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Effects of COVID-19 Infection and Vaccination on the Female Reproductive System: A Narrative Review

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Several studies and research papers have been published to elucidate and understand the mechanism of the coronavirus disease 2019 (COVID-19) pandemic and its long-term effects on the human body. COVID-19 affects a number of organs, including the female reproductive system. However, less attention has been given to the effects of COVID-19 on the female reproductive system due to their low morbidity. The results of studies investigating the relationship between COVID-19 infection and ovarian function in women of reproductive age have shown the harmless involvement of COVID-19 infection. Several studies have reported the involvement of COVID-19 infection in oocyte quality, ovarian function, and dysfunctions in the uterine endometrium and the menstrual cycle. The findings of these studies indicate that COVID-19 infection negatively affects the follicular microenvironment and dysregulate ovarian function. Although the COVID-19 pandemic and female reproductive health have been studied in humans and animals, very few studies have examined how COVID-19 affects the female reproductive system. The objective of this review is to summarize the current literature and categorize the effects of COVID-19 on the female reproductive system, including the ovaries, uterus, and hormonal profiles. The effects on oocyte maturation, oxidative stress, which causes chromosomal instability and apoptosis in ovaries, in vitro fertilization cycle, high-quality embryos, premature ovarian insufficiency, ovarian vein thrombosis, hypercoagulable state, women's menstrual cycle, the hypothalamus-pituitary-ovary axis, and sex hormones, including estrogen, progesterone, and the anti-Müllerian hormone, are discussed in particular.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic originated in China (Wuhan) in December 2019. Initially, the virus caused respiratory symptoms and pneumonia.[1] The World Health Organization (WHO) officially announced COVID-19 as an acute respiratory virus syndrome and the most important disease in 2020.[2] The COVID-19 pandemic resulted in several complex challenges for medical and public health systems worldwide. The extensive spread of COVID-19 from China to other countries became the main concern of governments and public health societies.[3] In October 2022, the WHO reported that COVID-19 infection had caused approximately 6.5 million human deaths worldwide.[4] Mortality rates remain high, especially in high-risk populations, including patients with heart disease, individuals with diabetes, and immunosuppressed patients with cancer.[5]

The COVID-19 pandemic has led to the undertaking of numerous studies and publications worldwide to elucidate the short- and long-term consequences of COVID-19 for the human body.[6] COVID-19 mortality is strongly associated with gender. COVID-19 data have shown that male mortality rates are higher than female mortality rates.[7,8] A meta-analysis revealed that although the numbers of men and women with confirmed COVID-19 infection are similar, the number of male patients admitted to intensive treatment units was three times greater than that of females.[9] The percentage of mortality in females increases significantly after 55 years of age.[8] Sex-related genetic factors, in combination with existing treatments, might represent an interesting mechanism and target for COVID-19 treatment.[10] The female reproductive system is an organ system affected by COVID-19 that has received less attention due to the lack of related deaths.[11] The angiotensin-converting enzyme (ACE2) receptor has been reported to be the main receptor involved in the penetration of coronaviruses into cells. Postcell invasion, COVID-19 disrupts the renin-angiotensin system (RAS) by down-regulating ACE2 expression in host cells, leading to an exacerbated proinflammatory response by angiotensin-II.[12] This receptor is present in the female reproductive system, particularly in the ovaries and uterus, where it affects folliculogenesis, steroidogenesis, oocyte maturation, ovulation, and endometrial regeneration.[13]

Immunologic research has demonstrated that coronavirus infection triggers the induction of a cascade of ACE2 mediators. Under continuous infection conditions, other cascades are induced by transmembrane serine protease 2 (TMPRSS2) on infected cells, and elevated inflammatory responses and cytokine secretion are the main fatal factors in cases of COVID-19 infection.[14,15] Following the elucidation of the immunological process, the vaccine production has become essential for disease prevention.[16]

Recent research has failed to provide strong clinical evidence supporting the presence of the COVID-19 virus in the female reproductive system, uterus, and vaginal secretions.[17,18] However, according to some other reports, COVID-19 can disrupt fertility in women.[19,20] Although no study has confirmed that oocytes can be directly affected by COVID-19 infection,[21,22] the expression of ACE2 in the female reproductive system may affect steroidogenesis, folliculogenesis, oocyte maturation, and ovulation. Several reports have demonstrated a reduction in oocyte quality, impaired ovarian function, and disruptions in the uterus and menstrual cycles.[20,23]

In a previous review published in 2022, we assessed the effects of COVID-19 on the male reproductive system. The results of this review showed that COVID-19 and vaccination have no negative effects on sperm parameters and male fertility potential[24] but can affect gametes or reproductive germ cells. Therefore, the COVID-19 pandemic can be considered to be a problem for natural pregnancy and artificial fertilization, including assisted reproductive technology (ART) and in vitro fertilization (IVF). Given that very few studies have been conducted on the relationship between COVID-19 and human/animal reproduction, investigations on the latest pathophysiological impact of the COVID-19 pandemic on the female reproductive system (ovaries, uterus, and sex hormones) and ART, the main fertility treatment procedure, are important.

The aim, therefore, of this study is to review the literature and categorize the effects of COVID-19 on the female reproductive

system, including the ovaries, uterus, and hormonal profiles. Moreover, the effects of COVID-19 infection and vaccination on oocytes and embryos in the ART and IVF cycles were assessed.

SEARCH METHODS

For this review, an extensive literature search was performed on PubMed, Web of Science, and Scopus between 2019 and 2023. The following keywords, alone or in combination, were used for the search: COVID-19, COVID vaccine, SARS-CoV-2 vaccination, female reproductive system, fertility potential, ovary, uterus, menstrual cycle, sex hormones, ART, and IVF. Literature and articles published in English and available between 2019 and up to May 2023 were included. Studies without full text, marine experimental studies, and studies on factors of male infertility were excluded from assessment. The resulting articles were selected by screening their titles and reviewing their full text. Finally, only

TABLE 1. Summary of the Main Studies on the Effects of COVID-19 Infection and Vaccination on the Female Reproductive System.

Author's name	Type of study	Findings and conclusion
Ovary		
Bowman et al.[40]	Experimental	**COVID-19 vaccination** has no effect on ovarian or uterine parameters and female mating performance
Orvieto et al.[31]	Clinical study	**COVID-19 vaccination** has no effect on the function and ovarian reserves of patients in their immediate subsequent IVF cycle
Yao et al.[41]	Cohort study	SARS-CoV2 is not found in the ovaries of women infected with COVID-19
Madendag et al.[42]	Observational study	COVID-19 has no visible effect on ovarian reserves
de Medeiros et al.[46]	Review study	Antiendogen administration has a beneficial effect on the manifestations of COVID-19
Wilkins and Al-Inizi[49]	Observational study	A case of developed premature ovarian insufficiency in a patient who was infected with COVID-19 is reported for the first time, and hormonal defects are detected in this case
Uterus		
Komine-Aizawa et al.[61]	Observational study	Vaccination status and the adverse effects of the COVID-19 vaccine are associated with uterine pain, tension, and contraction
Saadedine et al.[62]	Review study	COVID-19 infection has negative effects on the uterus and pregnancy potential
Menstrual cycle		
Saadedine et al.[62]	Review study	The interaction between the HPA and HPG axes is responsible for menstrual defects after COVID-19 infection
Muhaidat et al.[67]	Cross-sectional study	The COVID-19 vaccine can induce menstrual abnormalities in women
Male[68]	Letter to the editor	COVID-19 infection and vaccination can affect the female menstrual cycle
Wong et al.[70]	Cohort study	Menstrual irregularities and vaginal bleeding are observed after COVID-19 vaccination
Lebar et al.[73]	Systematic review	Menstural cycle is prolonged and menstrual volume is decreased during COVID-19 infection and vaccination
Hypothalamic-pituitary-ovarian axis		
Li et al.[8]	Review study	Sex steroids may have a protective role against COVID-19
Li et al.[38]	Retrospective, cross-sectional study	The AMH level in patients infected with COVID-19 is not different from that in the control group
Mao et al.[84]	Retrospective case series study	SARS-CoV-2 is present in the pituitary gland and can directly damage the nervous system and cause hormonal disorders
Ding et al.[86]	Observational study	48% of patients with COVID-19 infection have a psychological disorder, such as anxiety, depression, or insomnia, at the peak of the disease; such disorders which may lead to increased prolactin levels and HPO axis dysfunction
Adelakun et al.[88]	Randomized control trial study	Lifestyle changes in women result in an elevation in LH levels, consequently increasing testosterone production by ovarian theca cells and leading to secondary ovulation disruption
Mal'tseva et al.[97]	Review study	The regulation of proinflammatory immune processes against COVID-19 appears to be associated with increased anti-inflammatory regulation and antiviral defense
Costeira et al.[98]	Cohort study	High levels of estrogen in premenopausal women have a protective effect against COVID-19 infection
Gordon et al.[105]	Review study	Progesterone, as an antiviral hormone, can protect the human body against COVID-19 infection
Soysal and Yılmaz[107]	Prospective cross-sectional study	No significant difference is found between pre- and postvaccine AMH values in the study group
ART and IVF		
Bentov et al.[21]	Cohort study	COVID-19 is detectable in patients with acute infection after treatment and during the recovery period and in patients without infection symptoms.

