more in the testes when compared with the lungs as well (Hikmet et al. 2020). Spermatogonia, seminiferous duct, Sertoli cells, and Leydig cells are the major cell types that have ACE2 expression. Moreover, the expression of ACE2 could be very high when compared to ovarian cells (Malki 2022). The involvement of ACE2 in SARS-CoV2 transmission coupled with data on higher expression of ACE2 in male testicular tissues lead to speculation on the potential SARS-CoV-2 impact on male gonadal functions. Until today, there is no clear mechanism of how ACE2-mediated SARS-CoV-2 infection affects the reproductive potential of both men and women (Verma et al. 2020; Sadeghi et al. 2022). During the epidemic of SARS, in 2002, Orchitis studied the infected patients and found that SARS-CoV-2 could affect spermatogenesis, and germ cell damage and further lead to poor semen quality (Payne et al. 2020). Also, previous studies revealed the presence of inflammatory infiltrates in the seminiferous tubules (Li et al. 2020b). SARS-CoV was found in the semen of infected patients; however, there are no reports of traces of COVID 19 in semen samples of infected patients to date (Guo et al. 2020; Donders et al. 2022). The inflammatory responses and immune responses take a major role in COVID-19-mediated testicular damage. ACE2 expression level could be based on the age group. Hence, only young male patients could be the target for COVID 19 in testicular damage (Jin et al. 2020; Pallotti et al. 2022).

TMPRSS2 cleaves the ACE2 receptor and this mechanism helps the entry of the virus into the host cell. Like other infections, COVID 19 also utilizes the host machinery for its growth, reproduction, and survival during infection (Perico et al. 2020;

Sultan et al. 2022). Always the viral host and protein-protein interactions can be utilized effectively for evaluating the mode of transmission, mechanism of infection, the route follows up, and, a probable drug against infection (Ji et al. 2020). The infectivity rate can be higher in case a combinatorial mutation occurs at ACE2 and S-priming residues. Previously antiviral targets were the treatment methods for viral infections like SARS, MERS, Zika, and Ebola virus during their epidemics in various countries (Tse et al. 2020).

All the antiviral drugs potentially target the reproductive functions in both men and women. SARS-CoV-2 infection mediated by ACE2 receptors causes direct testicular damage, in some cases affecting only the inflammatory and immunological responses (Bourgonje et al. 2020; Delli Muti et al. 2022). Since male and female fertility is already in decline worldwide, further frequent viral epidemics and pandemics will pose a major threat to humankind in the case of fertility and reproductive functions. In this review, we analyzed exhaustively, how ACE2 receptors help the foreign body COVID 19 with its entry, replication, and further processes at reproductive junctions (Rogers et al.2020).

We analyzed and summarized the role of ACE2 and other genes, and macromolecules involved in the COVID infection on the reproductive path, we elucidated the role of ACE2 in both men's and women's reproductive paths. We included the ACE2 role and its expression in testes cells especially Leydig and Sertoli cells, and the role of ACE2 in the prostate, epididymis, seminal vesicles, and male reproductive tract. This study also summarized the ACE2-mediated infection in the ovary, uterus, and vagina for analyzing the female reproductive potential. We also summarized the role of ACE2 during pregnancy and the developing embryo. We also summarized the impact of COVID 19 on both male and female infertility during the global pandemic.

2 Presence of ACE2 in Testes- Role in Leydig and Sertoli Cells

Many recent studies revealed the importance and potential routes of SARS-CoV2 entry and infection in the cardiovascular, digestive, respiratory, urinary, and reproductive systems (Zhang et al. 2020b; Shen et al. 2022). Reports on SARS-infected patients presented thickened membranes in the testes, destroyed germ cells, and, absence of active sperm cells in the seminiferous tubules (Vishvkarma and Rajender 2020). However, the available data on SARS-CoV-2 infection has failed to give clues on the effect of COVID 19 on the reproductive system. The single-cell resolution method is the choice for estimating the RNA expression level of ACE 2 in adult testes. This could enhance further ideas about ACE2 and its impact on the testes as well as human reproduction (Calicchio et al. 2014; Nayar et al. 2022). Researchers also revealed that the presence and expression of ACE2 are predominant in Leydig and Sertoli cells (Salonia et al. 2021). Positive ACE2 cells showed more transcripts associated with transmission and viral reproduction (Douglas et al. 2004; Temena and Acar 2022). Genes responsible for viral entry transmission and reproduction were abundantly found in ACE2-positive spermatogonia when compared to negative ones. COVID 19 also shares the same receptor as SARS disease; collectively, these observations lead to speculation on the possibility of COVID 19 to have testes as the route of infection (Leal et al. 2009). Differentiation of spermatogonial stem cells is controlled and monitored by testicle seminiferous tubules. Leydig cells help in producing testosterone that supports spermatogenic sperm cell differentiation. Any problem that arises with male germ cells or somatic cells may cause male infertility and or male reproductive system failure (Corona et al. 2020). Positive Sertoli and Leydig cells at many times express higher genes involved in cell-to-cell junction and immunity. All such findings reveal the risk of testes vulnerability through SARS-CoV2 infection that might lead to failure of spermatogenesis (Corona et al. 2020).

