Review Article

Can Coronavirus Disease 2019 Effect on Human Reproduction?

Abstract

Since the main role in the pathogenesis of the coronavirus is attributed to the angiotensin-converting enzyme (ACE) receptor, it could possibly be a hypothesis in the differential sex-based pathogenesis of the coronavirus. The virus inserts its genetic material into the cell through its ACE2 receptors and replicates it by intracellular proteins. ACE2 receptors are highly expressed in cell membranes of various tissues in the body, including cardiovascular, gastrointestinal, renal, macrophage cells, and especially on the surface of type 2 pneumocytes in the lungs, ovaries, uterus, vagina, placenta, and testes. Therefore, cells having a higher expression of the ACE2 may be a specific target for coronavirus binding and infectivity. Due to the increase of infections in males, concerns have been appeared about the potential impact of coronavirus disease 2019 (COVID-19) on their fertility and reproductive organs. Thus, it is necessary to investigate if COVID-19 disturbs female and male fertility, so this review aimed to study the comprehensive evidences on the association of COVID-19 with human reproduction.

Keywords: *Angiotensin-converting enzyme 2, coronavirus disease 2019, female, fertility, male, reproduction*

Ali Abdolrazaghnejad, Sepideh Miraj[1]

Department of Emergency Medicine, Khatam-Al-Anbia Hospital, Clinical Immunology Research Center at Zahedan University of Medical Sciences, Zahedan University of Medical Sciences, Zahedan, [1]Department of Obstetrics and Gynecology, Nekouei-Hedayati-Forghani Hospital, Qom University of Medical Sciences, Qom, Iran

Introduction

In December 2019, a new severe respiratory disease was appeared in Wuhan, China, for the first time and has widely spread to many countries and affected the people all around the world (World Health Organization [WHO], 2020). It was named coronavirus disease 2019 (COVID-19) by the WHO and found to be caused by a novel virus of Coronaviridae family which due to high homology with the severe acute respiratory syndrome coronavirus (SARS-CoV) it was named SARS-CoV-2.[1,2]

Coronaviruses have caused major health epidemics in the past, with SARS-CoV causing a health epidemic in 2003, and another widespread outbreak of Middle East respiratory syndrome (MERS-CoV) in 2012. Both the SARS-CoV and SARS-CoV-2 recognize angiotensin-converting enzyme 2 (ACE2) as the same human cell receptor, while MERS-CoV binds to another receptor named dipeptidyl peptidase 4.[3,4]

COVID-19 is transmitted from person to person through direct contact and by transmission of small droplets from infected individuals.[4] As of Friday, October 15, 2021, around 240,648,551 people had confirmed COVID-19 cases and around 4,901,289 people have died in more than 180 countries around the world, and the numbers are increasing dramatically everyday (https://www.worldometers.info/coronavirus/).

COVID-19 affects the respiratory system, and the patients present some symptoms at the onset of illness such as dry cough, fatigue, fever, and breathing difficulties. The most clinical COVID-2019-associated characteristics are mild flu-like conditions, which can be worsened to respiratory failure, and be lethal in about 1%–2% of cases. It also affects more men (58.1%) and young adults, and 55.1% of cases occur in the people aged 15–49 years.[5] For decades, the association between viral infections and infertility has been considered, but there are no reports in the literature on the impact of SARS-CoV and MERS-CoV infections on human fertility.[6]

Recently, a study showed unique characteristics in the protein structure of the novel coronavirus (2019-nCoV), suggesting a potentially more closeness link to its receptor than SARS-CoV. Because of these characteristics, a very small number of viruses are needed to infect one cell, as well as the higher affinity of 2019-nCoV

Address for correspondence:
Dr. Sepideh Miraj,
Associate Professor of Infertility and IVF, Department of Obstetrics and Gynecology, Nekouei-Hedayati-Forghani Hospital, Qom University of Medical Sciences, Qom, Iran.
E-mail: miraj.sepideh@gmail.com

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for organs and tissues. That's why this virus appears to be more aggressive than the SARS-CoV and MERS-CoV and may present a different clinical feature.[6,7] By entering the virus into the host cell in different tissues and organs including kidney, testis, lungs, intestine, and many others it is predicted that cells expressing ACE2 receptor, through binding to its receptor, may cause the risk of being affected.[8,9] An important issue in COVID-19 is the ability of the virus to affect the reproductive abilities of men and women, and whether pregnant women with COVID-19 are at risk for death or comorbidities. This paper attempts to investigate the impact of COVID-19 pandemic on male and female fertility to improve our knowledge about the relation between COVID-19 and function of human reproduction system.

