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# COVID-19 and Reproductive Function: A Detailed Review of Fertility Outcomes, Sperm Alterations, and Vertical Transmission Concerns

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**ABSTRACT**

**Background:** The global COVID-19 pandemic, caused by SARS-CoV-2, raises concerns about its effects on reproductive health. Emerging evidence suggests potential impacts on male and female fertility, including hormonal changes, immune responses, and organ damage, though the virus's direct influence on reproductive tissues and vertical transmission remains unclear.

**Objective:** This review summarizes current evidence on COVID-19's effects on male and female reproductive health, focusing on sperm count, fertility, and vertical transmission.

**Methods:** A comprehensive literature review was conducted using databases such as PubMed, Scopus, and Web of Science. Peer-reviewed studies were included based on their relevance to reproductive outcomes, sperm count, hormonal changes, and vertical transmission of SARS-CoV-2.

**Results:** Most studies found no direct evidence of SARS-CoV-2 in male or female reproductive tissues. However, a temporary decline in sperm count and quality has been reported in men recovering from COVID-19. Hormonal fluctuations, particularly increased luteinizing hormone (LH) levels, were observed in some male patients. In females, the presence of ACE2 receptors in reproductive organs suggests a potential risk, but no conclusive evidence of impaired fertility has been found. Vertical transmission remains uncertain, with isolated cases reporting elevated IgM antibodies in newborns.

**Conclusion:** Although direct evidence of SARS-CoV-2 impacting fertility is limited, temporary reproductive disruptions in males, including reduced sperm count, have been noted. The risk of vertical transmission remains unclear. Further research is essential to determine COVID-19's long-term reproductive effects.

**Keywords:** COVID-19, Fertility, Reproductive Health, Sperm Count, Vertical Transmission, SARS-CoV-2, Male Reproduction, Female Reproduction.



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## INTRODUCTION

The corona virus (SARS-coV-19) relates with the family of viruses named as Coronaviridae. Latin word “crown” means corona. The name was given to it due to the “crown-like” appearance of this virus in the ultra-micrograph imaging. It was first identified in 1965 by Tyrell Bynoe[1]. Almost 46 species of CoV were discovered in animals and humans .Although some Covids show flu like symptoms in humans, other species such as SARS-CoV causes severe acute infection and have a high rate of infection so, receives significant attention[2]. The Worldwide Virus Taxonomy Committee named a new CoV SARS-CoV-2 in December 2019 because of its in the genetic links to the SARS-Covid virus about 80%. This virus has outperformed other viruses of this family in terms of infection ratio, and it has quickly spread all over since its discovery in Wuhan city, China. Because this is a CoV-related sickness that was first detected in 2019, the illness has been dubbed "COVID-19" (corona virus disease-19). In past few years about more than 50M people have been infected by SARSCoV-2. It is estimated this disease can last for more few years[3]. Below **Table-1** summarizes key information related to COVID-19, including symptoms, prevention measures, and vaccination information. The SARS-CoV-2 is transmitted through the droplet’s contamination or from the surface that is contaminated by the virus. After entering the host cells the S1 domain present in the spike protein plays role in the attachment, whereas for the fusion of cell membrane and viral cell membrane so replicates using host cell machinery in a complex way the S2 domain is responsible. The symptoms of this disease include SARS-coV-2, dry cough, flu, weakness, fever, anosmia, headache, shortness of breath, nausea, rhinorrhea[4].Many microorganisms like bacteria and viruses can get into the reproductive organs of men and can affect the sperm count by diminishing the sperm viability[5]. Viruses can reach the testicles by spreading all over the body; the immune response of testicular area can defend the germ cells from the inflammatory responses of the host to a systematic infection. But certain viruses like that of SARS-CoV can cross the testicular barriers. So, the basic physiology of infection of certain viruses is need to know the long- and short-term impacts of corona virus on male and female fertility. For entrance into human cells, the virus uses the ACE 2(angiotensin-converting enzyme 2) receptor. ACE2 is possible to found in a variety of organs, prompting worries regarding whether or not the virus can impact these organs. Even though the mechanisms by which SARS-CoV-2 impacts the male reproductive system are yet understood, the testis seems to be a region with high levels of ACE2. The ability of SARS corona virus 2 is to pass through the blood and testis barriers and can affect the fertility system in male. The presence of virus in the testicular area is possible due to the angiotensin converting enzyme 2 also known as ACE-2, and transmembrane protease serine 2 also known as TMPRSS-2[6].Previous studies showed a few male patients with positive test of presence of CoV-19 in the testes, but the most studies published no presence of SARScoV-19 traces in the semen of both men patients with the active disease and those who recovered, a recent review and researches determined the likelihood

presence of SARScoV-2 in the semen of patient but in a very small amount[7].

**Table 1:** summarizes key information related to COVID-19, including symptoms, prevention measures, and vaccination information:

| Aspect | Details |
|---|---|
| Virus | SARS-CoV-2 |
| Common Symptoms | Fever, cough, fatigue, loss of taste/smell, difficulty breathing |
| Prevention Measures | Wear masks, maintain physical distance, Wash hands regularly, avoid crowded places |
| Vaccines Available | Pfizer-BioNTech, Moderna, Johnson & Johnson, AstraZeneca |
| Vaccine Efficacy | Varies by vaccine (approx. 70-95%) |
| Booster Recommendations | Depends on age, health status, and original vaccine type |
| Long-term Effects | Fatigue, respiratory issues, "long COVID" |
| Global Response | Travel restrictions, lockdowns, testing, and contact tracing |

In females the novel Corona virus targets the cell by binding to the ACE2 receptor that is present in the ovaries, uterus and vagina in excess quantity. So, by regulating the ACE2 receptor SARS-CoV-2 interrupts the fertility. So it should be concerned to investigate this issue .Although there is no systematic or comprehensive on the COVID-19 association with the female fertility as shown in fig-1 [8].