A complete analysis of ACE2 is mandatory for exploring the route of infection and transmission. Nonetheless, the testes are the key organ for the male reproductive system, and expression of SARS CoV2 in the testes has been revealed by many researchers. However, the detection of SARS CoV2 antibodies in testicular tissue is tough and non-specific (Parra-Medina et al. 2021; Masterson et al. 2022). In recent times, single-cell RNA sequencing can help us to effectively outline the cell types. This will enable the specificity of ACE2 expression levels. The analysis of ACE2 expression was compared between ACE2 in healthy and also in infertile men for concluding remarks and a similar tendency was noticed in both groups (McClelland et al. 2015). The expression of ACE2 can be possibly correlated with reproductive disorders. Testicle tissue damage is reported in infected patients. Further, IgG was highly expressed in Sertoli and Leydig cells (McClelland et al. 2015). The overall mechanism and theme of the article are explained in figure 1.

The biological process of ACE2 includes but is not limited to angiotensin maturation, regulatory functions in amino acid transport, positive regulation in cardiac muscle contraction, activating the receptor-mediated virion attachment to the host cell, blood vessel diameter regulation, regulation of germ cell proliferation, regulation of spermatogonia proliferation, and differentiation, regulation of cytokine production, inflammatory response regulation, transport of tryptophan and viral entry into the host cell (Sorour et al. 2020; Thakur et al. 2022). The major molecular functions of ACE2 are carboxylation, endopeptidase activity, protein binding, Zn binding, and virus receptor activity (McClelland et al. 2015).