TABLE 1. Continued

Orvieto et al.[31]	Clinical study	COVID-19 infection has no effect on the patient's ovarian reserves, but the number of high-quality embryos decreased
Herrero et al.[37]	Cohort study	COVID-19 infection adversely affects the follicular microenvironment and dysregulates ovarian function
Ding et al.[39]	Cohort study	COVID-19 infection leads to ovarian injury, including reductions in ovarian reserves and reproductive endocrine disorders in patients.
Colaco et al.[123]	Study	Blastocysts may have COVID-19 virus receptors
Oguejiofor et al.[125]	Experimental study	No flaviviruses are detected in IVF bovine embryos after 7 days

COVID-19, Coronavirus disease 2019; IVF, in vitro fertilization; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; HPA, hypothalamic-pituitary-adrenal axis; HPG, hypothalamic-pituitary-gonadal; LH, luteinizing hormone.

articles corresponding to the topics of interest were selected for this review. In addition, references from relevant reviews and ongoing studies were manually searched to locate other potentially eligible materials.

SUMMARY of EVIDENCE

Role of COVID-19 and Vaccination in the Female Reproductive System

Several pieces of evidence showed that after binding to target host cells, the coronavirus can create an immune response.[19,23] ACE2 has been reported to be expressed in the female reproductive system. It plays an enzymatic role in RAS. Therefore, the connection between ACE2 and RAS is considered to be an important function in the physiology of the ovaries and uterus.[12] Recent studies have demonstrated that COVID-19 can cause disruptions in female fertility potential.[19,20] COVID-19 can infect granulosa cells and ovarian tissue, reduce oocyte quality and ovarian function, and lead to infertility or abortions.[23,25] In addition, COVID-19 may harm endometrium epithelial cells and lead to premature implantation and early abortion.[15] How COVID-19 affects fallopian tubes remains unknown, but COVID-19 may damage fallopian tubes indirectly.[23] In 2020, Jing et al.[26] evaluated the potential impact of COVID-19/ACE2 on the female reproductive system, demonstrating that ACE2 is widely expressed in the ovaries, uterus, vagina, and placenta. Moreover, angiotensin 1-7 and ACE-2 have been reported to control follicular growth and ovulation, degeneration, and angiogenesis in the yolk sac. In addition, several changes in the endometrial tissue can affect embryonic development.[26] Wei et al.[27] analyzed follicular fluid from ART treatment cases and demonstrated that the angiotensin 1-7 receptor correlates positively with oocyte maturity and is an indicator of ovulation development.[27] Another recent study illustrated that COVID-19 can affect oocyte maturation by increasing oxidative stress.[23] Oxidative stress causes chromosomal instability and apoptosis in the reproductive system.[28,29]

Antivaccination sentiments and actions arose following the introduction of vaccination. Vaccines were implied to result in negative effects on the female reproductive system and consequently in infertility or abortion.[30] Therefore, reviewing the studies and documents regarding the various effects of COVID-19 and vaccines on the female reproductive system is an important requirement. Orvieto et al.[31] recently reported that they found no significant differences in implantation rates and high-quality embryos between cases with or without COVID-19 vaccination. They also showed that the implantation rate and embryo qualities in COVID-19-infected patients were significantly lower than those in healthy women.[31] Bentov et al.[21] reported that the quality of oocytes in COVID-19-vaccinated women was statistically similar to that in unvaccinated women. These clinical trials suggest that the COVID-19 vaccine has no negative effects on the human reproductive system.[21,31]

Ovaries

The symptoms of COVID-19 infection may vary from patient to patient. Although many studies have been conducted and reported on the respiratory,[32] cardiac,[33] eye,[34] neurological,[35] and urological[36] symptoms related to COVID-19 infection, the ovarian outcomes in patients with COVID-19 infection have been less studied. Some studies have reported that COVID-19 has negative effects on ovarian function, whereas other works have reported favorable effects.[37,38] A study conducted with the aim of investigating the relationship between COVID-19 infection and ovarian function in women of reproductive age demonstrated that COVID-19 leads to ovarian injury, including a reduction in ovarian reserves and reproductive endocrine responses.[39] Herrero et al.[37] investigated the effect of COVID-19 infection on ovarian function by comparing follicular fluid between the two control groups. They examined a group that had recovered from COVID-19 infection and the effect on follicular fluid in nonluteinized granulosa and human endothelial cell cultures. They concluded that COVID-19 infection adversely affected the follicular microenvironment and led to ovarian function dysregulation.[37] However, most of the studies found no negative effect on the ovaries (Figure 1).

Bowman et al.[40] evaluated the effect of BNT162b2 (Pfizer-BioNTech), mRNA-based COVID-19 vaccine, on 44 female rats. They prescribed a full human BNT162b2 dose of 30 μg mRNA/dose on days 14 and 21 before mating and on days 9 and 20 of pregnancy. They found that vaccination had no effect on ovarian or uterine parameters and female mating performance.[40]

A cohort autopsy study that investigated the systemic pathogenesis of COVID-19 in 26 autopsied cases[41] did not find COVID-19 in the ovaries (n = 7). Another observational study conducted on 132

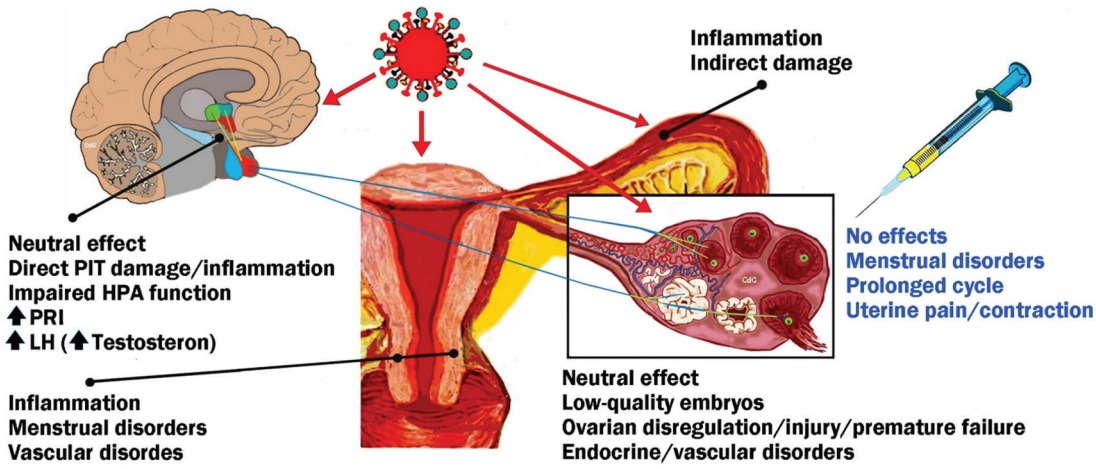

FIG. 1. Current evidence showing that after binding to the cellular ACE2 receptors of the female reproductive system, the coronavirus can directly affect tissues as well as create an immune response. The figure displays the various target-organ effects of either infection or immune-mediated reactive responses. Although studies have registered neutral effects on the HPA/gonadal axis, uterine, and ovarian functions, menstrual and ovulatory abnormalities have been reported in women with SARS-CoV-2 infection. Although rare, some negative effects (text in blue color) have also been reported after COVID-19 vaccination (see text for further information).
COVID-19, Coronavirus disease 2019; HPA, hypothalamic-pituitary-adrenal; LH, luteinizing hormone; PIT, pituitary; PRI, prolactin.

young women aged 18-40 years old before and after COVID-19 infection reported no visible effect on ovarian reserves.[42]

