The Pathophysiology of COVID-19 and SARS-CoV-2 Infection

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Abstract

The outcomes of coronavirus disease 2019 (COVID-19) vary between men and women. Some statistical reports have shown that men have a higher risk of developing COVID-19 and suffer from worse outcomes than females. Although there are many factors that can explain the high prevalence of COVID-19 in men, such as lifestyle habits and the different profile of comorbidities among sexes, the distinctions between male and female immune systems cannot be ignored. It has been sufficiently shown that sex differences have a critical influence on the shaping of immune response, which then leads to different pathogenesis in infectious diseases. Compared with males, females typically have a more effective innate and adaptive immune response to viral infections in COVID-19. What's more, there is a growing body of evidence showing that estrogen exerts an effect on the regulation of immune response. This article examines the effect and mechanism of estrogen on COVID-19.

COVID-19; estrogen; immune response; SARS-CoV-2; sex difference

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a major public health crisis (1). One report published in The Lancet indicates that the median age of patients with COVID-19 is 56 yr and the proportion of male patients is 62% (2). Unhealthy habits such as smoking, drinking, and circadian misalignment have been found to be more common in men and such behaviors could make the lungs and other organs of men more susceptible to damage (3–5). Furthermore, men may have higher risks of suffering from potential illnesses, including high blood pressure, cardiovascular disease, and chronic lung disease (6). In addition, it is worth noting that there are distinctions between the immune systems of men and women (7). There is increasing evidence that the prevalence (the number of infected individuals in the population) and intensity (the amount of viral load within individuals) of viral infections vary between men and women (8). Some studies have demonstrated that biological sex differences can lead to different immune responses after infection. Compared with men, women are generally less susceptible to viral infections because they have a more effective immune response (9, 10). Men and women have different innate recognition and downstream adaptive immune responses during viral infection (11). So the outcomes of COVID-19 vary between men and women which can be explained by sex differences in immune responses. What’s more, estrogen plays an important role in the female immune response.

In this review, existing studies on COVID-19 related to sex differences are summarized. In addition, the effects of estrogen against viral infection, as well as its beneficial impact on the immune system, are focused on. This review explains the effect of estrogen on COVID-19 from the perspective of the positive impact of estrogen on the immune system because of the lack of direct evidence and research on the effect of estrogen in COVID-19.

SEX DIFFERENCES IN COVID-19

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has led to the COVID-19 pandemic (12). A recent study showed that men accounted for 58% of the 13,882 confirmed cases under investigation and 72% of the 803 deaths. Furthermore, the mortality rate of males was 75% higher than that of females in hospitalized patients with COVID-19 (13). Data compiled from Europe showed a male-to-female ratio of 1.5 for COVID-19 hospitalizations and of 1.7–1.8 for COVID-19 case fatality rates (6). An Iranian report indicated that males constituted the majority of the 2,964 confirmed cases of COVID-19 (66%) and that the ratio of males to females was 1.93 to 1. Of the 239 deaths examined in the study, 167 occurred in males and 72 in females, with case fatality rates (CFRs) of 8.54% and 7.13% for men and women, respectively (14). Another study revealed that 12.8% of 86 male patients with severe COVID-19 (11/86) had died and 75.6% (65/86) had been discharged from hospitals, whereas 7.3% of the 82 female patients (6/82) had died and 86.6% (71/
20) had been discharged from hospitals (15). In addition, the fact that deaths from severe COVID-19 are related to the male sex has been also confirmed by a survival analysis of 548 severe patients (16). In the UK COVID Symptom Study, data from more than 2.5 million users of the COVID Symptom Tracker App further confirmed that men with COVID-19 were more likely than women to need respiratory support (odds ratio: 2.14 [95% confidence interval (CI): 1.72–2.66]) (4). Finally, a study that analyzed 19 databases and 45 publications indicated that hospitalization rates were higher for males than for females in all reported countries, ranging from 55% to 62%. In addition, the likelihood of men entering the ICU was even higher, ranging from 65% to 74%, and male mortality rates were also higher than female mortality rates, ranging from 59% to 69%. Most (but not all) early publications from China reported that men presented to the hospital three times more often with prolonged SARS-CoV-2 RNA shedding and had twice the risk of developing kidney disease, as well as more frequent refractory pneumonia and metabolic associated fatty liver disease (MAFLD). In addition, men showed higher risk of increased disease severity as well as increased risk for the development of complications and mortality (17). A sex bias in COVID-19 mortality has to date been reported in 37 of the 38 countries that have provided sex-disaggregated data (4, 18). Mounting evidence confirms that women show lower prevalence and mortality (19–23). However, another report showed that the advantages of the female sex for COVID-19 were lost after menopause. If the male death rate is considered equal to 100%, the female death rate is 27.8% of this (~72.2%) for ages 20–59 yr and 50.6% of this (~49.4%) for ages 60–89 yr (24).