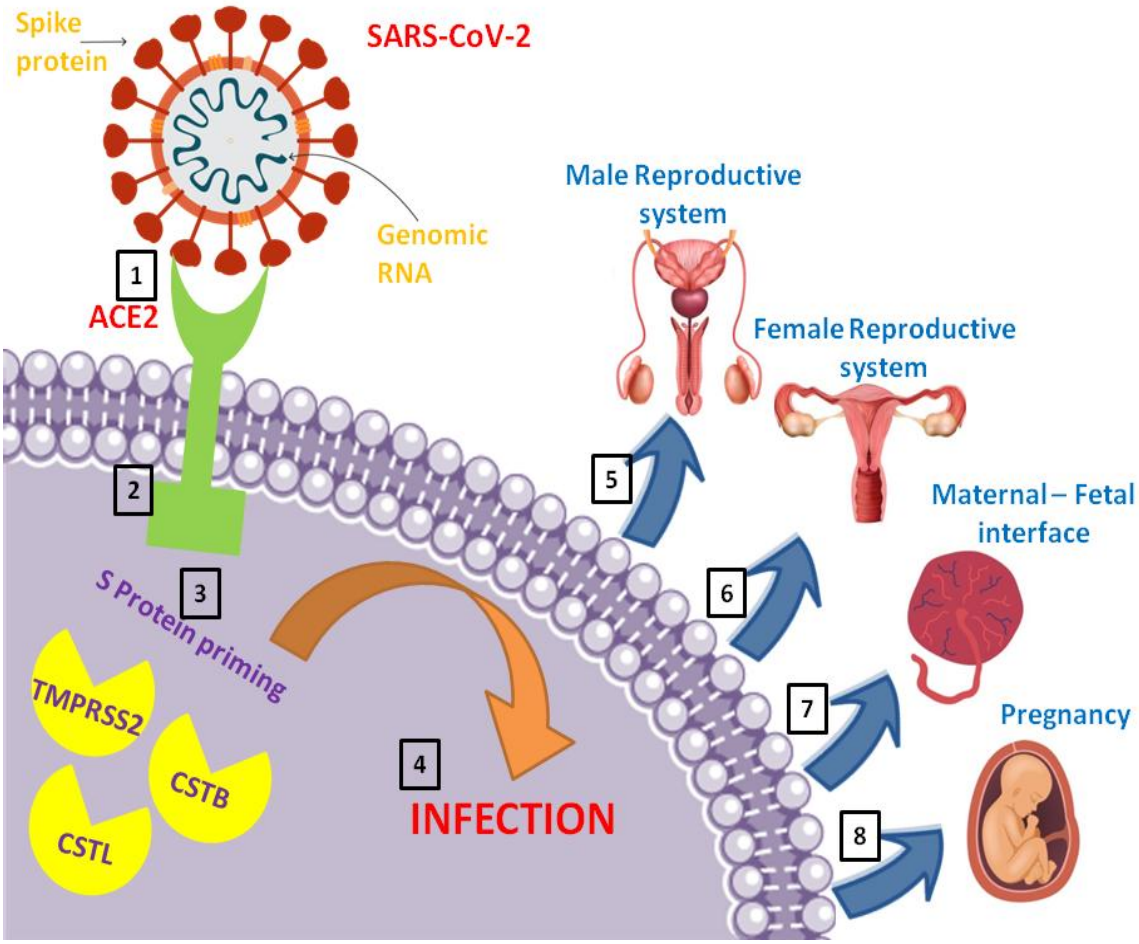


Figure 1 Illustration of the mechanism of SARS-CoV-2 infection and its effect on human reproduction; 1. Binding of S protein (Spike protein) of SARS-CoV-2 and ACE receptor; 2 Entry of the virus; 3 S priming by TMPRSS2, CSTB, and CSTL; 4 Release of genomic RNA causing COVID 19 infection; This mechanism may affect; 5 Testes and prostate of the male reproductive system; 6 Uterus, vagina and ovary of the female reproductive system; 7 Placenta and umbilical cord in the maternal-fetal interface, and 8 the developing embryo and breastfeeding during pregnancy

3 Expression of mRNA of ACE2 in testes

SARS-CoV2 showed variation in the case of infection percentage, way of abnormality, and death rates between age groups (Shen et al. 2020; Barletta 2022). In the case of healthy men in the reproductive age group, ACE2 expression showed the highest percentage with 2.8%, the percentage was 1.39 in the case of youngsters the age of 20 or less, and around 0.88 % in the case of 60 year age group (Harmer et al. 2002).

4 Expression of ACE2 in the prostate

Many on-going and completed research works on ACE2 and its expression studies on the prostate shows that the prostate is most susceptible to COVID 19 infection (Song et al. 2020; Abdolmaleki et al. 2022). The double-positive cells with both ACE2 and TMPRSS2 expression can act as a medium or reservoir of COVID 19 infection (Singh et al. 2020; Tanaka et al. 2022). This, in turn, damages the prostate gland to some extent. As we know, the prostate gland secrets Zn abundantly into the seminal plasma for sperm protection. In this case, damage in the prostate gland due to COVID 19 infection can stop the essential need or energy supply to sperm cells (Mollica et al. 2020).

This hypothesis further supports the correlation between COVID infection and human male infertility. Further, the common genetic signature shared between prostate club cell and lung club cell strengthen the hypothesis (Bhowmick et al. 2020). The similar club cells in the lung and prostate for ACE2 and TMPRSS2 expression were compared and found that 0.62% of prostate cells exhibit the co-expression. This implies that the COVID 19 infiltration in the prostate gland is through club cells (Zhang et al. 2020c). The mechanism behind this study is unclear and further clinical studies need to be conducted to warrant the hypothesis (Bhowmick et al. 2020).

5 ACE2 expression in Non-obstructive azoospermia

Many authors are investigating ACE2 and its impact on COVID 19 transmission, particularly on SARS-CoV-2 process-related genes. This will provide enormous ideas about virus transmission and reproduction (Liu et al. 2020a; Ezechukwu et al. 2022). The single-cell RNA sequencing method helps the researchers to tabulate all the data required. The sequence of Sertoli cells of non-obstructive azoospermia patients can help us in understanding the current state of the disease. To analyze the effect of COVID 19 on testes, the expression pattern of ACE2 and functions of ACE-positive cells between healthy men and non-obstructive azoospermia will give a clue for COVID 19 infection and its reproductive potential (Reis et al. 2010). TMPRSS2, CTSL, CTSB, and BSG are possible COVID-19 transmission-related genes that are expressed in testes. TMPRSS2 plays a major role apart from ACE2 in infecting the host through transmission (Liu et al. 2020b).