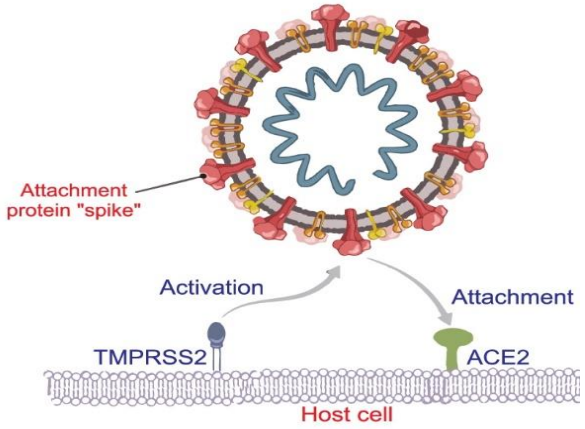


**Fig-1:** Attachment of corona virus and the host cell surface.

COVID-19 was hypothesized to have a potential impact on both male and female fertility, possibly affecting sperm count, reproductive organ function, and leading to vertical transmission from mother to offspring. However, the direct effects of the virus on fertility remained unclear due to limited research available. The aim of the review was to investigate the impact of SARS-CoV-2 on male and female reproductive health, with a particular focus

on its potential effects on fertility, sperm count, and vertical transmission.

The objectives of this study were fourfold. First, it aimed to review the existing literature on the presence of SARS-CoV-2 in male and female reproductive tissues. Second, it analyzed the impact of COVID-19 on sperm count and other reproductive parameters in males. Third, it assessed the potential risks of vertical transmission of SARS-CoV-2 from mother to offspring during pregnancy or breastfeeding. Finally, the review sought to identify gaps in the current research and propose future directions for studies to better understand the long-term effects of COVID-19 on reproductive health.

**Taxonomy of SARS-CoV-2:**

SARS-CoV-2 is a corona virus that has a single-stranded RNA. The first four viruses in this family, 229E, NL63, OC43, and HKU1, can infect humans and cause moderate viral symptoms. SARS, MERS, and SARS-CoV-2 are the other three viruses that can cause serious respiratory infections. The CoV-2 is covered by 20nm envelope that has spikes and so, the virus looks like crown under electron microscope. The corona virus is among the known RNA viruses with the largest genomes. The protein matrix is embedded in envelope of virus with the spike protein that is important for the recognition of receptor then the attachment and fusing of virus and host cell membrane. These S proteins are present in all human Corona viruses[9].

**Alteration of Hormones in patients infected with SARS-CoV-2:**

A recently published case looked at the levels of sex hormones and gonadotropins in the blood of patients got treated with COVID-19 to see if corona virus causes hormonal changes and man gonadal dysfunction. There was a considerable increase in blood LH levels in this trial, but no major changes in testosterone or FSH levels. T/LH and FSH/LH levels were observed to be significantly lower in COVID-19 patient's comparison to healthy people. LH promotes the production of testosterone by Leydig cells and the secretion of B by Sertoli cells, both of which have negative feedback on FSH. As a result, our research suggests that SARS-CoV-2 affects Leydig cells more often than Sertoli cells. Furthermore, infected patients had a significant increase in blood prolactin (PRL)[10]. Although increased amounts of PRL are linked to a variety of causes, including medications and stress, hyperprolactinemia can suppress the pituitary gland, resulting in a reduction in gonadotropins. It is possible that SARSCoV-2 interferes with masculine gonadal function; nevertheless, the hormones were assessed in the acute stage of the sickness in the study cited. Long-term adopt and surveillance of these patients' hormonal condition are critical, highlighting the need for more expected long-term studies of sex-related fluctuations in hormones of SARS-CoV-2 patients as an indication of male gonadal function[11].

**Mechanism of SARS-COV-2 viral entry:**

The Fig-2 shows the interaction of the SARS-CoV-2 spikes (S) compound protein with the host sensor ACE 2 is needed for adhesion (ACE-2). Host proteolytic-enzyme, such as transmembrane serine protease 2 (TMPRSS2), must then split open the S protein in virus, causing an arrangement shift in S protein that allows both host and viral cell membranes to unite permanently. The importance of TMPRSS-2 has been demonstrated by studies that shows blocking it stops severe acute

respiratory corona virus from invading and proliferating in lung cells. Because TMPRSS2 is much more widely demonstrate in body cells than ACE-2, it's likely that ACE2 is one of the most important indicators of whether a tissue type is infectious. Single-cell sequencing of RNA in human and non - human ie; monkeys organ of respiration revealed co intimation of ACE-2 and TMPRSS-2 in pneumocytes in the bronchi and goblet secretary cells in the nose[12].

The detection of the virus occurs only in one patient who was loaded with the virus in high quantity. Yang *et al*. (2020) used RT-PCR and electron microscopy to examine pathological alterations in 12 testis samples taken from COVID-19 patients and found almost negligeable evidence of SARS-CoV-2 virus in the male testes in the large number of cases. Sertoli cells and semi-inferior tubules were severely damaged, and Leydig cells were lost, as well as minor inflammation in the interstitial. During the COVID-19 course, these data may provide proof recommendations for indirect testicular injury[13].The blood–testis barrier defends male gonads from immunogenicity and improves immunity in the testes. Over production of inflammatory cytokines produced by viruses can trigger autoimmunity and leukocyte infiltration, disrupting sperm production and interfering with the secretion of sex-related hormones. An increase of IL-6 in the serum concentration and its receptors, a cytokine that controls inflammatory and immunological response, was linked to the pathogenesis of autoimmunity orchitis in mice with autoimmune orchitis in a prior study. The presence of a massive proportion of IL-6 in more extreme situations of COVID-19 has been reported, and its receptors are strongly expressed in testicular tissues. This could explain the possible role of the male gonadal system and, as a result, the likelihood of orchitis as a SARS-CoV-2 consequence[14].