Patients with polycystic ovary syndrome (PCOS) are at risk of COVID-19 infection due to underlying diseases, such as diabetes, heart disease, and obesity.[43,44] Women with PCOS suffer from COVID-19 infection at rates approximately 5-20% higher than men[45] and are at a 28-50% higher risk for COVID-19 infection than women of the same age without PCOS.[46] Women with PCOS who are infected with COVID-19 should receive appropriate emergency treatment because 80% of these females have hyperandrogenism, which inhibits immunity and controls TMPRSS2 and ACE2 that further facilitate the entry of virus into the cells.[47] In these cases, the administration of antiendogens has a beneficial effect on the manifestations of COVID-19.[46]

Premature ovarian insufficiency is another ovarian disease that occurs when the ovaries stop functioning before the age of 40. Here, the ovaries do not produce normal amounts of estrogen, and eggs are not released regularly, leading to infertility. This condition is also called premature ovarian failure.[48]

In July 2021, Wilkins and Al-Inizi[49] presented the first report of premature ovarian insufficiency that developed in a woman who was infected with COVID-19. Two months before COVID-19 infection, the patient had normal regular periods; normal gonadotropin levels; and follicle stimulation hormone (FSH) and luteinizing hormone (LH) levels of 8 and 2 U/L, respectively. Seven months after the infection, her FSH and LH levels increased to 78 and 43 U/L, respectively. Two months later, when the test was repeated, her gonadotropin level remained high, indicating that she will need assisted reproductive methods to become pregnant.[49]

The reproductive tissue expresses the ACE2 receptor, which may be used by the COVID-19 virus to enter cells.[26] Very few studies have shown the histological destruction of ovarian tissue following infection with COVID-19 and its treatment.[49,50] The ACE2 receptor is speculated to be expressed at lower levels in ovarian tissue than in testicular tissue, further reducing the chance of viral invasion and glandular damage.[49]

COVID-19 infection is associated with a high risk of venous thromboembolism.[51] Ovarian vein thrombosis (OVT) is a rare, serious, and uncommon condition and is mostly reported in the postpartum state.[52] However, cases of OVT associated with COVID-19 have been reported. DeBoer et al.[53] reported a case of OVT secondary to COVID-19 infection in a 56-year-old woman without a previous history of thromboembolism. The patient experienced abdominal pain that led to further evaluation through the computerized tomography of the abdomen and pelvis, and OVT was proven. The only risk factor in the patient was thrombosis induced by COVID-19 infection.[53] The exact cause of OVT is unknown but is attributed to abnormal blood flow due to turbulence at vessel bifurcations and/or stenotic regions that can lead to blood stasis; abnormalities in the vessel wall due to endothelial damage and/or dysfunction; and abnormal blood constituents, namely, platelet and coagulation impairment leading to hypercoagulability.[54] This triad, which is called Virchow's triad, was described by Virchow over 150 years ago and revised in 2020.[55] Pregnancy can lead to excessive coagulability, and the pregnant uterus can cause the compression of the right ovarian vein and inferior vena cava. Furthermore, uterine infection can lead to endothelial damage. In this review, the authors considered the most probable cause of OVT COVID-19 given the absence of other factors, such as a history of thromboembolic disorders, recent surgeries, and postpartum status.[53]

A number of studies have reported hypercoagulability in the form of venous and arterial thromboembolism with unknown pathogenesis in patients with COVID-19. Interestingly, changes in thrombotic factors, such as fibrinogen, factor VIII, Willebrand

factor, and D-dimer, that can cause a hypercoagulable state have been reported in a number of other studies.[56,57]

Uterus

Several hormonal receptors, such as estrogen and progesterone receptors, are present in the uterus. Therefore, the uterine function is under hormonal control. These receptors are expressed in endometrial stromal cells. Hormone binding to receptors regulates endometrial growth, decidualization, cytokine secretion, and immune response activity.[58]

With the use of radioimmunoassay, angiotensin was detected in endometrial wash fluid at picomolar concentrations. Angiotensin is localized in the endometrium throughout the menstrual cycle and is more concentrated in the glandular epithelium during the mid- and late-secretory phases. This pattern corresponds to the pattern of ACE2 mRNA, which is more abundant in epithelial cells than in stromal cells (2-fold increase, $p < 0.05$) and in the secretory versus proliferative phase (6.6-fold increase, $p < 0.01$).[59] The G-protein-coupled Mas receptor is similarly circulated between epithelial and stromal cells without any change during the menstrual cycle.[59] The reduction in endometrial function has negative effects on fertility potential.[60] RAS has been confirmed to be expressed at high levels in the uterus.[26] Rare nonserious defects, including uterine pain, tension, and contraction, have been associated with COVID-19 infection and vaccination.[61,62]

Menstrual cycle

Women of reproductive age seek healthcare for abnormal uterine bleeding (AUB) more often than for any other condition, and AUB accounts for one-third of women's outpatient visits to a gynecologist.[63] Up to approximately 30% of the population is affected by AUB.[64] This wide range may be explained by different ages and symptoms and, most importantly, underreporting. AUB has been studied mostly in relation to heavy menstrual bleeding, with little information available about other symptoms.[65] Available evidence shows that as many as half of the affected women do not seek medical treatment for AUB despite having access to a healthcare provider.[65,66] Although the menstrual cycle is poorly studied, evidence showed that infection with COVID-19 and vaccination with the BNT162b2 vaccine can affect the menstrual cycle.[67,68]

The increase in the prevalence of menstrual disorders before the start of vaccination is due to stress and sleep disorders. Moreover, in females, severe acute illness may alter the function of the hypothalamic-pituitary-gonadal (HPG) axis, decreasing the endogenous production of estrogen and progesterone.[69]

In a study in the USA between 2020 and 2022, women over 18 years of age who had received the COVID-19 vaccine were asked to report changes in their menstrual cycle. The most reported change was related to the increase in the duration of menses (83%). In this study, 67% of women mentioned an increase in menstrual symptoms, 4% reported bleeding after menopause, and 2.8% mentioned the resumption of bleeding in menopause.[70] Another study found that COVID-19 infection and the BNT162b2 vaccine increased menstrual bleeding in the first and second cycles.[65] In a study on 177 patients positive for COVID-19, 75% reported no change in bleeding volume, and 20% reported a reduction in bleeding volume. An increase in bleeding volume was found in only 9% of the cases. Although no difference in the volume of bleeding was found between patients with moderate and severe diseases, the duration of menstrual bleeding was longer in patients with severe disease.[38]

COVID-19 infection causes menstrual changes without long-term consequences. This effect is possible due to the interaction[62] between the hypothalamic-pituitary-adrenal axis (HPA) and HPG. Research has shown that the effects of COVID-19 infection on the menstrual cycle are transient and may be caused by the response of the immune system to stress.[71] Furthermore, the effect on the HPG axis causes changes in menstruation.[72] An Italian study reported that menstrual disorders, such as delayed menstruation, menorrhagia, metrorrhagia, and menometrorrhagia, had a prevalence of 23-77% in the first 3 weeks after vaccination, especially after the second dose.[62] In another study, Male[68] demonstrated that mRNA and adenovirus-vectored COVID-19 vaccines do not cause menstrual changes, indicating that the immune response, rather than some specific vaccine component, may be responsible.[68] A recent review stated that most women reported a prolonged cycle and decreased menstrual volume during COVID-19 infection and vaccination.[73] However, infection severity did not affect the rate of cycle changes.[67,74]

Sex Hormones

The regulation of physiological hormonal responses in the female reproductive system stems from the hypothalamus. The hypothalamus controls the female reproductive cycle by regulating pituitary gland secretion. The hypothalamus receives internal and external stimulating factors and produces several hormones that regulate the function of the anterior pituitary gland.[75] The direct effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on brain tissue is a possible hypothesis in the field of female fertility and COVID-19.[76] The neurological symptoms experienced by patients with COVID-19 experience are evidence supporting the above hypothesis.[77,78]

ACE2 is known to be the entry gate of coronaviruses into human cells.[79] ACE2 expression by the supporting cells of the olfactory epithelium may be the main gateway of viral entry into the brain tissue.[80] However, the exact point of entry of the SARS-CoV-2 virus into the central nervous system remains unknown, but may occur via a blood-borne route or directly through the olfactory epithelium.[81] Given that hypothalamic and pituitary tissues express high levels of ACE2, theoretically, these brain structures constitute targets for viral infections.[82] In fact, evidence has revealed edema and apoptosis in hypothalamus nerve cells in patients with COVID-19. Moreover, the SARS-CoV-2 genome has been discovered in the brain.[83]

The Hypothalamus-Pituitary-Ovary axis (HPO) controls the human menstrual cycle through positive and negative feedback.[69]