Both ACE2 and TMPRSS2 were compared and unfortunately, the pattern of expression was different. ACE2 expression is more in Sertoli cells and less in spermatogenic stem cells and vice versa for TMPRSS2 (Matsuyama et al. 2020; Harb et al. 2022). Hence, for the invasion of COVID 19, the combined action of ACE2 and TMPRSS2 is necessary. The interaction and expression studies of CTSL (Darbani 2020) and CTSB (Brann et al. 2020) show that both are needed for the COVID 19 infection transmission via S protein priming (McKee et al. 2020), and this phenomenon exists at all four stages of spermatid. The spermatogenic cells of patients with Non-obstructive azoospermia could be the potential target identification since mature sperms are absent. Researchers compared the ACE expression pattern between healthy men and NOA donors for the identification of diseased conditions (Khawar et al. 2019; Wu et al. 2022). Both ACE-positive cells and ACE expression levels in both these groups were compared. The ACE2 expression level was significantly reduced in the case of NOA donors when compared to healthy men. Rennin angiotensin system (RAS) also correlates with human fertility through various sperm functions (Bernie et al. 2015). ACE2 expression levels showed a significant difference in the dataset of NOA patients when compared with Sertoli cells. The effect of ACE2 on human male infertility and sperm functions can be elucidated with more functional clinical studies (Riordan 2003).

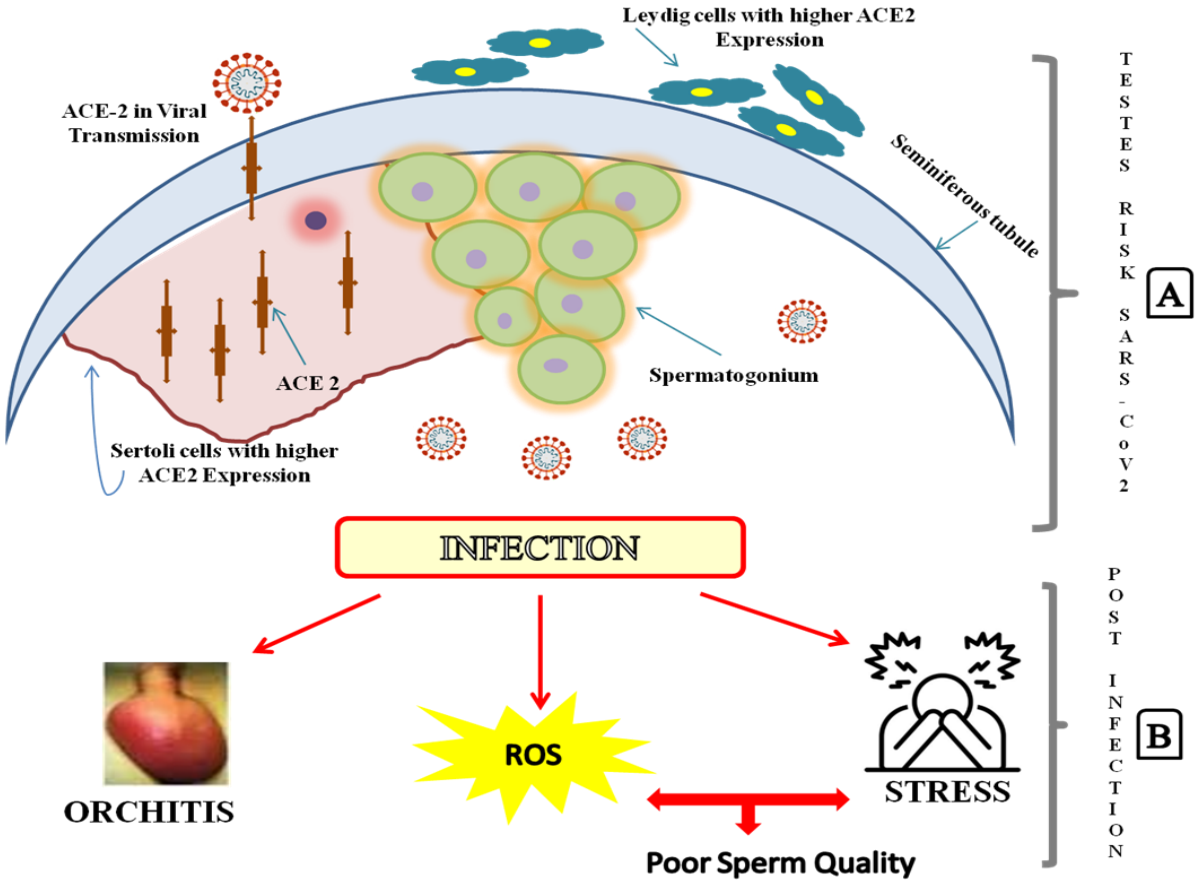
6 ACE2 mediated SARS-CoV-2 male infertility

COVID 19 can disturb the male reproductive function through multiple mechanisms. Oxidative stress (OS) is the major mechanism on which many normal functions of male reproduction rely (Menezo et al. 2016; Delli Muti et al. 2022). It can be hypothesized that COVID 19 virus activates pathways mediated by inflammatory responses. The viral entry could be because of ACE2 activation and expression in male reproductive organs (Tay et al. 2020). Oxidative stress mediates male infertility in numerous ways and this mechanism is documented and supported by data to a large extent (Smith et al. 2006; Xue et al. 2022).