Studies that have examined other pathogenic coronaviruses (CoV) including severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) have also shown this sex-dependent pattern (25). One study found that the morbidity and mortality rate of male patients after SARS-CoV infection was higher than that of female patients (male infection rate 62%, female 38%; male mortality 52%, female 23%) (26). The advantages, however, disappeared for the lower incidence of coronavirus infection and mortality in women over 70 yr of age (27).

**Mechanism of Estrogen in COVID-19**

Estrogen is a hormone with a wide range of regulatory effects that are closely related to the development of the immune system as well as the occurrence of infectious diseases, autoimmune diseases, and tumors; therefore, it has attracted much attention. A large number of studies have shown that the body’s susceptibility and immune response to viruses can be modified by estrogen. Estrogen can directly inhibit SARS-CoV replication by regulating cell metabolism, which can protect mice from viral infection. Furthermore, gonadectomy or antiandrogen therapy in male mice infected with SARS-CoV did not affect morbidity or mortality, suggesting that a lack of androgen does not affect the immune response (25). Influenza A virus (IAV) mouse experiments have shown that estrogen treatment can reduce morbidity and mortality caused by the infection (42, 43). Female mice receiving high levels of estrogen have been reported to have increased survival and lower cytokine production in the lungs after influenza infection (43, 44). Adult female mice exhibit a stronger innate immune response and a more sensitive influenza-specific antibody response than male mice during influenza virus infection. This is because AT1R pathway induces pulmonary vasoconstriction and microvascular damage with increased vascular permeability, resulting in enlarged and “leaky” pulmonary microvessels and damaged alveoli filled with plasma proteins (33). The lung disease following SARS-CoV-2 infection can frequently cause interstitial pneumonia and evolve into pulmonary fibrosis. The broad tissue expression of ACE2 further enables SARS-CoV-2 to spread to other tissues, resulting in multiorgan failure accompanied by vasoocclusion, enhanced coagulation and impairment of vital functions (34). After entering the host cell, viral RNA is recognized by Toll-like receptors (TLR3, TLR7, TLR8), retinoic acid-induced gene protein I (RIG-I), and melanoma differentiation-associated gene 5 (MDA5) (35, 36). These complex signal molecule recruitment adaptors (such as IFN-β, MAVS, and STING) trigger downstream cascade molecules and induce the activation of nuclear factor κB (NF-κB) and interferon regulatory factor 3 (interferon regulatory factor 3; IRF3) as well as the production of interferon IFN-α/β and a series of inflammatory cytokines. Among them, NF-κB promotes the transcription of proinflammatory cytokines (such as TNF-α, IL-1β, and IL-6), further triggers the Th1 and Th17 inflammatory responses, and subsequently secretes IFN-γ and IL-17 (37). Therefore, the interaction of viruses and cells makes the body’s immune system produce a variety of immune media against invading viruses. Some plasma cytokines and chemokines that have been observed to be increased in patients with COVID-19 included IL-1, IL-2, IL-7, IL-12, IL-13, IL-17, GCSF, M-CSF, IP-10, MCP-1, MIP-1α, HGF, IFN-γ, and TNF-α (38, 39). In critically ill patients, neutrophil counts, D-dimer, urea, and creatinine typically increase significantly and lymphocyte counts continue to decline. In addition, inflammatory factors such as IL-6 and TNF-α are augmented as well (40). The levels of IL-2, IL-7, IL-10, GCSF, IP-10, MCP-1, MIP-1α, and TNF-α in the plasma are higher in patients transferred to intensive care units (ICUs) than in patients with mild symptoms (41).
there exist more virus-specific memory T cells in their lungs, and thus they are better protected from secondary immune attacks (45, 46). In addition, estrogen can inhibit the replication of influenza virus in nasal epithelial cells and upregulate the estrogen receptor signaling pathway at the same time. Estrogen can also help maintain cell integrity through genetic modification and improve metabolic function (47). It has long been recognized that estrogen plays a role in the immune response to infection and that it regulates the innate immune system (monocytes/macrophages, granulocytes, natural killer cells, dendritic cells) and the adaptive immune system (T and B cells) (48).