A study reported serious endocrine disorders and a significant increase in the two pituitary hormones LH and prolactin in patients suffering from COVID-19.[84] This study discovered the presence of the SARS-CoV-2 virus in the pituitary gland, suggesting that the SARS-CoV-2 virus can directly damage the nervous system and cause hormonal disorders.[84] The increase in hormones may be partially due to a direct effect on brain tissue. Humans suffering from anxiety during the COVID-19 pandemic, especially women, can also suffer from endocrine disorders.[85] Ding et al.[86] reported that 48% of patients with COVID-19 infection had a psychological disorder, such as anxiety, depression, or insomnia, at the peak of the disease; this situation could lead to increased prolactin and dysfunction via the HPO axis. Changes in lifestyle due to extensive quarantines and the fear of contracting the virus have induced high levels of anxiety in women. Anxiety is reported in cases that have not been infected with COVID-19.[85] Changes in the pattern of daily and sports activities during the pandemic can increase anxiety in people.[87] In women, these lifestyle changes can increase LH levels; consequently, ovarian theca cells produce more testosterone and lead to secondary ovulation disruption.[88] Hormonal defects may be more serious and challenging in women with PCOS or thyroid disorders who previously had endocrine problems.[46] Several studies have demonstrated that the virus or immune responses following infection cause direct damage to ovarian follicles, infection, and inflammation. Abnormal sex hormone production and HPO axis disruption are the possible negative consequences of COVID-19 infection of the female reproductive system.[89,90]

Estrogen

SARS-CoV-2 replication and maturation have been shown to be influenced by the estrogen hormone.[91] Inflammatory responses to pathogens and infections are well known to be mediated by estrogen, and estrogen receptors (ERα/β) have been implicated in the suppression of viral gene transcription.[92] Zafari Zangeneh and Sarmast Shoushtari[93] reported that in a hepatitis C model, the selective estrogen receptor degrader fulvestran can block the effect of 17-estradiol in vitro. Numerous studies have confirmed estradiol's modulatory function in systemic and pulmonary inflammatory responses.[94] Estrogen receptor alpha (ERα), estrogen receptor beta (ERβ), and ERα/β are expressed in most immune cells. This expression pattern confirms the prominent role of ERs in innate/adaptive immune function responses.[92] For example, the important influence of estrogen and its receptors on B-cell and dendritic cell functions are well recognized in lupus. As in arthritis models, ERα has a multifactorial immune-protective effect in lupus. ERα agonists act to facilitate this immune-protective effect. Therefore, the modulatory function of ERα can be an important therapeutic target for autoimmunity.[95] ER2 influences the expression of human ACE2 protein (as the host cell receptor), which can have an important role in coronavirus uptake.[96] In women, the regulation of proinflammatory immune processes against COVID-19 appears to be associated with increased anti-inflammatory regulation and antiviral defens[97](Figure 1).

Costeira et al.[98] investigated the relationship between estrogen and COVID-19 severity. Their results showed that in premenopausal women, a high level of estrogen had a protective effect against COVID-19 infection.[98]

Progesterone

Progesterone is a steroid sex hormone with a main role in the menstrual cycle, pregnancy, and human embryonic development. This hormone has an anti-inflammatory role. Before menstruation, the level of progesterone decreases rapidly, and inflammatory cells attack the endometrium, leading to an inflammatory response.[99] In addition to its known role in reproduction, progesterone can change the balance of cytokines in immune responses and may cause a high level of regulatory T-cells with a cluster of differentiation 4 and CD8 marker expansion.[100] Moreover, progesterone causes immune adaptation and tolerance that facilitates and maintains pregnancy.[101]

Evidence showed that the severity of symptoms and mortality rate of COVID-19 are higher in men than in women.[7,102] Researchers have suggested that sex steroids may have a protective role against COVID-19.[7,8] Estrogen and progesterone, which are both female sex steroids, and their metabolite allopregnanolone have an anti-inflammatory role that can change immune cell responses.[8] These changes may facilitate the proliferation and repair of respiratory epithelial cells and protect cells against COVID-19 infection.[8] Several studies were designed on the basis of this theory to assess the effect of progesterone and estrogen treatment on COVID-19 infection.[103,104] In 2020, Gordon et al.[105] reported that progesterone is an antiviral hormone that can protect the human body against COVID-19 infection. However, the potential of progesterone to reduce COVID-19 symptoms in men remains ambiguous.

Anti-Müllerin Hormone

Anti-Müllerin hormone (AMH) is secreted by small antral follicles; it is an important index for evaluating ovarian reserves that is not influenced by the menstrual cycle, exogenous sex hormones, or pregnancy.[106] Li et al.[38] evaluated the level of AMH in COVID-19-infected women to assess the effects of COVID-19 on AMH. They reported that the level of AMH in patients with COVID-19 was not different from that in the control group. In consideration of the reversible menstrual changes and the absence of reductions in estradiol and progesterone levels in women with COVID-19 infection, SARS-CoV-2 infection is assumed to have a small effect on ovarian reserves. However, long-term studies are suggested.[38]

Soysal and Yılmaz[107] performed a prospective cross-sectional study on 60 female patients aged 25-30 years old to evaluate the effect of mRNA COVID-19 vaccines on ovarian reserves. They examined AMH levels in patients 1-5 days before vaccination and 60-90 days after vaccination and compared them with those in the control group that did not receive the vaccine. Postvaccine AMH values in the study group were similar to those in the control group, and no significant difference was found between prevaccine and postvaccine AMH values in the study group. These researchers stated that people who intend to get pregnant should know that the vaccine, which is the most important tool for fighting against COVID-19 infections, has no effect on ovarian reserves.[107]

In another study, AMH levels were evaluated before and 3 months after two mRNA SARS-CoV-2 vaccinations. Analyses were performed in different age groups, and no significant changes were observed. Anti-COVID 19 antibody levels increased in all vaccinated women in 3 months, and the correlation between antibody and AMH levels was not reported. COVID-19 vaccination was concluded to be unassociated with a reduction in ovarian reserves at 3 months.[108]

Role of COVID-19 in Assisted Reproductive Technology

At the start of the COVID-19 pandemic, hospitals were overwhelmed by sick patients, resulting in a shortage of intensive care unit beds and personal protective equipment for medical workers. The main medical societies in the field of reproductive medicine, including the *European Society of Human Reproduction and Embryology,* American Society for Reproductive Medicine (ASRM), International Federation of Fertility Societies, and Red Latinoamericana de Reproducción Asistida, recommended patients with infertility to consider deferring pregnancy.[109] Many infertility clinics temporarily halted their practice between March and April 2020 to reduce SARS-CoV-2 transmission and conserve medical resources.[110] Fertility societies worldwide also suggested the suspension of ovulation induction, intrauterine insemination, IVF, sperm and oocyte cryopreservation, fresh/frozen embryo transfers, and other reproductive treatments.[111]

These extraordinary measures were taken for the following reasons:

1) Medical emergencies were kept at bay by avoiding complications associated with assisted reproduction and pregnancy. Concerns about horizontal transmission to the fetus and potential complications related to the virus during pregnancy in patients positive for COVID-19 were raised.

2) SARS-CoV-2 infection and mortality rates led specialty professional organizations to create task forces to regulate measures to reduce COVID-19 transmission to health care workers and patients.

3) Worldwide, fertility clinic staff worked hard throughout the COVID-19 pandemic to maintain effective fertility services.[112]

The guidelines released by ASRM on March 17, 2020, stated that new treatment cycles should be suspended and ongoing cycles paused while embryos were transferred and cryopreserved. As a result of the suspension, only nonelective fertility preservation (for example, storing eggs or sperm before chemotherapy) was permitted.[110] Whether the infection of the reproductive system by COVID-19 can affect gametes or reproductive germ cells must be assessed. The COVID-19 pandemic can be considered as a crisis for ART and natural pregnancy.[113] Annually, ART is used worldwide with millions of treatment cycles for infertile patients. During the acute phase of the COVID-19 pandemic, fertility treatments were postponed despite the rarity of the data on the infection of the female reproductive system. Therefore, assessing the risk of viral transmission by sexual fluids and gametes is necessary to transfer embryos and ensure laboratory safety during ART.[114]

Oocytes and Embryos in IVF Cycles

Considering the known mechanisms of SARS-CoV-2 penetration into cells (i.e., the need for the expression of the ACE2 and TMPRSS2 receptors), the assessment and screening of oocytes and embryos in ART are necessary to determine whether or not SARS-CoV-2 can infect oocytes and embryos.[115]