Oxidative stress affects sperm quality, especially motility and morphology. Cellular oxidation damages the spermatozoa and DNA and leads to lipid peroxidation of the sperm membrane (Smith et al. 2006). SARS-2002 infection affects the male fertility status by inducing more ROS production in the semen leading to poor sperm quality and DNA damage (De Iuliis et al. 2009). On the contrary, the release of cytokines also mediated by OS leads to inflammatory responses. COVID 19 may cause orchitis which is one of the causes of oxidative stress. Sometimes, the treatment procedures for COVID 19 infection cause psychological symptoms leading to oxidative stress and in turn loss of fertility status (Rihayat et al. 2019). The treatment of COVID 19 uses ribavirin and other antiviral drugs that have negative effects on men's fertility status (Vellingiri et al. 2020). These medications lead to the induction of oxidative stress, decreased amount of testosterone, impaired spermatogenesis, and other sperm malfunctions. The available animal studies support these data (Asadi et al. 2017).

COVID 19 may result in acute hypogonadism, and such androgenic reduction action can lead to very fatal conditions. Hypogonadism increases the inflammatory cytokines which in turn act as an important mediator for COVID 19 pathophysiology (Gemmati et al. 2020; Mintziori et al. 2022). Researchers confirmed the suppressive activity of the hypothalamic-pituitary axis if critical inflammatory conditions exist along with COVID 19 (Coronel-Restrepo et al. 2017). This causes hormonal imbalance by reducing LH, FSH, and testosterone levels in the body. These changes terminate in male infertility. COVID 19 infection and intonation of sex hormones could be the point where the research should focus on in the future since there are no supporting documents for the effect of COVID 19 infection on sex hormones (Hanscom et al. 2020; Kokkinaki and Hatzidaki 2022). A possible hypothesis explaining the effect of SARS-CoV2 infection on male infertility was shown in figure 2.

During the SARS epidemic, the use of antiviral medications led to a reduction in sperm count, impaired spermatogenesis, and sperm DNA damage or fragmentation (Sengupta and Dutta 2020; de Albuquerque et al. 2022). All these changes were sustained for a minimum of 8 months after recovery by treatment. Previously, it was discussed how COVID 19 damages the testes, and from the male infertility point of view, the testes might be the potential organ target for SARS-CoV-2 (Zheng et al. 2021). Primarily, COVID 19 affects the testes and causes direct testicular damage mediated by ACE2 receptors, and in some cases, secondary inflammatory responses (Cheng et al. 2020).



Possible hypothesis explaining the effect of SARS-CoV2 infection on male fertility
A: Higher expression levels of ACE2 genes in Leydig and Sertoli cells increases the risk of SARS-CoV2 transmission in testicular tissues
B: Increased Reactive oxygen species (ROS) levels , Orchitis and Psychological stress due to SARS-CoV2 infection affects spermatogenesis and results in poor sperm quality.

Figure 2 Possible hypothesis explaining the effect of SARS-CoV2 infection on male infertility

Male infertility term cannot be missed during COVID 19 pandemic since fertility is already going down worldwide due to various abnormalities and this infection further decreases the number (Tufvesson et al. 2022). But at the same time, a decline in sperm quality may be temporary in many cases and we cannot consider the count as infertility during this period (Purvis and Christiansen 1993). Till now there is no track record of men for male fertility status and follow-up, as only 8 months have passed over after the pandemic. More data and follow-up are needed for the patients who have recovered from COVID 19, concerning their reproductive functions (Qiu et al. 2020). Also, the data for reproductive functions during treatment can be taken. These all coherently help the andrologists and clinicians to come up with a new hypothesis for male infertility mediated by ACE2 and COVID 19 (Pan et al. 2020a; Ocanas 2022).

7 Expression of ACE2 in the uterus and vagina

Research has confirmed the expression of ACE2 in the uterus and vagina of females. As already discussed, the ACE2 expression is more in epithelial cells as compared to stroma cells (Chadchan et al. 2021; Saadedine et al. 2022). Although COVID 19 can infect the vaginal tract, the infection through sexual transmission to the partner is not yet elucidated clearly (Qin et al. 2013). ACE2 expression is very important for the endometrium maintenance and menstruation cycle (Abhari and Kawwass 2020). Many researchers proved the role of ACE2 in the regular menstrual cycle, and the absence of ACE2 in the vagina and uterus may lead to endometrial carcinoma (Cui et al. 2020). Hence, although ACE2 is an important protein in the female reproductive system, it can behave as a potential target for virus transmission as well (Stanley et al. 2020).