**ACE2.**

ACE2 has been identified as a receptor for SARS-CoV-2, which is the key to the virus entering the body. SARS-CoV-2 infects human airways and enters cells by binding its S protein envelope to ACE2 after S protein priming by host serine protease TMPRSS2 (49). The distribution and expression of ACE2 is crucial for the target organs infected by SARS-CoV-2 because SARS-CoV-2 must be bound to ACE2 before entering human host cells (50). ACE2 is abundantly expressed on the cell surface of alveolar type II epithelial cells (type II pneumocytes), which are small cylindrical cells very close to pulmonary capillaries and responsible for the synthesis of alveolar surfactant. ACE2 is also widely expressed in other airway cells, from the epithelial cells of the oral mucosa to bronchial transient secretory cells (31, 51, 52). Therefore, the SARS-CoV-2 infection of pneumocytes, the hallmark of the COVID-19 involving both alveolar interstitium and capillaries, is linked to ACE2 binding and its functional downregulation (32). Some reports have indicated that circulating levels of ACE2 are higher in healthy and diabetic men, as well as in men with renal disease, compared with women (10). Studies have demonstrated that ACE2 expression is lower in the lung tissues of women compared with men (53). The expression of the ACE2 protein is different between males and females, which might contribute to the sex disparity in morbidity and mortality rates from the COVID-19 disease (31). It has been suggested that estrogen-related receptor (ERR) binding fragments exist in the promoter region of ACE2, and ERR inhibits the expression of the ACE2 gene (54). Estrogen treatment in rats after bilateral ovariectomy has been found to significantly reduce the expression of ACE2 (55). A recent study has also shown that the mRNA expression level of ACE2 is low in normal human bronchial epithelial cells treated with estrogen (56). These findings indicate that estrogen can regulate the expression of the SARS-CoV-2 receptor ACE2. However, ACE2 is also a key enzyme for the balance between the two main arms of the RAS: the ACE/angiotensin (ANG) II/ANG II type 1 receptor axis (“classic RAS”) and the ACE2/Ang(1–7)/Mas receptor (MasR) axis (“anti-RAS”) (32). The lung disease following SARS-CoV-2 infection can evolve into pulmonary fibrosis (57). The evolution of alveolar exudation from damaged and leaky capillaries can lead to extensive fibrosis due to secondary hyperstimulation of local fibroblasts, which is believed to be driven by ANG II/AT1R (32). A decrease in ACE2 activity leaves the effects of the ANG II/AT1R axis unopposed, whereas increased ACE2 activity leads to the activation of both the Ang(1–7)/MasR and alamandine-MrgD pathways and possibly the Ang(1–9)-AT2R axis. This would contribute to protecting against microvascular damage due to its antifibrotic and anti-inflammatory activities (58). It has been reported that sex differences in renal ACE2 activity in mice are in part due to estrogen and are not due to the testicular milieu or to differences in sex chromosome dosage (59). Another study showed that estrogenic activity decreases the vascular response [vasoconstriction and NAD(P)H oxidase activation] to ANG II and facilitates the action of ACE2/Ang(1–7) in animal models (60). In addition, estrogen increases angiotensinogen, AT2 receptors, and Ang(1–7) but decreases renin levels, ACE activity, AT1 receptor density, and aldosterone (60–62). The effect of estrogen on ACE2 remains to be further studied.