The placement of the testis creates an atmosphere for germ cell development that is cooler than the body's body temp. Infections with SARS-CoV-2, on the other hand, are commonly accompanied by inflammation and indications such as fever which can interfere sperm production Based on the evidence presented, as well as the fact that SARSCoV-2 and SARS-CoV have the same receptors and genetic content, it is possible that masculine gonadal involvement, reduced sperm production, and resultant reproductive loss could constitute a SARS-CoV-2 consequence [15].

**Immune response to CoV-2 in males:**

The corona virus is mostly transmitted through the droplets of infected person. The incubation time for the SARS-CoV-2 is 14 days and the patient with the viral infection shows the symptoms after the $5^{th}$ day of viral entering the host. The ACE-2 and TMPRSS-2 plays the role in the attachment and virus entry, the viral replication starts in the airway epithelial cells. This can cause fever, sore throat, shortness in breath and myalgia. Whereas, in severe cases corona virus can cause acute respiratory infection, pneumonia, septic shocks and death[16]. The effectiveness of SARS-CoV-2 on the reproductive health of male is a challenge to understand. One of the hypotheses is the viral load of virus in the blood can lead to hematopoietic spreading and the virus can

reach to the reproductive tract and can cause heightening the immune response in the testicles. Like other viruses SARS-CoV-2 can also affect the male reproduction[17]. As shown in fig-2

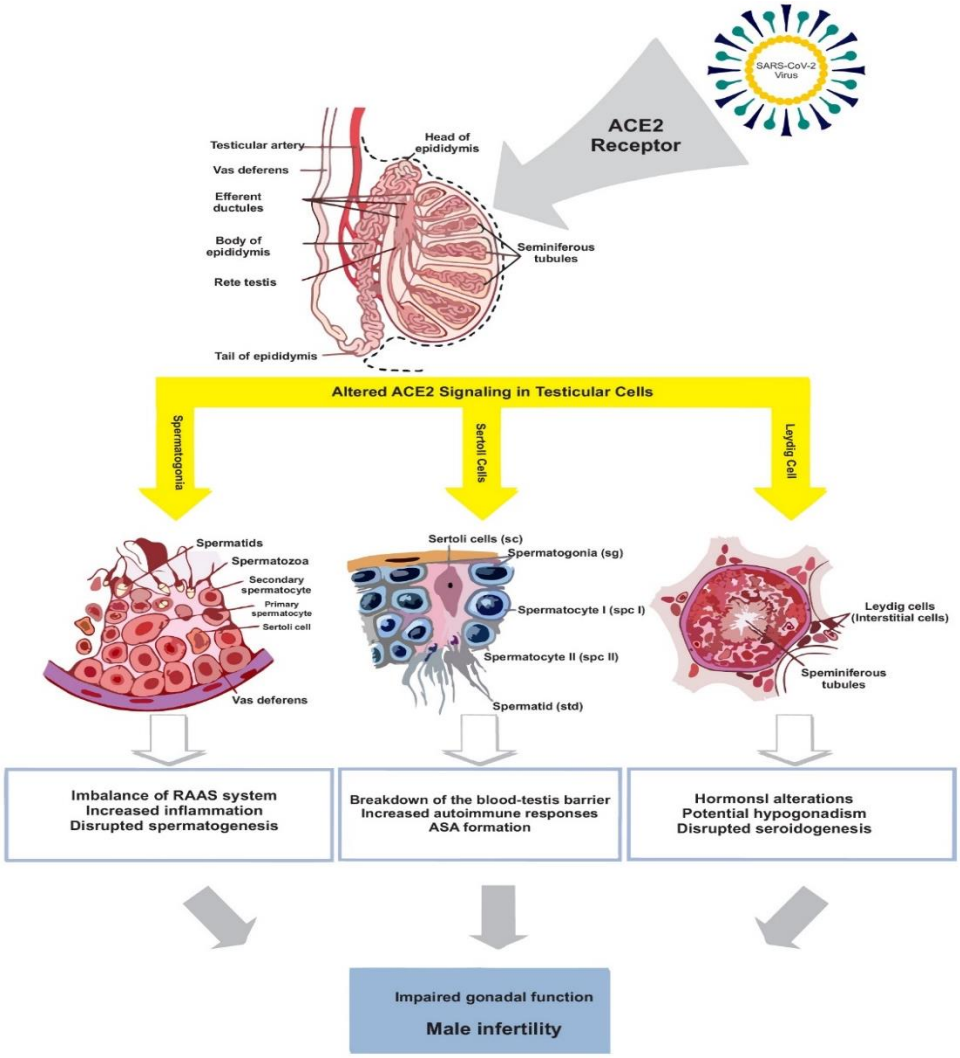


**Fig-2:** SARS-CoV-2's impact on ACE2 signaling in testicular cells, leading to impaired spermatogenesis, hormonal disruptions, and potential male infertility.