8 ACE2 expression in the human ovary

ACE presence and its expression were studied in the human ovary and were found that ACE2 activity is more in the case of postmenopausal women's ovary when compared with pre and menopausal women (Liu et al. 2020b; Carp-Veliscu et al. 2022). At the serum level, significant ACE2 activity in the ovary was not recorded and there was not much difference in the ACE2 activity during pre and postovulatory phases for human beings (Dominska 2020). ACE2 expression was also found in the luteinized granulose (La Vignera et al. 2020). The presence of ACE2 in the ovary has many physiological functions but the involvement of ACE2 in ovary-related diseases has been confirmed by many researchers like PCOS (polycystic ovary syndrome), ovarian hyperstimulation, and ovarian cancer. Further findings also indicate FSH mediates the ovarian RAS launch (Palumbo et al. 2016). Studies have confirmed that ACE2 plays a major role in inhibiting cancer cell proliferation and differentiation in the ovary (Kobayashi et al. 2009; Nagappan et al. 2022). Any changes in ACE2 activity and its expression can lead to ovarian dysfunction and sometimes ovarian cancer (Kajihara et al. 2010).

9 Expression of ACE2 in the human maternal-fetal interface

The specific expression pattern of ACE2 is very less in maternal-interface cells (Li et al. 2020c; Miller et al. 2022). The cells where maximum ACE2 expression can be identified are perivascular cells cluster 1, syncytiotrophoblast, stromal and decidual cells. Researchers also confirmed that SARS-CoV-2 is not evolved properly enough to capture perivascular cells cluster 1 for its transmission (Chen et al. 2020a). This could be the reason behind the low risk of early maternal-fetal interface for COVID 19 infection (Liu et al. 2020c; Sufriyana et al. 2022). In the case of the Zika virus and MERS, there were chances of vertical transmission of infection from mother to fetus, but in the case of COVID 19, no reported vertical transmission is reported yet (Schwartz 2020).

From December 2019 to March 2020, we don't have much data to support COVID 19 infection in the male reproductive system. But previous infections like SARS and MERS (epidemic diseases) have shown the impact of infection on male reproductive functions (Adhikari et al. 2020). During SARS, many researchers worked on the impact of the reproductive system and proved that there exists a negative correlation with reproductive functions (Knez 2013). The fertility status of men belonging to the reproductive group declined in SARS survivors. As we know SARS-CoV and SARS-CoV-2 share 76% sequence similarity and since both use ACE2 as a receptor for transmission, it is necessary to investigate the reproductive status of men after COVID 19 recovery (de Souza Silva et al. 2020). Researchers also investigated a group of men and their semen samples for COVID 19 virus presence, nearly 16% of patients' semen samples showed the presence of COVID 19. This raises an alarm about the high chance of sexually transmitting the COVID 19 to the partner (Paoli et al. 2021). We have already discussed the expression of ACE2 in the vagina, so when COVID 19 enters via semen during intercourse, the vaginal fluid supports the expression of ACE2 receptor activation (Hoffman et al. 2020). Although the acidic nature of vaginal fluid can curtail virus survival, the presence of the ACE2 receptor overcomes this block. The antibacterial activity of seminal plasma (Bourgeon et al. 2004) might kill the lactobacilli present in the vaginal tract, so that the acidic medium may not exist for long durations. The occurrence of such a situation is a hypothesis and if it happens, then it is easy for COVID 19 to infect via the female reproductive system and start reproducing on its own (Korber et al. 2020; Saadedine et al. 2022). Although the SARS-CoV-2 presence was identified in semen, no further studies on sperm quality including motility and morphology, or even the immunological response of semen samples were studied (Payne et al. 2020).

10 ACE2 in developing embryo

The present scenario necessitates 1 in 6 couples to rely on IVF methods to conceive a child (Inhorn and Patrizi 2015). COVID 19 infections were found to be asymptomatic in many cases, some or many of the infected individuals have already been conceived or some even tried to get conceived during the pandemic period (Schwartz 2020; Shams et al. 2022). In all these cases, a careful watch on the mechanism of COVID 19 infection risk in the developing embryo is needed (Chen et al. 2020b). Researchers analyzed the dataset of developing embryos for the expression level of ACE2, BSG, CTSL, and other genes involved (Colaco et al. 2020).