Relationships between severe acute respiratory syndrome coronavirus, 2019-nCoV, angiotensin-converting enzyme 2 receptor, and renin–angiotensin system

The SARS-CoV-2 virus enters the body by ACE2 expressed binding on target host cells. Similar to SARS-CoV-1, the spike protein of SARS-CoV-2 attaches to this receptor and facilitates endocytosis and cellular infection.[10] The angiotensin II (Ang II) and Ang-(1-7) hormones have contrary effects as the former is pro-inflammatory, pro-fibrotic, and pro-apoptotic with tissue remodeling properties, and the latter is anti-inflammatory and anti-fibrotic.[11] Generally, ACE1 and ACE2 counterbalance each other, and their roles are essential in balancing RAS. ACE2 activity and downregulation is reduced by SARS-CoV-2 infection and it causes to increase circulating Ang II in the patients[12] explains the inflammatory and fibrotic effects seen in COVID-19 lung injuries. There are increasing reports of SARS-CoV-2 multi-organ involvement found in stools, saliva, urine, and blood.[13-14] ACE2 may contribute to the pathophysiology of COVID-19 dissemination through viremia in different organ systems, and due to its presence in the testes and female reproductive system, it is assumed that SARS-CoV-2 may also affect the reproductive system.[15]

Previous studies identified the affinity of 2019-nCoV and SARS-CoV for cells that express ACE2 on their surface since ACE2 serves as a functional host receptor for the two types of coronaviruses. Paradoxically, ACE2 expression levels in the lungs are very low compared to other tissues. Thus, the predominance of pulmonary symptoms in patients with 2019-nCoV indicates that ACE2 is overexpressed in specific lung cells.[16,17]

ACE2 is an enzyme that participates in the renin–angiotensin system (RAS) which expresses in many organs and tissues, such as digestive tract, followed by the kidneys and testes with varying levels of expression that in the ovaries is greater than in the lungs.[17] It has been shown that RAS plays a role in regulating blood pressure as well as RAS circulating; local RAS also plays an important role in the physiology of the kidneys, heart, nervous system, and adrenals as well as the ovaries and testes.[16]

Studies have shown the central role of the ovarian RAS (OVRAS) in the physiology and diseases of the ovaries. OVRAS is actively involved in oocyte maturation, steroidogenesis, folliculogenesis, ovulation, angiogenesis, and the mechanisms of apoptosis and ovarian atresia. There are higher plasma levels of renin in the patients with polycystic ovarian syndrome undergoing ovarian stimulation than the women with tubal infertility, supporting an abnormal OVRAS expression in this disease. It appears that OVRAS participates in the pathophysiology of ovarian hyperstimulation syndrome (OHSS). It seems that locally activated OVRAS induces neovascularization and capillary permeability, a typical OHSS finding, by increasing ACE2 activity.[17]

Influence of Coronavirus Disease 2019 on the Female Reproductive System

It was shown in some studies that SARS-CoV-2 may affect female fertility and impair female reproductive function.[8,9] According to the COVID-19 epidemic scale, there seems to be a potential decrease in fertility.[10] It is reported in one study that many young adults had sexual and reproductive health problems because of COVID-19 pandemic and related inhibitory measures.[11] COVID-19 has been reported to be commonly associated with high levels of interleukin (IL)-6, IL-8, tumor necrosis factor-α, and other cytokines, leading to a precoagulation state that is unfavorable for blastocyst or fetal growth in a normal uterus.[18] Evidence suggests that 2019-nCoV/ACE2 may interfere with female reproductive functions and lead to menstrual irregularities, infertility, and fetal distress.[19] ACE2 regulates follicular growth and ovulation, angiogenesis, and luteal degeneration, and affects regular changes in endometrial tissue and fetal growth. It also significantly plays a regulatory role in reproduction. Given these factors, SARS-CoV-2 may impair female fertility by attacking ovarian tissue and granulosa cells or damaging endometrial epithelial cells.[20] Basigin (BSG) is also one of the most important receptors for COVID-19, through which it enters host cells[21] and it is expressed not only in the uterus but also in the stroma and ovarian granulosa cells.[22] BSG may play a role during follicle development, corpus luteum formation, and embryo implantation. In addition to COVID-19, an impaired immune system may alter hypothalamic–pituitary–gonadal function.[23] Sex steroids are potent immunomodulators, so different concentrations of progesterone and androgens may affect the immune response and inflammatory consequences of COVID-19.[24] However, the association between COVID-19 and female fertility is unclear.