**COVID-19 & vertical transmission:**

When Concern about viruses that causing teratogenicity. The issue whether of SARS–CoV-2 can transmit vertically remains unsettled. Although viruses related to respiration such as SARS and MERS have not been linked to vertical transmission, this cannot be presumed for SARS–CoV. Expecting women infected with SARS–CoV-2 were reported in a number of cases. COVID-19 infection did not involve in maternal deaths in a study of 38 Chinese women, and there were negligible confirmed cases of transfer of infection from mother to the infant. No viral RNA was found in the amniotic fluid, cord blood, or breast milk of nine COVID positive women those who gave birth through

caesarean section. However, according to a recent report published in JAMA, transmission from mother to the infant may also be conceivable. A rather healthy child was born with caesarean to almost 30years old woman with CoV infection verified by reverse transcriptase polymerase chain reaction (RT-PCR)[18].This newborn was placed in isolation right away, and a blood sample taken at two hours of age showed an increased SARS–CoV-2 IgG level. Moreover, the IgG could be due to transmission through transplacental, the newborn tested positive for SARS–CoV-2 IgM, which cannot be understood by maternal to fetal transmission. IgM antibodies typically take few days to emerge following infection. Corona virus was found negative in all RT-PCR assays performed on the newborn[19]. This infant's antibody profile suggests that he was exposed to SARS–CoV-2 while still in the womb. Two of the six children delivered to COVID-19 positive moms were positive for IgM antibodies in a follow-up examination. Despite this, all of the neonates' throat swabs and blood samples came back negative for the virus. Overall, there are still insufficient proofs of transmission vertically in the context of COVID 19 infection. As new data becomes available during the duration of the outbreak, continued monitoring is required[20].

**Effects of Coronavirus on pregnancy:**

SARS in 2003, MERS-CoV in 2012, and COVID-19 in 2020 are the three epidemics of corona virus that occurred in the last 15-20 years. Despite the fact it is potentially more dangerous than SARS and MERS spread more slowly than COVID-19 and COVID-19. They all induce respiratory sickness, but their effects are different throughout pregnancy[21].

**Severe Acute Respiratory Syndrome (SARS):**

In all documented cases of COVID in pregnancy (n = 17), the case fatality rate (CFR) was 15%. Pregnant women had a greater rate than women without pregnancy. Pregnant ladies required ventilator support three times more than non-pregnant women. A controlled trial comparing of 10 pregnant and 40 women without pregnancy who were both infected with SARS found that the pregnant group had a 60% chance to get admit in ICU and a 40% rate of incident fatality, compared to only 18% and 0% in the group of nonpregnant[22].

In the first gestation, four out of seven pregnant SARS patients were miscarried. At 26, 28, and 32 weeks of pregnancy, 4 out of 5 women got infected after 24.5 weeks of pregnancy and were delivered before time, owing to their maternal state deteriorating because to SARS. The babies born in 7 months had respiratory suffering conditions and needed emulsifier, although their weight was appropriate for gestational time. Fetal development retardation and fibrin accumulation on the interface of placenta were found in about three pregnancies among children born almost 2 months after first infection, indicating instability. No confirmed evidences of vertical transmission were found. SARS was a pretty hazardous disease for expecting female and their infants[23].

**Middle East Respiratory Syndrome (MERS):**

MERS patients who were pregnant (n = 12) thought up 63 percent of the overall. Three people died. The only lady known to have contracted MERS in the first gestation gave birth to a fully healthy baby at full terms. One experienced a spontaneously losing at 20 weeks of pregnancy, another patient presented in 8.5 months of pregnancy with

toxemia and an intra-uterine fetal death occurred, and a third with already existing respiratory difficulties had MERS after 5.5 months of pregnancy and then critical respiratory distress syndrome. Both the neonate and mother died as a result of the ventilation and caesarean delivery. Due to maternal hypertension, three of the nine other patients were born prematurely. MERS has a significant death rate as well as a high rate of premature births transmitted to the intensive care unit[24].

**Coronavirus infection & male reproduction:**

Since there is a lot of individual variety, some infections have the capability to spread virus through ejaculate for a long period of time. RNA from the Ebola virus could be used to treat the disease. The reproductive infection of men can also be caused by the drug use to treat infection it can also trigger fever. Invasion or damage of the male reproductive system is one of the reported outcomes of viral infection. Current studies have documented that SARS-CoV-2, which causes COVID-19, can damage the male reproductive system in large part by inflammatory damage caused by a cytokine storm. However, whether SARS-CoV-2 can infect the human testis directly and enter semen is controversial. Other adverse effects of SARS-CoV-2 on male reproduction are also of concern and require comprehensive evaluation. Here, we analyze the invasiveness of SARS-CoV-2 in the testis and examine reported mechanisms by which SARS-CoV-2 interferes with male reproduction. Long-term implications of SARS-CoV-2 infection on male reproduction are also discussed. It should be emphasized that although COVID-19 may induce testicular damage, a substantial decrease in male reproductive capacity awaits clinical evidence. We propose that there is an urgent need to track male COVID-19 patients during their recovery. The development of suitable experimental models, including human reproductive organoids, will be valuable to further investigate the viral impact on reproduction for current and future pandemics. After more than 13 months, this was discovered in seminal fluid. It's still questionable if the SARS-CoV-2 virus from the testicle, seminal duct, and other associated sex glands, or perhaps even in the urogenital system, based on the information so far[25].