ACE2 expression was checked in gametes, morula, zygotes, and other predominant stages. ACE2 expression was more in the blastocyst embryos and very low in compact morula (Cremades et al. 2004). We know ACE2 could be essential for the COVID 19 infection, but the viral infectivity and promotion are majorly done by TMPRSS2. In another study done by the researcher, 80% of the cells exhibit ACE2 expression, but none of them show expression of TMPRSS2 in ICM (later stage of the embryo) (Chanana et al.2020). Whereas, in the case of epiblast and trophectodermal cells, ACE2 and TMPRSS2 were co-expressed (Singh et al. 2018).

This indicates that early embryonic cells could be vulnerable to COVID 19 infection as a mode of entry (Sungnak et al. 2020; Andrews et al. 2022). In the absence of ACE2 in particular organs, an extracellular metalloproteinase enhancer, CD147 (Tang et al. 2004) has been found to have the capacity to biding both COVID 19 and SARS. This shows that the promotion of viral entry could be possible independent of ACE2 and TMPRSS2. In addition, BSG and CTSL need to be co-expressed alongside the entry of the virus, similar to the co-expression of ACE2 and TMPRSS2

(Menon et al. 2020). BSG and CTSL were found to be co-expressed in almost all the cells of the developing embryo. In the case of trophectodermal cells, both ACE2 and CD147 mediate the viral entry and require cathepsin L for COVID 19 infection (Colaco et al. 2020; Louis et al. 2022). It is well known that the entry of viruses by various mechanisms, but what happens after the virus enters the cells? The next step is the replication of the virus, which needs the interaction of viral proteins and the host proteins (Akhtar and Shukla 2009). In the embryos, the blastocyst shows the expression of host proteins that leads to viral replication. Through the available data, researchers also suggest that various genes might be involved in endocytosis and replication of the virus, and are expressed in a majority of the cells of developing embryos (Villalba et al. 2016). Cells of trophectoderm and epiblast have been found with genes of endocytosis and replication even in the absence of ACE2 and TMPRSS2 (Hoffmann et al. 2020). In human embryos, many proteins might play role in interacting with COVID19 in absence of ACE2 (Datta et al. 2020). Both epiblast and trophectoderm undergo further gastrula and placental stage and any damage to these cells will cause lethality in the later embryo development (Stephens et al. 1995). Epiblast retains the pluripotent capacity for a longer time and self-renewal is also observed. A lipid profile is mandatory for optimal viral production and further replication. Enriched lysosomes in epiblast prove the process of viral replication in the host (Rambhatla and Carpenter 2007).

11 ACE2 expression during pregnancy and COVID 19 infection

Many researchers proved the presence of ACE2 and its expression in the placenta region, especially in cytotrophoblast (Hecht et al. 2020; Abdolrazaghnejad and Miraj 2022). During maternity, in the maternal stroma (Meteeb and Al-Dhalimy 2020), the ACE2 is expressed at higher levels at the intravascular trophoblast. The next major part of ACE2 expression is found in the umbilical cord, and its expression is more in the early gestation period (Goolam et al. 2020). With the available data sources, it was proven that the expression of ACE2 is more in the placenta than in the lung (Hikmet et al. 2020). This shows the possibility of COVID 19 infection at the placenta. There is no proven information or data existing for intrauterine infection. But when analyzing the COVID

Table 1 Important studies with COVID-19 and human fertility status

Author studied	Year	Concluding remarks	Link to Human reproduction with relevance to COVID 19
Segars et al. 2020; Gizzi et al. 2022	2020, 2022	COVID 19 infection leads to severe alternation in female pregnant women and affects the offspring too	COVID 19 affects both male and female sex gametes
Cavalcante et al. 2020	2020	The affinity of COVID 19 towards ACE2 in female reproductive organs were explored and ACE2 acts as a source of entry for COVID 19	COVID 19 enters via the female reproductive system and results in female infertility, still more research is needed to support the data
Anifandis et al. 2020	2020	COVID 19 affects the IVF outcomes	COVID 19 affects both sperm functions and egg performance and leads to give more stress on the IVF patients
Espinola et al. 2021; Minich et al. 2022	2021, 2022	Supplementation of Vitamin D and Myo-inosital during COVID 19 pandemic will act as a preventive measure for pregnant women and women who undergoing IVF	COVID 19 pandemic affects IVF outcomes severely in many countries
Dutta and Sengupta 2021	2021	Theoretical prediction proved that the testes could be the primary target of SARS CoV-2, which severely damages the testes and further results in male infertility	COVID 19 virus severely affects the testes and affects male reproduction further leading to male infertility
Rennu et al. 2020	2020	The disturbed IL-4 decreases the level of ACE-2 with the inflammation	COVID 19 infection leads to male infertility via Th2 cells and JAK-STAT signaling.
Younis et al. 2020	2020	ACE2 is found more abundant in testes and it acts as a receptor for COVID 19 entry	COVID 19 infection affects the process of spermatogenesis and leads to male infertility
Olaniyan et al. 2020; Balawender et al. 2022	2020, 2022	SARS-CoV-2 can also affect the urogenital tract	Role of ACE2 receptors in promoting SARS-CoV-2-induced blood-testis/epididymal barrier infiltration and testicular dysfunction.
Aitken 2020	2020	ACE2 receptors mediate SARS-CoV-2-induced blood-testis/epididymal barrier infiltration and testicular dysfunction	COVID 19 indirectly correlates the male sexual dysfunction
Li et al. 2020a	2020	Autopsied testicular and epididymal specimens of COVID-19 showed the presence of interstitial edema, congestion, and red blood cell exudation in testes, and epididymides.	Impairment of spermatogenesis was observed in COVID-19 patients leading to male infertility