Coronavirus and the Effect of Cytokines on Male Infertility

In a study, a marked decrease in serum testosterone levels in patients with severe coronavirus type showed a poor

prognosis for these patients.[25] Inflammatory cytokines such as IL-6 also destroy the blood–testicular barrier, and the testicular parenchyma will be directly attacked by the virus and the inflammation caused by its infectivity. Therefore, it is recommended to assess serum testosterone levels in men who test positive for COVID-19.[26,27]

Evidence from laboratory studies and evaluations suggests that testicular tissue is the target of proper coronavirus binding in men due to the high expression of ACE2 and TMPRSS2 receptors. Binding of the coronavirus to its receptors on the surface of these cells leads to increased immune responses, the production of cytokines, and consequently increased inflammation and infiltration of lymphocytes, leukocytes, and macrophages.[28-32] With the intensification of the infectious process, the blood barrier of the testis, which has the role of protecting the testicles against infectious agents, will be broken and the testicular parenchyma will be necrotic and destroyed. Decreased testosterone as a result of coronavirus infection in men can lead to hypogonadotropic hypogonadism. Binding of the virus to Sertoli cells, which are closely related to spermatogenesis cells, also reduces spermatogenesis and damage spermatogonia cells. On the other hand, inflammation in the small arteries of the testicles causes vasculitis, epididymitis, and orchitis. One of the causes of infertility in men is orchitis. Fever, as a prominent feature of coronavirus, also has a significant effect on impaired spermatogenesis. Due to the possibility of hypogonadism, testicular dysfunction, and infertility, there is a need for further laboratory and clinical researches and evaluation in male patients recovered from coronavirus infection.[28,29]

Hormonal Changes in Patients with Coronavirus Disease 2019: Signs of Hypogonadism

Numerous studies have shown that among the male COVID patients serum luteinizing hormone (LH) and prolactin levels significantly increase[30] but there is a significant decrease in the ratio of testosterone to LH and follicle-stimulating hormone to LH.[31] The increase in LH of COVID-19 patients is thought to be due to the early stages of testosterone production abnormalities and a decrease of Leydig cells that may cause negative feedback to stimulate Leydig cells and temporarily increase of testosterone production.[32]

There may be a risk of clinical hypogonadism with disease progression, so it is important to do at least 3–6 months' postrecovery follow-up for patients, with serum LH and testosterone-to-LH ratio as clinical indicators of primary hypogonadism.[33]

Testosterone is also involved in the immune response through binding to the androgen receptor and activating antiviral pathway.[34] Thus, a decrease in testosterone levels may impact on the immune response against COVID-19. Moreover, it is also associated with higher levels of inflammatory cytokines and severity factors such as LDH, neutrophil count, procalcitonin levels, C-reactive protein, and lymphocyte count.[30,31] Additionally, higher prolactin level and lower testosterone: LH ratio, follicle-stimulating hormone (FSH):LH ratio, and dihydrotestosterone levels which are probably due to low testosterone levels were reported as well as elevated estradiol levels. The latter was associated with IL-6 level that is a poor prognostic marker in COVID-19 patients. In contrast, women had lower FSH levels which may indicate loss of ovarian function, higher levels of testosterone, and cortisol that correlated with elevated inflammatory cytokines, and normal dihydrotestosterone levels.[32]

In a study by Li et al., it has been concluded that the average concentrations of sex hormone and ovarian reserve in COVID-19 women of child-bearing age have no significant change. The menstrual volume decrease or cycle prolongation has been observed in nearly one-fifth of the patients that might be due to transient sex hormone changes induced by suppression of ovarian function that restart immediately after recovery.[35]

Inflammation due to Coronavirus Infection and Infertility in Men

The occurrence of inflammatory conditions in the testicular microenvironment leads to increased production of inflammatory cytokines, recall, and infiltration of leukocytes into the interstitial space of the testicular parenchyma and ultimately leads to orchitis. One of the causes of male infertility is orchitis. The results of the studies confirmed the orchitis caused by T-lymphocyte infiltration in patients with COVID-19. Pan et al. assessed six patients with COVID-19 suffered from orchitis.[36] In addition, Yang et al. studied 12 deceased patients with COVID-19 and showed the presence of viral orchitis features with T-lymphocyte infiltration into the testicular parenchyma along with seminiferous tubular injury.[37] Interestingly, the histopathological examinations of the testes in patients with SARS and COVID-19 overlapped. In both histopathological results, the infiltration of leukocytes into the testicular tissue and the extensive destruction of germ cells with thickening of the basement membrane were observed.[38] These findings support the hypothesis that the adaptive immune response to coronavirus plays a vital role in the process of testicular damage and affects the fertility of recovered men. Accumulation of macrophages at the site of injury will also lead to worsening of the injury and atrophy of the testicular parenchyma. These findings overlap with the results of histopathological evaluation of testicular tissue in patients with SARS. However, confirmation of such hypotheses requires animal-based experiments.[11]