ACE2 mRNA expression in human ovarian tissue has been determined on the basis of an RNA sequencing database. Ovarian tissue is susceptible to COVID-19.[49] During oocyte retrieval in ART, mature follicles and oocyte-cumulus complexes (COCs) are aspirated. In this procedure, the female gamete (oocyte) is naturally out of reach.[116] Kong et al.[117] reported that in COCs, ACE2 is highly expressed, whereas TMPRSS2 is not expressed or expressed at low levels; moreover, cumulus cells have the potential to be infected because they are possible targets of SARS-CoV-2 for cell entry. Therefore, COCs may not act as a barrier to the entry of viruses into oocytes. A similar study reported on the expression of ACE2 and TMPRSS2 in oocytes.[118] The researchers showed that ACE2 and TMPRSS2 expression levels increase in relation to oocyte maturation.[118] Mature oocytes may be exposed to the risk of infection and viral transmission. The oocyte retrieval process is an alternative route for oocyte infection. Vaginal oocyte retrieval is an invasive procedure, and preventing the contamination of follicular fluid samples by blood or vaginal fluid is difficult.[119] Indeed, coronaviruses have been found to be present in the blood samples of infected patients.[120]

Evidence showing that the RAS system plays an important role in reproductive processes, such as folliculogenesis, steroidogenesis, oocyte maturation, and ovulation, exists.[20] Jing et al.[26] reported that the angiotensin 1-7 receptor ACE2 is present at all stages of follicle maturation in the human ovaries. ACE2 is expressed in the endometrium and in epithelial and stromal cells. In addition, the expression of this gene changes with the menstrual cycle and is higher in the secretory phase than in the proliferative phase. This state can be related to angiotensin-II homeostasis and can regulate endometrial regeneration.[59] Previous studies have demonstrated that ACE2 is expressed in rat and bovine ovarian granulosa cells.[37,121] Orvieto et al.[31] investigated the effect of infection with COVID-19 on subsequent IVF cycles, revealing that although COVID-19 has no effect on the patient's ovarian reserves, the number of high-quality embryos decreased. They suggested postponing IVF treatment for at least 3 months after recovery to achieve better effects and to choose healthy gametes that have not been exposed to infection.[31] In another observational study, researchers attempted to evaluate the effect of the COVID-19 vaccine on subsequent IVF cycles and reported that the COVID-19 vaccine has no effect on the function and ovarian reserves of patients in their immediate subsequent IVF cycles.[122] In a cohort study, Bentov et al.[21] investigated the effect of COVID-19 infection and the BNT162b2 mRNA vaccine on ovarian follicles and their function. This study included 32 consecutive patients undergoing oocyte retrieval who were divided into three groups, namely, the nonvaccinated, uninfected control (n = 14), vaccinated (n = 9), and recovering from COVID-19 (n = 9) groups. Bentov et al.[21] analyzed

anti-COVID-19 immunglobulin (Ig)G, progesterone, estrogen, and heparin sulfate levels in serum and follicular fluid samples and the number and maturity of aspirated oocytes. Their results showed that although the coronavirus and BNT162b2 mRNA vaccine led to the rapid formation of anti-COVID-19 IgG in the serum and follicular fluid, infection, vaccination, and immune response did not exert a measurable harmful effect on ovarian function.[21]

The answer to the question of whether embryos can be infected by SARS-CoV-2 remains unclear. The available evidence shows that blastocysts may have viral receptors. During development, human embryos could be susceptible to coronavirus entry. Moreover, blastocysts can express the genes for proteins involved in viral endocytosis and duplication.[123] Other researchers have investigated the risks of COVID-19 transmission through embryos.[124] Oguejiofor et al.[125] investigated viral transmission in bovines infected by flaviviruses through IVF. Although viruses were found in follicular fluid and COCs after in vitro maturation, no virus was detected in the embryos after 7 days.[125]

In conclusion, information about COVID-19 and its effects; the methods of COVID-19 transmission; and the mortality rates of pregnant women, fetuses, and infants remains inadequate. Currently, the available information on pregnant women with COVID-19 and the transmission of COVID-19 to embryos remains limited but can still be used to provide recommendations to infertile cases undergoing IVF cycles and pregnant women.

The strength of the present study is that it considered parts of the female reproductive system (organs and hormonal axis), allowing the review and summarization of important points about the pathophysiology of COVID-19 and vaccination in the female reproductive system. The present study is a narrative review and did not assess female fertility, COVID-19, and COVID-19 vaccination systematically. Therefore, some aspects of these topics may not have been investigated. A systematic review and meta-analysis of the above topics, based on the findings presented here, could be more beneficial.

Recent studies on the female reproductive system during COVID-19 infection and vaccination showed that in women, the reproductive system may be harmlessly involved in COVID-19 infection. Although low ovarian reserves and menstrual cycle and hormonal defects were reported in cases of COVID-19 infection, scientific evidence showing that COVID-19 vaccination has negative effects on the female reproductive system does not exist. Current studies support the view that vaccination against COVID-19 infection is not harmful to the female reproductive system. However, future studies are needed to support and investigate this assumption. Moreover, studies monitoring people who have received COVID-19 vaccination during pregnancy have not identified any pregnancy-specific safety concerns. Additional information on non-mRNA vaccines, vaccination early in pregnancy, and the longer-term outcomes of infants is also needed. Preventive methods should be taken as long as the pathogenesis and complications of COVID-19 in pregnant women, oocytes, and embryos remain unclear. Awareness of the updated information related to the COVID-19 is necessary.

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REFERENCES

1. Sahin AR, Erdogan A, Agaoglu PM, et al. 2019 novel coronavirus (COVID-19) outbreak: a review of the current literature. *EJMO.* 2020;4:1-7. [CrossRef]
2. Hageman JR. The Coronavirus Disease 2019 (COVID-19). *Pediatr Ann.* 2020;49:e99-e100. [CrossRef]
3. Peeri NC, Shrestha N, Rahman MS, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? *Int J Epidemiol.* 2020;49:717-726. [CrossRef]
4. World Health Organization. COVID-19 weekly epidemiological update, edition 115, 26 October 2022. [CrossRef]
5. Mirabelli M, Chiefari E, Puccio L, Foti DP, Brunetti A. Potential Benefits and Harms of Novel Antidiabetic Drugs During COVID-19 Crisis. *Int J Environ Res Public Health.* 2020;17:3664. [CrossRef]
6. O'Connor DB, Aggleton JP, Chakrabarti B, et al. Research priorities for the COVID-19 pandemic and beyond: A call to action for psychological science. *Br J Psychol.* 2020;111:603-629. [CrossRef]
7. Pradhan A, Olsson PE. Sex differences in severity and mortality from COVID-19: are males more vulnerable? *Biol Sex Differ.* 2020;11:53. [CrossRef]
8. Li F, Boon ACM, Michelson AP, Foraker RE, Zhan M, Payne PRO. Estrogen hormone is an essential sex factor inhibiting inflammation and immune response in COVID-19. *Sci Rep.* 2022;12:9462. [CrossRef]
9. Peckham H, de Gruijter NM, Raine C, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. *Nat Commun.* 2020;11:6317. [CrossRef]
10. Mohamed MS, Moulin TC, Schiöth HB. Sex differences in COVID-19: the role of androgens in disease severity and progression. *Endocrine.* 2021;71:3-8. [CrossRef]
11. Madjunkov M, Dviri M, Librach C. A comprehensive review of the impact of COVID-19 on human reproductive biology, assisted reproduction care and pregnancy: a Canadian perspective. *J Ovarian Res*. 2020;13:140. [CrossRef]
12. Rohilla S. Designing therapeutic strategies to combat severe acute respiratory syndrome coronavirus-2 disease: COVID-19. *Drug Dev Res.* 2021;82:12-26. [CrossRef]
13. Varlas VN, Bors RG, Nasui B, Mititelu M, Gheorghiu ARA, Pop A. Key points in fertility preservation treatment strategies during covid-19 pandemic. an update on pharmacological therapies. *Farmacia.* 2021;69:189-199. [CrossRef]
14. Janiuk K, Jabłońska E, Garley M. Significance of NETs Formation in COVID-19. *Cells.* 2021;10:151. [CrossRef]
15. Singh HO, Jakhar K, Nema V, Krishnaraj A, Choudhari R. Effect of miRNAs, Proinflammatory Cytokines and ACE2 in COVID-19 Pathophysiology. *Coronaviruses.* 2021;2:7-14. [CrossRef]
16. Chumakov K, Avidan MS, Benn CS, et al. Old vaccines for new infections: Exploiting innate immunity to control COVID-19 and prevent future pandemics. *Proc Natl Acad Sci U S A.* 2021;118:e2101718118. [CrossRef]
17. Aslan MM, Uslu Yuvacı H, Köse O, et al. SARS-CoV-2 is not present in the vaginal fluid of pregnant women with COVID-19. J Matern Fetal Neonatal Med. 2022;35:2876-2878. [CrossRef]
18. Tur-Kaspa I, Tur-Kaspa T, Hildebrand G, Cohen D. COVID-19 may affect male fertility but is not sexually transmitted: a systematic review. F S Rev. 2021;2:140-149. [CrossRef]
19. Li F, Lu H, Zhang Q, et al. Impact of COVID-19 on female fertility: a systematic review and meta-analysis protocol. *BMJ Open.* 2021;11:e045524. [CrossRef]
20. Rajak P, Roy S, Dutta M, et al. Understanding the cross-talk between mediators of infertility and COVID-19. *Reprod Biol.* 2021;21:100559. [CrossRef]