19 infection history, it has affected newborns in many countries. The first such case was filed at Wuhan hospital, later many countries reported positive COVID newborn cases (Pan et al. 2020b).

Many researchers postulate that COVID 19 may infect the fetus in the early gestation itself and hence diagnose positive for the newborn (Prochaska et al. 2020). Also, other available databases show the presence of ACE2 in the female breast. There is no proven data for the presence of COVID 19 in breast milk, but this can probably act as a medium of transmission (Contini et al. 2020). There are no conclusive reports available for COVID 19 infection and breast milk or breastfeeding (Thomas et al. 2022). Even though no active virus is present in breast milk, it could affect newborn that is fed with breast milk with infections (Williams et al. 2020). Hence, newborn babies that generally have less immunity can avoid breastfeeding from affected mothers. So far, the functions of ACE2 during pregnancy are regulating the blood pressure & the fetus development, stimulating trophoblast invasion, and acting as a paracrine regulator during the entire pregnancy term (Shoemaker et al. 2019).

The major function of ACE2 is exhibited as a balance in maintaining hydro-salinity during the pregnancy term. COVID 19 infection and its spread created a threat to both pregnant women and babies. It can cause fetal distress, premature birth, and rupture of the foetus membrane (Karimi-Zarchi et al. 2020). Also, the renal and kidneys express ACE2, and researchers commented on the presence of higher ACE2 in renal tubules of pregnancy. Research and survey show that COVID 19 had very low maternal cases and fatality than other previously existing viral respiratory disorders like SARS, and MERS. There are no special symptoms of pregnant women when compared with non-pregnant women. In case of severe illness due to COVID 19, it results in premature labor pain and or early delivery. The important studies on COVID 19 and its impact on human reproduction were tabulated in table 1.

12 Conclusions

Based on our exhaustive review of the published articles, ACE2 expression is found to be more in the testes, ovary, and vagina. ACE2 can be the key to COVID 19 infection alongside other important genes associated. Based on the available reports, SARS-nCoV-2 targets testes because of its potential ACE2 expression level and other genes favoring the virus transmission and replication inside the host cell. COVID 19 infection spreads among men widely when compared to women and the fatality is more in the case of men. A suggested theoretical hypothesis is that SARS-CoV-2 may lead to testicular damage and further to male infertility and poor sperm quality. Similar to the ovary, uterus could be the target for SARS-CoV-2 in the female. ACE2 receptors mediate and cause direct damage to testes or infect through secondary inflammatory and immunological responses. SARS-Co-V-2 can be a setback in human reproduction for a while. However, available data ensures there will not be a lifelong threatening factor for SARS-CoV-2 in terms of fertility and the threat will be only for a minimum of 8 months to 1 year post-recovery from COVID 19 for both men and women.

13 Future Prospective

From December 2019 to date, limited data is available on the impact of SARS-Co-V-2 on human reproduction and fertility status. Previously, we have data on SARS Co-V and its presence in semen, but we don't have any data for n-Co V 2019 presence in a semen sample and vaginal fluid. However, scientific hypotheses suggest the impact of SARS-Co-V-2 on human reproduction in both men and women. The mechanism of ACE2 and its expression level can be studied in vivo in the testes, epididymis, seminal vesicles, ovary, uterus, and vagina, and during early embryonic development. Though, clinicians and physicians aim at controlling and treating COVID 19, andrologists and researchers look at the impact of COVID 19 on human reproduction. COVID 19 can have either an immediate or delayed impact on male and female fertility and extensive research in this area is required to prove the hypothesis. So far we don't have data on men and women who have recovered from COVID 19 and their track record on reproductive functions. Since the infertility rate is already on the rise globally, these types of infections may worsen the situation. We suggest more research initiatives for understanding the concepts of COVID 19 and its impact on human reproduction.

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Conflict of Interest

The authors declare that there are no such conflicts

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