SARS-1-CoV and other CoVs have been linked to the development of orchitis. In patients who died from SARS, pathological testicular alterations such as germ cell destruction, thicker basal cells, and leukocyte infiltration were documented, along with few if any spermatozoa in the seminiferous tubules. Viral orchitis are a viral infection complication caused by hematogenous spreading by viral antigens. In the acute context, mumps is one of most prevalent viral diseases associated with the orchitis, manifesting as discomfort, inflammation, cosines, and hickey in the testes[26]. Spermatogenesis and testosterone generation are two separate processes. Orchitis caused by a virus may be a problem. Infection with a virus Perivascular lymphocytic tissue is linked to testicular tissue. Interstitial edema and infiltration, which can result in hyalinization of the tubules seminiferous, as well as fibrosis and shrinkage of the male genitalia. In the early stages during infection, pain in testicles and may be common orchid ptosis, with varying degrees of severity. Fever, a typical sign of viral infections, is well documented for impairing spermatogenesis temporarily. Nonetheless, it is thought that the prolonged

drop in semen parameters observed during post-pubertal mumps orchitis is related to viral induced injury to the seminiferous tubules. Testosterone hormone has a sex-specific anti-inflammatory and anti-vascular-aging impact. Low testosterone levels are linked to elevated expression of cytokines like interferon and interleukin-2 in COVID-19 patients. Because hypogonadism is common symptom of systemic infections, it's still unclear if the lower testosterone levels seen in COVID-19 individuals are the effect of a severe infection or the cause. Furthermore, testosterone possesses anti-inflammatory and immune modulatory characteristics due to its ability to modulate T-lymphocyte differentiation. Others, however, have hypothesized that COVID-19 infection might be controlled by testosterone, despite testosterone's potentially protective role. This is due to the fact that androgen receptors activate TMPRSS-2, which is thought for viral spread and transmission is an important protease. TMPRSS-2 could also divide both ACE2 & viral S protein, allowing viruses to enter cells more easily. The male preponderance of COVID-19 infections is thought to be due to modulation of testosterone-mediation of TMPRSS-2 expression. These findings support the necessity for additional investigation into the bridge between levels of testosterone and COVID-19 infection as shown in fig-3 [27]

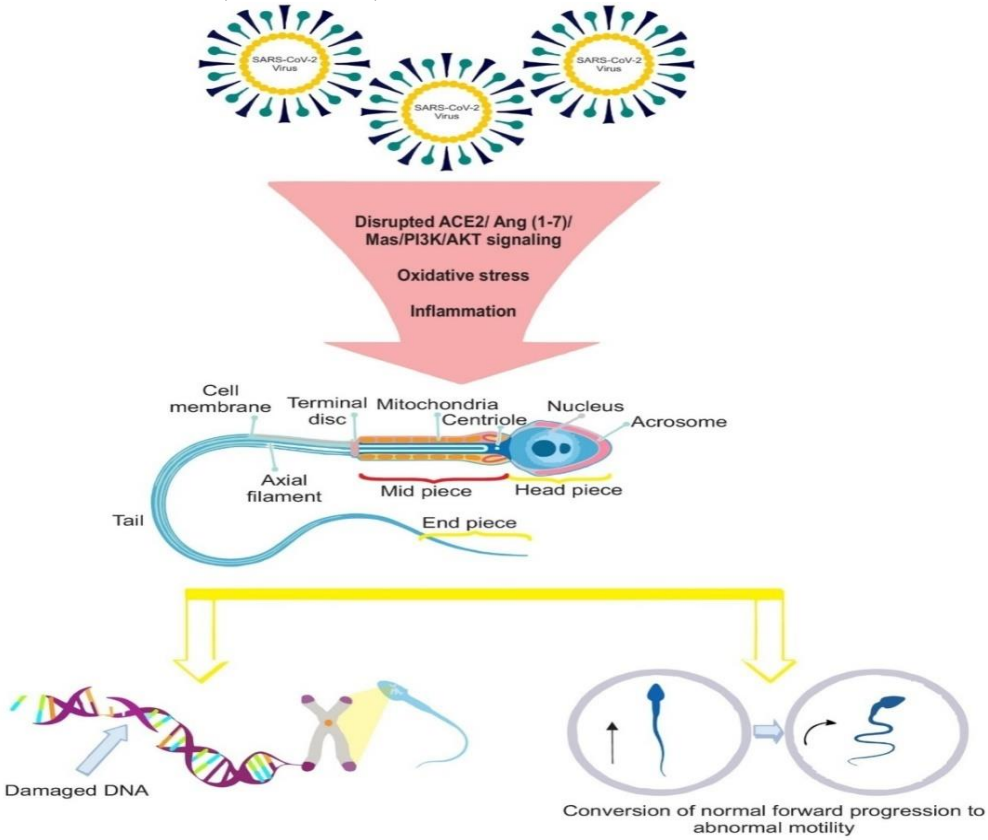


**Fig 3:** SARS-CoV-2 infection disrupts ACE2/Ang (1-7)/Mas/PI3K/AKT signaling, leading to oxidative stress, inflammation, and potential damage to sperm DNA and motility, contributing to abnormal sperm function.

**Coronavirus effects on male & female gametes:**

SARS-CoV-2 is a new recently exposed humans infecting virus; there is a scarcity of information about its effects on human reproduction (Silverio-Murillo *et al.*, 2021a). So yet, no reports have surfaced. The virus's presence within female reproductive system, namely in genital secretions, in either amniotic or abdominal fluid. Although there is no proof that infection with SARS–CoV-2 or other corona viruses affects different sexual gametes directly, there is information that temperature can affect spermatogenesis. As a result of decreased sperm concentration and motility, fertility in men may be reduced for about 90 days after exposure to corona virus. To enter human tissue, the SARS-CoV-2 needs ACE-2 receptors. Within mature Leydig cells in the testicle, the male reproductive system releases ACE-2, and there is evidence that ACE-2 plays an important part in sperm production. Although gonadotropin hormones dependent expression of Angiotensin converting enzyme has also been documented in female reproductive areas, the presence of ACE-2 receptors is significantly very prominent in the male and female genitals but in males it is more prominent. It is still not cleared, In the reproductive organs, the SARS–CoV-2 virus utilizes ACE2 receptors, and what effect, if any, this might have on the quality of the oocytes The development of the embryo or the subsequent pregnancy[28].