21. Bentov Y, Beharier O, Moav-Zafrir A, et al. Ovarian follicular function is not altered by SARS-CoV-2 infection or BNT162b2 mRNA COVID-19 vaccination. *Hum Reprod.* 2021;36:2506-2513. [CrossRef]
22. Albeitawi S, Al-Alami ZM, Hamadneh J, Alqam H, Qublan H, Al Natsheh M. COVID-19 infection and vaccine have no impact on in-vitro fertilization (IVF) outcome. *Sci Rep.* 2022;12:21702. [CrossRef]
23. Lee WY, Mok A, Chung JPW. Potential effects of COVID-19 on reproductive systems and fertility; assisted reproductive technology guidelines and considerations: a review. *Hong Kong Med J.* 2021;27:118-126. [CrossRef]
24. Pourmasumi S, Nazari A, Ahmadi Z, et al. The Effect of Long COVID-19 Infection and Vaccination on Male Fertility; A Narrative Review. *Vaccines (Basel).* 2022;10:1982. [CrossRef]
25. 25.Li R, Yin T, Fang F, et al. Potential risks of SARS-CoV-2 infection on reproductive health. *Reprod Biomed Online.* 2020;41:89-95. [CrossRef]
26. Jing Y, Run-Qian L, Hao-Ran W, et al. Potential influence of COVID-19/ACE2 on the female reproductive system. *Mol Hum Reprod.* 2020;26:367-373. [CrossRef]
27. Wei L, Bo L, Zhou A, et al. Association of the Renin-Angiotensin System Components in Human Follicular Fluid with Age, Ovarian Function and IVF Outcome: *A Cross-Sectional Study.* 2022. [CrossRef]
28. Yan F, Zhao Q, Li Y, et al. The role of oxidative stress in ovarian aging: a review. *J Ovarian Res.* 2022;15:100. [CrossRef]
29. Pourmasumi S, Sabeti P. The effect of free radicals on sperm DNA and antioxidant protective role; an assessment and review. *Reviews in Clinical Medicine.* 2020;7:37-42. [CrossRef]
30. Prieto Curiel R, González Ramírez H. Vaccination strategies against COVID-19 and the diffusion of anti-vaccination views. *Sci Rep.* 2021;11:6626. [CrossRef]
31. Orvieto R, Segev-Zahav A, Aizer A. Does COVID-19 infection influence patients' performance during IVF-ET cycle?: an observational study. *Gynecol Endocrinol.* 2021;37:895-897. [CrossRef]
32. Lai CC, Ko WC, Lee PI, Jean SS, Hsueh PR. Extra-respiratory manifestations of COVID-19. Int J Antimicrob Agents. 2020;56:106024. [CrossRef]
33. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. *Am J Emerg Med.* 2020;38:1504-1507. [CrossRef]
34. Poyser A, Deol SS, Osman L, et al. Impact of COVID-19 pandemic and lockdown on eye emergencies. *Eur J Ophthalmol.* 2021;31:2894-2900. [CrossRef]
35. Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. *Lancet Neurol.* 2020;19:767-783. [CrossRef]
36. Chan VW, Chiu PK, Yee CH, Yuan Y, Ng CF, Teoh JY. A systematic review on COVID-19: urological manifestations, viral RNA detection and special considerations in urological conditions. *World J Urol.* 2021;39:3127-3138. [CrossRef]
37. Herrero Y, Pascuali N, Velázquez C, et al. SARS-CoV-2 infection negatively affects ovarian function in ART patients. *Biochim Biophys Acta Mol Basis Dis.* 2022;1868:166295. [CrossRef]
38. Li K, Chen G, Hou H, et al. Analysis of sex hormones and menstruation in COVID-19 women of child-bearing age. *Reprod Biomed Online.* 2021;42:260-267. [CrossRef]
39. Ding T, Wang T, Zhang J, et al. Analysis of Ovarian Injury Associated With COVID-19 Disease in Reproductive-Aged Women in Wuhan, China: An Observational Study. *Front Med (Lausanne).* 2021;8:635255. [CrossRef]
40. Bowman CJ, Bouressam M, Campion SN, et al. Lack of effects on female fertility and prenatal and postnatal offspring development in rats with BNT162b2, a mRNA-based COVID-19 vaccine. *Reprod Toxicol.* 2021;103:28-35. [CrossRef]
41. Yao XH, Luo T, Shi Y, et al. A cohort autopsy study defines COVID-19 systemic pathogenesis. *Cell Res.* 2021;31:836-846. [CrossRef]
42. Madendag IC, Madendag Y, Ozdemir AT. COVID-19 disease does not cause ovarian injury in women of reproductive age: an observational before-and-after COVID-19 study. *Reprod Biomed Online.* 2022;45:153-158. [CrossRef]
43. Dilbaz B. Are women with polycystic ovary syndrome more vulnerable to COVID-19 infection? *Turk J Obstet Gynecol.* 2021;18:221-223. [CrossRef]
44. Eftekhar M, Mirhashemi ES, Molaei B, Pourmasumi S. Is there any association between vitamin D levels and polycystic ovary syndrome (PCOS) phenotypes? *Arch Endocrinol Metab.* 2020;64:11-16. [CrossRef]
45. Jain T, Negris O, Brown D, Galic I, Salimgaraev R, Zhaunova L. Characterization of polycystic ovary syndrome among Flo app users around the world. *Reprod Biol Endocrinol.* 2021;19:36. [CrossRef]
46. de Medeiros SF, Yamamoto MMW, de Medeiros MAS, Yamamoto AKLW, Barbosa BB. Polycystic ovary syndrome and risks for COVID-19 infection: A comprehensive review : PCOS and COVID-19 relationship. *Rev Endocr Metab Disord.* 2022;23:251-264. [CrossRef]
47. Gotluru C, Roach A, Cherry SH, Runowicz CD. Sex, Hormones, Immune Functions, and Susceptibility to Coronavirus Disease 2019 (COVID-19)-Related Morbidity. *Obstet Gynecol.* 2021;137:423-429. [CrossRef]
48. Lew R. Natural history of ovarian function including assessment of ovarian reserve and premature ovarian failure. *Best Pract Res Clin Obstet Gynaecol.* 2019;55:2-13. [CrossRef]
49. Wilkins J, Al-Inizi S. Premature ovarian insufficiency secondary to COVID-19 infection: An original case report. *Int J Gynaecol Obstet.* 2021;154:179-180. [CrossRef]
50. Balcı S, Çöllüoğlu Ç, Yavuzer B, et al. Effect of low and high dose of favipiravir on ovarian and reproductive function in female rats: Biochemical and histopathological evaluation. *Gen Physiol Biophys.* 2022;41:457-463. [CrossRef]
51. Bellmunt-Montoya S, Riera C, Gil D, et al. COVID-19 Infection in Critically Ill Patients Carries a High Risk of Venous Thrombo-embolism. *Eur J Vasc Endovasc Surg.* 2021;61:628-634. [CrossRef]
52. Zabihi Mahmoudabadi H, Najjari K, Oklah E, Kor F. Ovarian vein and IVC thrombosis due to normal vaginal delivery; a case report and literature review. *Int J Surg Case Rep.* 2021;83:105975. [CrossRef]
53. DeBoer RE, Oladunjoye OO, Herb R. Right Ovarian Vein Thrombosis in the Setting of COVID-19 Infection. *Cureus*. 2021;13:e12796. [CrossRef]
54. Stevenson JC, Collins P, Hamoda H, et al. Cardiometabolic health in premature ovarian insufficiency. *Climacteric.* 2021;24:474-480. [CrossRef]
55. Ding WY, Gupta D, Lip GYH. Atrial fibrillation and the prothrombotic state: revisiting Virchow's triad in 2020. *Heart.* 2020;106:1463-1468. [CrossRef]
56. von Meijenfeldt FA, Havervall S, Adelmeijer J, et al. Prothrombotic changes in patients with COVID-19 are associated with disease severity and mortality. *Res Pract Thromb Haemost.* 2020;5:132-141. [CrossRef]
57. Gorog DA, Storey RF, Gurbel PA, et al. Current and novel biomarkers of thrombotic risk in COVID-19: a Consensus Statement from the International COVID-19 Thrombosis Biomarkers Colloquium. *Nat Rev Cardiol.* 2022;19:475-495. [CrossRef]
58. Lee SH, Lim CL, Shen W, et al. Activation function 1 of progesterone receptor is required for progesterone antagonism of oestrogen action in the uterus. *BMC Biol.* 2022;20:222. Erratum in: *BMC Biol.* 2023;21:34. [CrossRef]
59. Chadchan SB, Popli P, Maurya VK, Kommagani R. The SARS-CoV-2 receptor, angiotensin-converting enzyme 2, is required for human endometrial stromal cell decidualization†. *Biol Reprod.* 2021;104:336-343. [CrossRef]
60. Hur C, Rehmer J, Flyckt R, Falcone T. Uterine Factor Infertility: A Clinical Review. Clin Obstet Gynecol. 2019;62:257-270. [CrossRef]
61. Komine-Aizawa S, Haruyama Y, Deguchi M, et al. The vaccination status and adverse effects of COVID-19 vaccine among pregnant women in Japan in 2021. *J Obstet Gynaecol Res.* 2022;48:1561-1569. [CrossRef]
62. Saadedine M, El Sabeh M, Borahay MA, Daoud G. The influence of COVID-19 infection-associated immune response on the female reproductive system†. *Biol Reprod.* 2023;108:172-182. [CrossRef]
63. Khafaga A, Goldstein SR. Abnormal Uterine Bleeding. *Obstet Gynecol Clin North Am.* 2019;46:595-605. [CrossRef]
64. Wankhade A, Vagha S, Shukla S, et al. To correlate histopathological changes and transvaginal sonography findings in the endometrium of patients with abnormal uterine bleeding. *Journal of Datta Meghe Institute of Medical Sciences University.* 2019;14:11-15. [CrossRef]
65. Issakov G, Tzur Y, Friedman T, Tzur T. Abnormal Uterine Bleeding Among COVID-19 Vaccinated and Recovered Women: a National Survey. *Reprod Sci.* 2023;30:713-721. [CrossRef]
66. Jain V, Chodankar RR, Maybin JA, Critchley HOD. Uterine bleeding: how understanding endometrial physiology underpins menstrual health. *Nat Rev Endocrinol.* 2022;18:290-308. [CrossRef]
67. Muhaidat N, Alshrouf MA, Azzam MI, Karam AM, Al-Nazer MW, Al-Ani A. Menstrual Symptoms After COVID-19 Vaccine: A Cross-Sectional Investigation in the MENA Region. *Int J Womens* Health. 2022;14:395-404. [CrossRef]
68. Male V. Menstruation and covid-19 vaccination. BMJ. 2022;376:o142. [CrossRef]