Placenta and pregnancy

The adverse effects of coronaviruses on fetuses and infants including preterm delivery, intrauterine growth

restriction, spontaneous abortion, and even death have been demonstrated in an epidemiological study.[39]

It is obvious that the immune system is modulated but not suppressed during pregnancy.[40] Danza *et al.* have reported that the number of CD3+ T-cells totally decreases in pregnancy.[41] In the first trimester of pregnancy, thymus would be reversibly degenerated due to increase of estrogen and progesterone which eventually lead to CD4+ and CD8+ T-cells reduction.[42] In the study of Kraus *et al.*, the lower number and activity of natural killer cells and T-cells has been reported in late pregnancy compared to the postpartum period, which can increase the virus susceptibility.[43] Weakening of cell-mediated immunity by T-helper 1 (Th1) cells and dominance of Th2 (resulting in the production of IL-4, IL-10, IL-13, and transforming growth factor β) during the pregnancy, can make the mother susceptible to intracellular pathogens such as the viruses.[44] In patients with SARS-CoV-2 infection, Th1 cells become more active leading to an affecting increase in pro-inflammatory cytokines (interferon-γ, IL-1β, IL-6, and IL-12) that leads to severe lung damage.[45] In COVID-19 patients, a range of immune responses has been proposed and early adaptive immune responses may indicate a milder severity of the disease.[46] It is possible that hormonal changes affecting the immunological response to viruses as well as the physiological transition to Th2 and in result the expression of anti-inflammatory cytokines such as IL-4 and IL-10 and dominant response to SARS-CoV-2 in pregnancy would be increased which causes milder disease in pregnant than nonpregnant women.[43,47,48]

Moreover, the presence of SARS-CoV-2 across the placenta even in mild COVID-19 pregnant women has been documented in some studies which potentially can lead to fetal growth restriction and other gestational complications.[49] However, there are controversial in the studies of vertical transmission, and there is no sufficient evidence to confirm transplacental COVID-19 infection. In one study, SARS-CoV-2 has been detected in the placental and fetal membranes, but the infants' test was negative in the first 5 days of life. Maternal blood, vaginal secretions, and amniotic fluid can be considered as possible contamination sources.[50] However, the risk of placental/amniotic sac infection in COVID-19 is not yet ruled out and further research is needed. ACE2 expression is higher in the placenta than in the lung, which further confirms the risk of placental SARS-CoV-2. The association of low placental ACE2 and Ang-(1–7) with intrauterine growth restriction has been reported which has also been observed in pregnant women with COVID-19.[51] This suggests that COVID-19 placental infection may have severe subsequent complications for pregnancy. Local expression of RAS was detected in placenta and cell lines in the early 6th week of pregnancy, but its function is unclear. The possibility of RAS involvement in trophoblast invasion and angiogenesis has been reported in a study and showed that local RAS

alteration may contribute to abnormal uteroplacental perfusion, resulting in preeclampsia.[52] Ang II contained in the maternal decidua and pericytes of endometrial spiral arteries as well as its type 1 receptor are found in maternal decidua, fetal capillaries, cytotrophoblasts and syncytiotrophoblasts. The antagonistic proteins to Angiotensin II, namely Angiotensin (1–7) and ACE2 are localized in syncytiotrophoblasts, cytotrophoblasts and the endothelium and primary and secondary vascular smooth muscle.[53] The ACE is also found in invasive and intravascular trophoblasts and in maternal decidual stromal cells. ACE2 is localized in smooth muscles and the vascular endothelium in the umbilical cord, and all of these provide a potential SARS-CoV-2 entry point to the placenta as well as RAS expression fluctuates throughout pregnancy.[54] ACE2 peaks early in pregnancy, while during pregnancy, AT1R expression increases and peaks at the end.[55] However, whether this increases susceptibility to SARS-CoV-2 placental infection in early pregnancy is unknown.