Gametes retrieved from individuals with various viral illness, like the human immuno-deficiency virus (HIV) and cirrhosis; they must be handled with extra attention to avoid exposing the non-fetal spouse and adulterant of tissue of reproductive system in the lab Absences of confirmation for transfer by blood transfusion or sexually contact, these measures are not generally advised for SARS–CoV-2. Similarly, testing oviduct or sperm donors for SARS–CoV-2 is not recommended. Further research is needed in these areas to ensure the safety of reserved gametes as well as the ensuring of these patients having helped in reproduction[29].

**Angiotensin-converting enzyme 2:**

The fig-4 shows the impacts of SARS-CoV-2 on male fertility are not well defined. Bioinformatics study, on the other hand, reveals that this virus could attack reproductive tissues. Angiotensin Converting Enzyme 2 receptors are indicated in reproductive body parts of both male and female, according to the Human Protein Atlas database. This receptor is involved in both sperm function and oocyte fertilization. Testicular cells, including spermatogonia, zygote, and Leydig cells, as well as ductless skin cell clusters, endothelial, and small blood vessels, have been observed to increase ACE2 expression level. a high level of protease expression TMPRSS2 has been found in both reproductive and body cells[30]. Androgenic hormones are the one and only transcriptional regulators of TMPRSS-2 gene for expression that have been found. Because the TMPRSS-2 gene contains a 15 bp hormone for response element Castration reduces the declaration of both ACE2 and TMPRSS2, according to in vitro and in vivo studies, although therapy can reverse the testosterone supplemental by this drop. TMPRSS-2 and ACE-2 proteins, on the other side, have a distinct expression pattern, with the former being strongly elaborated in Stromal cells and latter being substantially expressed in spermatogonia cells (stem cells). This rule outs a infection of virus in testicular tissue, but an

interaction between non sexual cells and sexual cells could give the virus with the molecular components that needs to infect the cells[31].

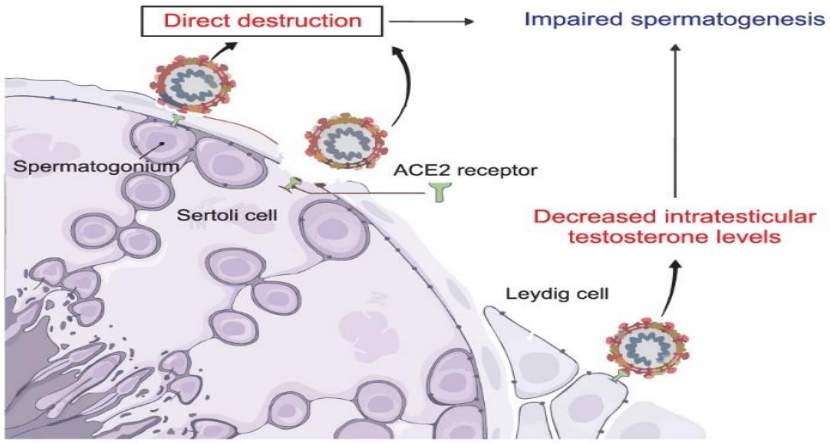


**Fig-4:** SARS-CoV-2 infection leads to direct destruction of spermatogonial and Leydig cells via ACE2 receptor binding, resulting in impaired spermatogenesis and decreased intratesticular testosterone levels.

**Implication for the children born to men recovered from CORONAVIRUS:**

The ramifications for babies born to male who have been affected with COVID-19 are still unknown. According to the Society for Women's health Medicine, there is a little chance of vertical transfer from mother to infant, but respiratory spread to a newborn fetus is a concern. The nature of transmission vertically, i.e., by placenta or by blood, has been debated in the few occurrences of vertical transmission. Longitudinal studies are necessary understand the ever lasting effects of babies born to parents who have been infected with COVID-19[32].

**Banning on the use of Potential remedy in pregnancy:**

There were no known vaccinations or targeted medicines for COVID-19 therapy as of March 31, 2020. Currently, treatment focuses on supporting measures including oxygenation and mechanical breathing, as well as the treatment of problems. Because there is no effective cure, a slew of putative treatments are being tested both in and out of study design. Although the list is always evolving, the bulk of these drugs work by inhibiting the virus's ability to replicate or by suppressing or modulating the defense system of body, reducing damage of inflammation. In time of gravidity, these prospective cures are divided into three categories: those that have been proven to be protected in childbirth, those with undetermined situation, and those with definite or relative problems[33]. It's important to remember while some of the therapies are safer during pregnancy, none of them has been recognized as a sure cure, and they all include few probabilities. These problems must be viewed as extra risks that conceived women must bear; some therapeutic remedies may pose a risk to the fetus or may be not available to expectant mothers. Several COVID-19 medicinal interventions have been found to be either safe or nonteratogenic throughout

gravitative time. defense modulators of body like hydroxychloroquine, methylprednisolone and antiviral medicines like lopinavir-ritonavir are among them. It's worth noting that, although being nonteratogenic, glucocorticoids have been linked to weight gain, diabetes, hypertension, preterm preterm rupture of membranes and, intrauterine growth retardation in pregnant women. Interferon therapy, which is commonly used to treat hepatitis C, has been shown to be risk free during pregnancy. The use of blood or blood plasma generated from people who had COVID 19, has been proven to minimize illness sequelae in those who have had the virus before. There are no apparent limitations in pregnancy, and the risk level should be identical to a blood transfusion[34].