**Innate immune response.**

From an immunological perspective, SARS-CoV-2 causes an increase in Th1 cytokine interferon (IFN-γ), inflammatory cytokines (IL-1, IL-6, and IL-12), and other related cytokines, as well as chemotactic factor (IL-8, CCL2, MCP-1, CXCL10, and IP-10) in the most severe cases (63). These inflammations and “cytokine storms” activate monocytes/macrophages and neutrophils, which can lead to multiple organ failure, ARDS, and disseminated intravascular coagulation (64). Monocyte chemoattractant protein 1 (MCP-1) is considered to be an initiator of the inflammatory response because it can induce and regulate the formation and release of other inflammatory factors, which forms a cascade reaction and mediates the inflammatory response. According to current research results, serum MCP-1 in perimenopausal and menopausal women is significantly higher than in women of childbearing age (65). In addition, estrogen therapy in ovariectomized animals is capable of reducing the expression of MCP-1 in the blood and the infiltration of white blood cells into injured tissues (such as arteries and lungs) (66, 67). The bronchoalveolar lavage fluid in patients with severe COVID-19 is rich in proinflammatory monocyte-derived macrophages (68, 69). Monocytes/macrophages can cause large-scale inflammatory reactions in the later stages of COVID-19, and uncontrolled production of proinflammatory mediators leads to acute respiratory distress syndrome (ARDS) and cytokine storm syndrome (70). IL-6, IL-1β, and IFN-1/III from infected pulmonary epithelia can induce inflammatory programs in resident (alternate) macrophages while recruiting inflammatory monocytes, granulocytes, and lymphocytes from the circulation (71). Estrogen treatment of human macrophages in vitro can inhibit the NF-κB signaling pathway and the production of IL-6 and TNF-α (72). Furthermore, at the physiological level, estradiol has been shown to reduce CCR2 and CXCR3 expression in mouse monocytes in vivo, which indicates that estrogen receptor signaling may reduce the recruitment of monocytes to tissues (73). The anti-inflammatory actions of estrogen on innate immunity includes the suppression of the production of proinflammatory cytokines, including IL-6, IL-1β, and TNF-α, by monocytes and macrophages (a major factor in the COVID-19 cytokine storm) and a strong inhibition of CCL2. This prevents the migration of innate immune cells, particularly neutrophils and monocytes, into inflamed areas (74). Estrogen can induce the expression of anti-inflammatory cytokines (IL-4 and IL-10) to exert anti-inflammatory effects.
In addition, high concentrations of estrogen have been reported to upregulate the estrogen receptor signaling pathway, silence the "cytokine storm," and eliminate the accumulation of inflammatory cells (25, 43). Therefore, it can be speculated that a loss of estrogen can promote an excessive inflammatory immune response to SARS-CoV-2 infection, and estrogen treatment can quench the inflammatory response.

Eosinophils contain and produce antiviral molecules and participate in adaptive immunity, which is typically recognized as the actions of antigen-presenting cells against viruses. An eosinophil count beneath the normal level may be a biomarker for COVID-19 diagnosis (76). Estrone can regulate the number of eosinophils and increase the migration, adhesion, survival, and degranulation of eosinophils in vitro and in vivo (73, 77). One relevant line of investigation has explored the ability of estrogen pretreated dendritic cells (DCs) to activate T cells (78).

**Adaptive immune response.**

*T lymphocytes.* According to existing reports, the common feature of most patients with COVID-19 is T lymphopenia, which is particularly prominent in critically ill patients. Therefore, lymphocyte levels can be used as indicators to predict the severity and prognosis of patients with COVID-19 (69). Estradiol can affect the growth of thymus tissue cells and promote the differentiation of extrathymic T cells (79). The phenomenon that circulating T lymphocytes are more abundant in women of childbearing age than in men can also be observed in other female mammals, indicating that the common feature of different species is that females have a faster and more effective immune response than males (80, 81). The decrease of estrogen in menopausal women has a noticeable effect on the relative and absolute number of T-lymphocyte subsets. In addition, estrogen changes the peripheral blood T-lymphocyte subsets through the sex hormone receptor pathway to transmit relevant information to the immune system (82, 83). At the tissue level, estrogen depletion appears to enhance the production of TNF-α by T lymphocytes, which is especially relevant at the bone marrow level (84). It can be speculated that estrogen could eliminate SARS-CoV-2 by increasing T lymphocytes.