69. Maher M, O' Keeffe A, Phelan N, et al. Female Reproductive Health Disturbance Experienced During the COVID-19 Pandemic Correlates With Mental Health Disturbance and Sleep Quality. *Front Endocrinol (Lausanne)*. 2022;13:838886. [CrossRef]
70. Wong KK, Heilig CM, Hause A, et al. Menstrual irregularities and vaginal bleeding after COVID-19 vaccination reported to v-safe active surveillance, USA in December, 2020–January, 2022: an observational cohort study. *The Lancet Digital Health*. 2022;4:e667-e675. [CrossRef]
71. Sharp GC, Fraser A, Sawyer G, et al. The COVID-19 pandemic and the menstrual cycle: research gaps and opportunities. *Int J Epidemiol*. 2022;51:691-700. [CrossRef]
72. Takmaz T, Gundogmus I, Okten SB, Gunduz A. The impact of COVID-19-related mental health issues on menstrual cycle characteristics of female healthcare providers. *J Obstet Gynaecol Res*. 2021;47:3241-3249. [CrossRef]
73. Lebar V, Laganà AS, Chiantera V, Kunič T, Lukanović D. The Effect of COVID-19 on the Menstrual Cycle: A Systematic Review. *J Clin Med*. 2022;11:3800. [CrossRef]
74. Bar-Zeev Y, Shauly M, Lee H, Neumark Y. Changes in Smoking Behaviour and Home-Smoking Rules during the Initial COVID-19 Lockdown Period in Israel. *Int J Environ Res Public Health*. 2021;18:1931. [CrossRef]
75. Valsamakis G, Chrousos G, Mastorakos G. Stress, female reproduction and pregnancy. *Psychoneuroendocrinology*. 2019;100:48-57. [CrossRef]
76. Li Z, Huang Y, Guo X. The brain, another potential target organ, needs early protection from SARS-CoV-2 neuroinvasion. Sci China Life Sci. 2020;63:771-773. [CrossRef]
77. Nicholson P, Alshafai L, Krings T. Neuroimaging Findings in Patients with COVID-19. *AJNR Am J Neuroradiol*. 2020;41:1380-1383. [CrossRef]
78. Gozdziewicz T, Jarzabek-Bielecka G, Luwanski D, et al. The Role of Visceral Therapy in the Sexual Health of Women with Endometriosis during the COVID-19 Pandemic: A Literature Review. *J Clin Med*. 2022;11:5825. [CrossRef]
79. Chan KK, Dorosky D, Sharma P, et al. Engineering human ACE2 to optimize binding to the spike protein of SARS coronavirus 2. *Science*. 2020;369:1261-1265. [CrossRef]
80. Butowt R, Bilinska K. SARS-CoV-2: Olfaction, Brain Infection, and the Urgent Need for Clinical Samples Allowing Earlier Virus Detection. *ACS Chem Neurosci*. 2020;11:1200-1203. [CrossRef]
81. Wan D, Du T, Hong W, et al. Neurological complications and infection mechanism of SARS-COV-2. *Signal Transduct Target Ther*. 2021;6:406. [CrossRef]
82. Soldevila B, Puig-Domingo M, Marazuela M. Basic mechanisms of SARS-CoV-2 infection. What endocrine systems could be implicated? *Rev Endocr Metab Disord*. 2022;23:137-150. [CrossRef]
83. Alquisiras-Burgos I, Peralta-Arrieta I, Alonso-Palomares LA, Zacapala-Gómez AE, Salmerón-Bárcenas EG, Aguilera P. Neurological Complications Associated with the Blood-Brain Barrier Damage Induced by the Inflammatory Response During SARS-CoV-2 Infection. *Mol Neurobiol*. 2021;58:520-535. [CrossRef]
84. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77:683-690. [CrossRef]
85. Tizenberg BN, Brenner LA, Lowry CA, et al. Biological and Psychological Factors Determining Neuropsychiatric Outcomes in COVID-19. *Curr Psychiatry Rep*. 2021;23:68. [CrossRef]
86. Ding T, Wang T, Zhang J, et al. Analysis of Ovarian Injury Associated With COVID-19 Disease in Reproductive-Aged Women in Wuhan, China: An Observational Study. *Front Med (Lausanne)*. 2021;8:635255. [CrossRef]
87. Stanton R, To QG, Khalesi S, et al. Depression, Anxiety and Stress during COVID-19: Associations with Changes in Physical Activity, Sleep, Tobacco and Alcohol Use in Australian Adults. *Int J Environ Res Public Health*. 2020;17:4065. [CrossRef]
88. Adelakun SA, Ukwenya VO, Peter AB, Siyanbade AJ, Akinwumiju CO. Therapeutic effects of aqueous extract of bioactive active component of Ageratum conyzoides on the ovarian-uterine and hypophysis-gonadal axis in rat with polycystic ovary syndrome: Histomorphometric evaluation and biochemical assessment. *Metabol Open*. 2022;15:100201. [CrossRef]
89. Bechmann N, Maccio U, Kotb R, et al. COVID-19 Infections in Gonads: Consequences on Fertility? *Horm Metab Res*. 2022;54:549-555. [CrossRef]
90. Liu C, Mu C, Zhang Q, Yang X, Yan H, Jiao H. Effects of Infection with SARS-CoV-2 on the Male and Female Reproductive Systems: A Review. *Med Sci Monit*. 2021;27:e930168. [CrossRef]
91. Conti P, Younes A. Coronavirus COV-19/SARS-CoV-2 affects women less than men: clinical response to viral infection. *J Biol Regul Homeost Agents*. 2020;34:339-343. [CrossRef]
92. Abramenko N, Vellieux F, Tesařová P, et al. Estrogen Receptor Modulators in Viral Infections Such as SARS-CoV-2: Therapeutic Consequences. *Int J Mol Sci*. 2021;22:6551. [CrossRef]
93. Zafari Zangeneh F, Sarmast Shoushtari M. Estradiol and COVID-19: Does 17-Estradiol Have an Immune-Protective Function in Women Against Coronavirus? *J Family Reprod Health*. 2021;15:150-159. [CrossRef]
94. Ricardo-da-Silva FY, Armstrong-Jr R, Vidal-Dos-Santos M, et al. Long-term lung inflammation is reduced by estradiol treatment in brain dead female rats. *Clinics (Sao Paulo)*. 2021;76:e3042.
95. Cunningham MA, Richard ML, Wirth JR, Scott JL, Eudaly J, Ruiz P, Gilkeson GS. Novel mechanism for estrogen receptor alpha modulation of murine lupus. *J Autoimmun*. 2019;97:59-69. [CrossRef]
96. Silva de Souza A, Rivera JD, Almeida VM, et al. Molecular Dynamics Reveals Complex Compensatory Effects of Ionic Strength on the Severe Acute Respiratory Syndrome Coronavirus 2 Spike/Human Angiotensin-Converting Enzyme 2 Interaction. *J Phys Chem Lett*. 2020;11:10446-10453. [CrossRef]
97. Mal'tseva VN, Goltyaev MV, Turovsky EA, Varlamova EG. Immunomodulatory and Anti-Inflammatory Properties of Selenium-Containing Agents: Their Role in the Regulation of Defense Mechanisms against COVID-19. *Int J Mol Sci*. 2022;23:2360. [CrossRef]
98. Costeira R, Lee KA, Murray B, et al. Estrogen and COVID-19 symptoms: Associations in women from the COVID Symptom Study. *PLoS One*. 2021;16:e0257051. [CrossRef]
99. Fedotcheva TA, Fedotcheva NI, Shimanovsky NL. Progesterone as an Anti-Inflammatory Drug and Immunomodulator: New Aspects in Hormonal Regulation of the Inflammation. *Biomolecules*. 2022;12:1299. [CrossRef]
100. Tsuda S, Nakashima A, Morita K, et al. The role of decidual regulatory T cells in the induction and maintenance of fetal antigen-specific tolerance: Imbalance between regulatory and cytotoxic T cells in pregnancy complications. *Hum Immunol*. 2021;82:346-352. [CrossRef]
101. Huang N, Chi H, Qiao J. Role of Regulatory T Cells in Regulating Fetal-Maternal Immune Tolerance in Healthy Pregnancies and Reproductive Diseases. *Front Immunol*. 2020;11:1023. [CrossRef]
102. Pinna G. Sex and COVID-19: A Protective Role for Reproductive Steroids. *Trends Endocrinol Metab*. 2021;32:3-6. [CrossRef]
103. Cattrini C, Bersanelli M, Latocca MM, Conte B, Vallome G, Boccardo F. Sex Hormones and Hormone Therapy during COVID-19 Pandemic: Implications for Patients with Cancer. *Cancers (Basel)*. 2020;12:2325. [CrossRef]
104. Lovre D, Bateman K, Sherman M, Fonseca VA, Lefante J, Mauvais-Jarvis F. Acute estradiol and progesterone therapy in hospitalised adults to reduce COVID-19 severity: a randomised control trial. *BMJ Open*. 2021;11:e053684. [CrossRef]
105. Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature*. 2020;583:459-468. [CrossRef]
106. Cedars MI. Evaluation of Female Fertility-AMH and Ovarian Reserve Testing. *J Clin Endocrinol Metab*. 2022;107:1510-1519. [CrossRef]
107. Soysal Ç, Yılmaz E. The effect of COVID-19 vaccine on ovarian reserve. *Saudi Med J*. 2022;43:486-490. [CrossRef]
108. Mohr-Sasson A, Haas J, Abuhasira S, et al. The effect of Covid-19 mRNA vaccine on serum anti-Müllerian hormone levels. *Hum Reprod*. 2022;37:534-541. [CrossRef]
109. Voultsos PP, Taniskidou AMI. Fertility treatment during the COVID-19 pandemic: A systematic review. *Afr J Reprod Health*. 2021;25:161-178. [CrossRef]
110. DSouza KN, Orellana M, Ainsworth AJ, Cummings G, Riggan KA, Shenoy CC, Allyse MA. Impact of the COVID-19 Pandemic on Patient Fertility Care. *J Patient Exp*. 2022;9:23743735221098255. [CrossRef]
111. Porcu E, Tranquillo ML, Notarangelo L, et al. High-security closed devices are efficient and safe to protect human oocytes from potential risk of viral contamination during vitrification and storage especially in the COVID-19 pandemic. *J Assist Reprod Genet*. 2021;38:681-688. [CrossRef]
112. Souza MDCB, Nakagawa H, Taitson PF, Cordts EB, Antunes RA. Management of ART and COVID-19: Infertility in times of pan- demic. What now? *JBRA Assist Reprod*. 2020;24:231-232. [CrossRef]