**SEX susceptibility to Coronavirus infection:**

The chances of critical COVID-19 indications and its mortality were shown to be much higher in men in early epidemiologic investigations from China. Similar patterns have been noticed in other countries. This vulnerability was assumed to mask by poor total health, severe illness, and other few lifestyle variables like tobacco smoking at first. Two different explanations, however, have been presented to describe and understand sex disparities in COVID-19 results. For starters, because ACE-2 is found on the shorter arm of the sex chromatin, female gender has 2 copies. 1 of these 2 sex chromatins is silent in the last of zygote development time, resulting in the condensation of sex chromatins into a chromatin body. Few genes are immune to the deactivation that is more often to happen on the shorter arm of (x) chromosome, in which the gene of ACE-2 is found. This could describe disparities in the activity of ACE-2 between men and women, albeit the evidence for this hasn't been conclusive. ACE-2 is also responsible as regulating component of angiotensin system, which protects against dysfunctioning of circulation and severe internal body damage. Because quick viral absorbance of ACE2 is less frequent in women, it is thought that greater ACE2 expression protects them from more severe COVID-19 symptoms. The link among TMPRSS-2 and androgen susceptibility is the secondary idea to describe the sex variations in COVID-19 indication and results[35].

The androgen responsiveness component is a transcriptional helper for TMPRSS-2, which was first discovered in the factor of prostate oncogenesis and the TMPRSS2-ERG recombinant part of gene. Reduced amounts of circulating the androgens in female are thought to contribute to lower cellular effects of TMPRSS-2 and bringing down the maintenance of this host receptor. During early epidemic researches have revealed that male have high risk of COVID-19 infection and temporality, the causative processes are unknown and need to be investigated further[36].

COVID-19 infection and its mortal behavior have also been reported in healthy and young ones. This leads us to research into genetically variations that can cause more serious COVID-19 courses due to a fundamental immunological deficiency that is asymptomatic. New evidence suggests that genetic polymorphisms may influence the seriousness of COVID-19 and men sex sensitivity, while more research is needed.

**Additional guide lines for promotion of fertility care:**

After risk expectations and mitigation, availability of resources considerations, and cautious counseling, several reproductive nursing schools have restarted promotion of

fertility care. The American Society of Reproductive Medicine has been publishing recent news on patient treatment monthly and therapeutic advice in the period of COVID-19 epidemic since March 2020. A few joint statements on laboratory guidelines during the pandemic of COVID-19 has been published by the Society for Assisted Reproductive Technology, the Society for Reproductive Biologists and Technologists, and the College of Reproductive Biology. Regarding the delivery of fertility healthcare in between time of the COVID-19 epidemic, we recommend consulting these guidelines as well as guidance from the Centers for Disease Control (CDC). Furthermore, due to limitations imposed by the pandemic, many practitioners treating infertile patients have turned to telemedicine to continue providing therapy to these patients. The Society for Male Reproductive Medicine and Urology has endorsed this[37]. The collection, preservation, and management of semen samples is one of the most important factors when it comes to coronavirus and men reproductive and sexual fitness. Coronavirus can also currently filter out from the sperm of a recovered or men with silent symptoms with SARS-CoV-2 infection, according to limited evidence. Before collecting on-site semen samples, patients should be screened for any symptoms of COVID or recently exposure or contact to someone treated with COVID-19 infection. The patients who previously symptomatic and had cured with COVID-19. After at least 8- 10 days have elapsed since when the onset of symptoms, at least 1full day has passed since treatment of fever, and certain other corona indicating signs have resolved, it is recommended that isolation be ended. Individuals infected with corona virus that show almost no signs or symptoms of COVID-19 may be released from isolation of almost 2 weeks on their first positive RT-PCR results. Strictly following to illness, cure and controlling methods like hand washing for cleanliness, 3 meter interspaced, ecological virulence control, and fully use of equipment's for self-protection should be set up to save the health of all covid victims, members of staff, and nursing team[38]. If practicable, sperm collecting laboratories might review off-site collection, such as collection at-home using conventional techniques. When handling semen samples from patients, the reproductive care center should apply proper threat assessment and mitigation measures. Presently, the CDC recommends that staff workers handle all body fluids, including sperm, with protective eyewear or a face mask, clinical gloves, and a clinical mask. Although semen samples splashing pose the greatest risk to employees, every effort is being made to avoid droplets in air generation at the time of technique, like syringe applicator, extraction, and mixing. For semen samples from COVID-19 patients, a physically isolated environment and dedicated apparatus and equipment should be used if possible. Another factor to consider is the cryopreservation of COVID-19 patient semen or testicular samples for use in assisted reproductive technologies (ART). There is currently negligible evidence that routine RTPCR screening of samples taken for SARS-CoV-2 before cryopreservation or ART is necessary. There is zero indication that any single toxicants or process protocols can defend a cured patient against virus infection[38].

However, as a guidance, published methods for sample handling collecting and performing ART on HIV or hepatitis B or C virus infected persons might use, however this procedure may differ between different

laboratories. Although cross-infection between conserved viral specimen has never been complained, using highly protected straws and separated freezing tankers for semen samples or tissue of testis from fully cured from COVID-19 should be considered if possible[39].

## MATERIALS AND METHODS

A comprehensive literature review was conducted to assess the impact of SARS-CoV-2 on male and female reproductive health, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[39].

**Data Sources:**

Databases such as PubMed, Scopus, Web of Science, and Google Scholar were searched for peer-reviewed articles published up until 2010-2024 The search terms included combinations of the following keywords: "COVID-19," "SARS-CoV-2," "fertility," "male reproduction," "female reproduction," "sperm count," "hormonal changes," "testicular injury," "pregnancy," and "vertical transmission." [37].

**Inclusion Criteria:**

- Studies published in English that focused on the effects of COVID-19 or similar coronaviruses (SARS, MERS) on male and female reproductive health.
- Articles that explored hormonal changes, sperm count, testicular or ovarian health, pregnancy outcomes, or vertical transmission in COVID-19 patients.
- Research studies, clinical trials, review articles, and meta-analyses related to reproductive health during the COVID-19 pandemic.