The Expression of Angiotensin-Converting Enzyme 2 Differs in Location throughout Pregnancy

In the early pregnancy, ACE2 appears in the primary and secondary decidual regions, duct area and glandular epithelium, and in late pregnancy in the labyrinthine placenta and epithelium of the yolk sac and amniotic sac.[56]

A recent report from a Wuhan university hospital in China found that none of the serum or throat swab samples from six confirmed neonates with COVID-19 showed reverse SARS-CoV-19 based on a polymerase chain reaction test, but virus-specific antibodies did display in their neonatal umbilical as five infants had elevated IgG concentrations and two of them had IgM antibodies. Unlike IgG, larger macromolecular IgM usually does not pass from the placenta to the fetus.[57,58] In another study, in the third trimester of mothers with SARS, abnormal weights and pathology were observed in the placentas of two patients infected with SARS-CoV.[59] It has been assumed that IgM detected in infants may be due to an abnormal or damaged placenta or, on the other hand, may have been induced by infants in response to transplacental viral infection.[60] These observations suggest a vertical transmission of viral infection through the placenta, which may be related to SARS-CoV infection from mother to fetus.

Assessment of severe acute respiratory syndrome coronavirus in human semen

The study by Stanley *et al.*[61] assessed the patterns of gene and protein expression of SARS-Cov-2 host entry proteins in several reproductive tissues. Co-expression of ACE2 and transmembrane protease, serine 2 (TMPRSS2) did not detect in the sperm or other testicular cells by single-cell RNA sequencing data. They also assessed basal receptor

expression (BSG/CD147), which may modulate virus entry, and cathepsin L-cysteine protease (CTSL), which potentially breaks down viral S protein and found that BSG was more widely expressed than ACE2 in testicular cell types and was expressed by CSTL in early and late spermatocytes (78.7% and 90.8% of cells with mRNA transcripts, respectively). In all of the 18 tested human cumulus cell samples, BSG and CTSL transcripts were similarly detectable with no, or low, expression of TMPRSS2 in these samples. They also concluded that it does not seem SARS-CoV-2 infection have long-term effects on male and female reproductive function, suggesting that ART/IVF risks are not altered by the COVID-19 pandemic.[62] It may be right and still we need to be alert and live with uncertainty, although reassuring because SARS-CoV-2 has been detected in various secretions, such as stool, urine, saliva, and the gastrointestinal tract. Hence, it is needed to answer the inevitable question of whether the virus is transmitted through semen. While the testicular blood barrier is incomplete, especially if there is inflammation, SARS-CoV-2 may inoculate the male reproductive system. To date, 27 viruses have been detected in human semen in association with viremia.[63] It seems that the presence of viruses in semen may be more common than previously thought, and traditional nonsexually transmitted viruses may be present in genital secretions.[64] Two of the 23 recovered patients in another study had a SARS-CoV-2 test in their semen with no difference in the days after clinical recovery, indicating that semen may be contagious to the virus not only in the acute phase of the disease but even later.[65]

Since there was no difference between positive and negative results, it is not yet clear how long the semen can be contagious, which is certainly alarming.

Outcomes

Early consequences include the proportion of women with reduced fertility, the association between COVID-19 and female and male fertility, or any risk estimate between COVID-19 and female and male fertility. Regarding the ACE2 is most widely expressed in the ovaries, it should be paid particular attention to the lower ovarian reserve function (mean decreased AMH, increased FSH or basal LH, and impaired FSH/LH ratio). The secondary outcomes are uterine receptivity (endometrial morphology, subendometrial blood flow, endometrial thickness, and uterine spiral artery blood flow), oviduct status, and menstrual status. Secondary consequences of uterine admission (endometrial thickness, uterine spiral artery blood flow, endometrial morphology, and submandibular blood flow) are ovarian duct condition and menstrual status.

Conclusion

According to the available data, there is no conclusive evidence on the effect of SARS-CoV-2 infection on fertility, but it is suggested that fertility is more affected in men than in women. The presence of ACE2 in the testes, along with reports about autoimmune orchitis and impaired spermatogenesis, changes in sex hormones, and some findings about virus shedding in semen, are obvious concerns. However, most observational studies are small in sample size and therefore controlled trials or large prospective studies are needed for definitive conclusions. So far, SARS-CoV-2 infection has been shown to have less dreadful pregnancy outcomes than SARS and MERS. Reproduction is an important concern, and due to the prolongation of the epidemic, normal pregnancy or ART requires more precautions. Because the impact on fertility can affect the socioeconomic dynamism of all countries, more attention should be paid to it, and there is an urgent need for global studies to assess the potential issue of male infertility.

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Conflicts of interest

There are no conflicts of interest.

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