The maintenance of normal immune function depends on moderate lymphocyte apoptosis and the Th1/Th2 balance of helper T cells. Th1 and Th2 are an important pair of regulatory cells. However, they are mutually inhibiting cells because the interferon IFN-γ secreted by Th1 cells can inhibit the differentiation and function of Th2 cells, whereas interleukin-4 (IL-4) from Th2 cells can also inhibit the differentiation and function of Th1 cells (85). The pathogenesis of COVID-19 is complex, but it is characterized by the Th1/Th17 immune response. Excessive activation of these cells may lead to the release of proinflammatory cytokines that can then leave the lungs damaged (86). The predominant Th2-type immunity and the action of Tregs can play an important role in preventing the excess systemic inflammatory reaction and the development of life-threatening complications, such as cytokine storm, and eliminate the accumulation of inflammatory immune response to SARS-CoV-2 infection.

### Table 1. Ongoing clinical trials of estrogen and hormone therapies in COVID-19

| Study ID  | Title                                                                 | Treatment                      | Population                      | Estimated Enrollment | Phase | Primary Outcome Measures                                                                 | Estimated Completion Date |
|----------|-----------------------------------------------------------------------|--------------------------------|---------------------------------|----------------------|-------|------------------------------------------------------------------------------------------|----------------------------|
| NCT04359329 | Estrogen Patch for COVID-19 Symptoms                                  | Estradiol patch                | Male ≥ 18 yr; Female ≥ 55 yr    | 110                  | 2     | Rate of hospitalization, rate of transfer to intensive care unit, rate of intubation, rate of death | 11/2020                    |
| NCT04539626 | Estrogen Therapy in Non-severe COVID-19 Patients                      | Ethinyl estradiol              | Male ≥ 18 years, female ≥ 55 years | 60                   | No    | Clinical improve to estrogen therapy in nonsevere patient with COVID-19                   | 12/2020                    |
| NCT04531748 | Selective estrogen modulation and melatonin in early COVID-19         | Toremifene plus Melatonin      | Age ≥ 18 yr, COVID-19            | 390                  | 2     | Peak increase in COVID-19 Sign and Symptom score of 2–8                                 | 09/2021                    |
| NCT04397718 | Hormonal Intervention for the Treatment in Veterans With COVID-19 Requiring Hospitalization | Degarelix                      | Male Veterans, Age 18 and 85 yr | 198                  | 2     | Mortality, ongoing need for hospitalization, or requirement for mechanical ventilation/extracorporeal membrane oxygenation (ECMO) | 07/2021                    |
| NCT04374279 | Trial to Promote Recovery From COVID-19 With Endocrine Therapy        | Bicalutamide                   | ≥ 18 yr of age                  | 60                   | 2     | Percentage of participants who have clinical improvement at day 7                        | 01/2022                    |
| NCT04389580 | Combination therapy with isotretinoin and tamoxifen expected to provide complete protection against severe acute respiratory syndrome coronavirus | Isotretinoin plus tamoxifen    | Severe respiratory failure within 48 h and requires admission to intensive care unit (ICU) | 160     | 2     | Lung injury score                                                                       | 08/2020                    |
as ARDS and MODS, in patients with COVID-19 (87). Studies have shown that an increase in Th1 cytokines in women after menopause is related to ovarian dysfunction (88), which indicates that low estrogen levels can cause Th1/Th2 imbalance in the body, favoring Th1. Estrogen therapy can reduce the secretion of the Th1-type cytokine IFN-γ in menopausal women, thereby correcting the Th1/Th2 imbalance, which in turn promotes antibody production and participation in humoral immunity. In addition, estrogen treatment can promote the secretion of Th2-type cytokine IL-4 to enhance the body’s ability to fight against infections by extracellular microorganisms (89). These findings suggest that estrogen could inhibit Th1 cells and generate a Th2 immune response to offset the symptoms and severity of COVID-19.

Regulatory T cells (Tregs) play a critical role in suppressing excessive immune responses caused by pathogens, cancer cells, and transplanted organs and control autoimmune development. Treg cells can limit lung function immunopathology in respiratory virus infections. A decrease in the number of Treg cells has also been observed in patients with COVID-19 (76), and excessive activation of the immune response is one of the causes of lung immunopathology in patients with COVID-19 (37). Nevertheless, estrogen can promote the expansion of Treg cells and upregulate the expression of FoxP3 and CTLA-4 (75, 90).