**Exclusion Criteria:**

- Articles not published in English.
- Studies that did not focus on reproductive health or fertility.
- Editorials, commentaries, or opinion pieces with no primary data.
- Studies published before 2010 that focused on outdated research methods or lacked relevance to current COVID-19 research.

**Data Extraction:**

For each selected article, data were extracted on the study design, sample size, methodology, and key findings related to the impact of SARS-CoV-2 on reproductive health. Particular attention was paid to the presence of the virus in reproductive tissues, changes in sperm count or quality, hormonal fluctuations, and evidence of vertical transmission[38].

**Analysis:**

A narrative synthesis of the findings was performed, summarizing the current state of knowledge and identifying gaps in research. Studies were categorized based on their focus (male reproduction, female reproduction, or pregnancy) and the outcomes they reported. Discrepancies between findings were noted, and the strength of evidence was evaluated based on study design, sample size, and methodological rigor [35].

**Bias Assessment:**

Potential sources of bias, including selection bias, publication bias, and reporting bias, were considered. Studies that lacked adequate sample sizes or presented inconsistent results were carefully analyzed to ensure balanced conclusions [36].

**Ethical Consideration:**

The study was ethically approved by ethical review committee of Institute of Molecular Biology and Biotechnology (IMBB), CRiMM, The University of Lahore, Lahore, Pakistan. Ref-IMBB-BBBC/22/880

## RESULTS

The current literature on the impact of SARS-CoV-2 on male and female reproductive health remains inconclusive but provides important insights. Studies on male reproduction have not found consistent evidence of viral presence in male reproductive tissues, such as semen or testes. However, there is growing concern about the potential for indirect testicular injury, particularly through immune responses and inflammation caused by COVID-19. Some studies report temporary declines in sperm count among males who have recovered from the virus, suggesting that reproductive function may be impaired in the short term. Additionally, hormonal changes such as elevated luteinizing hormone (LH) and prolactin levels have been observed, although these changes are not universally found, and their long-term effects remain uncertain. For female reproduction, research has focused on the virus's use of ACE2 receptors, which are abundant in female reproductive organs, including the ovaries, uterus, and placenta. While some hypotheses suggest that SARS-CoV-2 could affect ovarian function, there is no direct evidence indicating a significant impact on female fertility at this time. Studies have yet to conclusively demonstrate that COVID-19 disrupts ovarian reserve, menstrual cycles, or overall reproductive health in women. The issue of vertical transmission remains a key area of investigation. Most studies to date have reported no definitive evidence of the virus being transmitted from mother to child during pregnancy or childbirth. However, isolated cases have raised concerns, particularly in instances where newborns tested positive for elevated levels of SARS-CoV-2-specific IgM antibodies. This raises the possibility of intrauterine exposure, though further research is required to determine the significance and frequency of such cases. Regarding mRNA vaccines for COVID-19, the available data provides reassuring results for individuals concerned about reproductive health. Studies have shown that mRNA vaccines do not negatively affect sperm quality or female reproductive function. Therefore, vaccines do not pose risks to fertility, making them a safe option for individuals undergoing assisted reproductive technologies (ART) or planning to conceive. In summary, while there are some concerns about short-term reproductive impacts of COVID-19, particularly in males, the overall evidence remains limited and inconclusive. Long-term studies are needed to fully understand how the virus may affect reproductive health in both men and women, especially concerning the long-term effects of inflammation, hormonal changes, and the potential for vertical transmission as shown in table-2

**Table-2:** Summary of key studies on the impact of COVID-19 on reproductive health.

| Study | Focus | Key Findings |
|---|---|---|
| **He et al. (2021)** | Male fertility and hormonal changes | No significant decrease in testosterone, increase in LH and PRL in acute cases. |
| **Tian et al. (2021)** | Presence of virus in reproductive tissues | No viral presence in reproductive tissues, but concern over long-term effects. |
| **Seymen (2021)** | Impact on sperm count | Decreased sperm count in recovered COVID-19 patients. |
| **Khalili et al. (2020)** | Vertical transmission and reproductive health | No confirmed cases of vertical transmission, but concern remains. |
| **Chen et al. (2021)** | Effect of mRNA vaccines on fertility | No negative impact of mRNA vaccines on fertility. |

## DISCUSSION

Recent studies on COVID-19 have generally found no direct effects on male or female fertility, though the virus can infect organs that share similar receptors, including reproductive organs[37]. However, the impact of COVID-19 on fertility remains uncertain, with ongoing research addressing this question. Some studies hypothesized that the global spread of the virus may have contributed to a decline in birth rates in certain countries, while other regions showed no change. Fear of infection and social distancing led to reduced conception rates, and an increase in abortion cases was reported [39]. Additionally, there were reports of decreased sperm count in some male patients, but the exact cause remains unclear due to limited research. Questions also remain regarding vertical transmission (from mother to offspring) and the effects of breastfeeding. The key limitations of the current research include a lack of comprehensive studies, potential reporting biases, and the need for long-term data. While some studies have raised concerns, much remains unknown, and further research is needed to fully understand the virus's impact on fertility and reproduction. Researchers continue to explore these questions, and it is hoped that more conclusive findings will emerge as data collection expands[36].

## CONCLUSION

In conclusion, while current evidence suggests that SARS-CoV-2 may have some indirect effects on male and female reproductive health, such as temporary declines in sperm count and hormonal changes, there is no conclusive proof of long-term impacts. The risk of vertical transmission remains uncertain, and mRNA vaccines do not appear to affect fertility. Further research is necessary to fully understand the long-term reproductive effects of COVID-19.

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