113. Setti PEL, Cirillo F, Immediata V, et al. First trimester pregnancy outcomes in a large IVF center from the Lombardy County (Italy) during the peak COVID-19 pandemic. *Sci Rep.* 2021;11:16529. **[CrossRef]**
114. Adiga SK, Tholeti P, Uppangala S, Kalthur G, Gualtieri R, Talevi R. Fertility preservation during the COVID-19 pandemic: mitigating the viral contamination risk to reproductive cells in cryostorage. *Reprod Biomed Online.* 2020;41:991-997. **[CrossRef]**
115. Ata B, Vermeulen N, Mocanu E, et al. SARS-CoV-2, fertility and assisted reproduction. *Hum Reprod Update.* 2023;29:177-196. **[CrossRef]**
116. Vakili S, Savardashtaki A, Parsanezhad ME, et al. SARS-CoV-2 RNA in Follicular Fluid, Granulosa Cells, and Oocytes of COVID-19 Infected Women Applying for Assisted Reproductive Technology. *Galen Medical Journal.* 2022;11:e2638-e. **[CrossRef]**
117. Kong S, Yan Z, Yuan P, et al. Comprehensive evaluation of ACE2 expression in female ovary by single-cell RNA-seq analysis. *BioRxiv.* 2021. **[CrossRef]**
118. Boudry L, Essahib W, Mateizel I, et al. Undetectable viral RNA in follicular fluid, cumulus cells, and endometrial tissue samples in SARS-CoV-2-positive women. *Fertil Steril.* 2022;117:771-780. **[CrossRef]**
119. Entezami F, Samama M, Dejucq-Rainsford N, Bujan L. SARS-CoV-2 and human reproduction: An open question. *EClinicalMedicine.* 2020;25:100473. **[CrossRef]**
120. Wu J, Zhang P, Zhang L, et al. Rapid and accurate identification of COVID-19 infection through machine learning based on clinical available blood test results. *MedRxiv.* 2020. **[CrossRef]**
121. Domińska K. Involvement of ACE2/Ang-(1-7)/MAS1 Axis in the Regulation of Ovarian Function in Mammals. *Int J Mol Sci.* 2020;21:4572. **[CrossRef]**
122. Orvieto R, Noach-Hirsh M, Segev-Zahav A, Haas J, Nahum R, Aizer A. Does mRNA SARS-CoV-2 vaccine influence patients' performance during IVF-ET cycle? *Reprod Biol Endocrinol.* 2021;19:69. **[CrossRef]**
123. Colaco S, Chhabria K, Singh D, et al. A single-cell RNA expression map of coronavirus receptors and associated factors in developing human embryos. arXiv preprint. arXiv:200404935. 2020. **[CrossRef]**
124. Requena A, Cruz M, Vergara V, Prados N, Galliano D, Pellicer A. A picture of the covid-19 impact on IVIRMA fertility treatment clinics in Spain and Italy. *Reprod Biomed Online.* 2020;41:1-5. **[CrossRef]**
125. Oguejiofor CF, Thomas C, Cheng Z, Wathes DC. Mechanisms linking bovine viral diarrhea virus (BVDV) infection with infertility in cattle. *Anim Health Res Rev.* 2019;20:72-85. **[CrossRef]**