**B lymphocytes.** B cells can directly recognize the SARS-CoV-2 virus and be activated by it. They can also interact with CD4+ T cells to resist the virus. In addition, plasma cells that have differentiated from B cells can produce SARS-CoV-2-specific antibodies that are capable of neutralizing the virus (39). The ability of women to produce more elevated circulating levels of antibodies than men has been known for many decades (78). B cells have been shown to be reduced and proinflammatory cytokines (TNF-α, IL-1β, IL-2, and IL-6) have been shown to be increased in postmenopausal women and those with low estrogen because of surgical removal of the ovaries (91, 92). Estrogen can affect the development of B cells at different stages and modify humoral immunity (93). Furthermore, estrogen can also stimulate plasma cells to produce immunoglobulins, regulate the maturity of B cells, upregulate the expression of mediators that affect the survival of B cells (such as CD22, SHP-1, and Bcl-2), and downregulate mediators that promote B cell apoptosis (such as PD-1) (94, 95). These findings suggest that estrogen could eliminate SARS-CoV-2 by regulating B lymphocytes.

**Thrombosis.** COVID-19 may predispose patients to thrombotic disease, in both the venous and arterial circulations, because of excessive inflammation, platelet activation, endothelial dysfunction, and stasis (96). When dysfunctional, the endothelium promotes inflammation, prothrombotic factors, and vasoconstriction. Reports show that E2, when bound to either classical E2 receptors (ERs) or G-protein-coupled ER (GPR30), can help maintain endothelial homeostasis and vasodilation by activating the transcription of eNOS and subsequent upregulation of NO through genomic and non-genomic pathways (97). A chronic high physiological level of estradiol (E2) in mice leads to a marked decrease in platelet responsiveness ex vivo and in vivo compared with

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**Figure 1.** The effect of estrogen in COVID-19. An illustrative summary of the effect of estrogen in COVID-19. Estrogen could control infection and eliminate pathogens by regulating ACE2, innate immune response, cytokines, adaptive immune response, and thrombosis.
ovariectomized controls. In addition, E₂ treatment has been shown to modulate the expression of platelet proteins, including β₁ tubulin and a few other proteins, that may impact platelet production and activation. In vitro, estradiol is able to inhibit platelet aggregation by promoting Ca²⁺ extrusion or reuptake activity, and its action is dependent on an increase in NO synthesis (98). E₂ treatment has been show to lead to resistance to thromboembolism (99).

### CLINICAL TRIALS

As the COVID-19 pandemic has spread, it has been observed that adult men of all ages and older women are at higher risk of developing serious complications from infection with the virus. Indeed, in response to the urgency of the COVID-19 health crisis, sex-based treatment options in patients with COVID-19, including the use of estrogen, estrogen antagonists, and androgen antagonists (NCT04359329, NCT04539626, NCT04531748, NCT04397718, NCT04374279, and NCT04389580), are currently being tested and planned (Table 1; 53). There has been already an ongoing phase II clinical trial of estradiol to reduce the severity of COVID-19 infection in patients who are COVID-19 positive or presumptive COVID-19+ (NCT04359329). The purpose of this study (NCT04359329) is to find if estrogen given as a patch placed on the skin of patients who are COVID-19 positive or presumptive positive for 7 days can reduce the severity of COVID-19 symptoms compared with regular care. This review explains the effect of estrogen on COVID-19 from the perspective of the positive impact of estrogen on the immune system, which provides a theoretical basis for clinical research. A critical advantage of estrogen is the depth of knowledge regarding its clinical efficacy and toxicity that has been accumulated from decades of clinical and basic studies. It is widely available in hospitals, inexpensive, and manufacturable to scale. However, the dosage, duration of exposure, and method of administration of estrogen in clinical research are worth considering and exploring.

### CONCLUSIONS

Estrogen can produce a more effective innate immunity, humoral immunity, and cellular immunity in response to viral infections. In this review, the sex differences in COVID-19 infections were found to be associated with the effects of estrogen on the immune response. Furthermore, this review described the effects of estrogen on antiviral immunity and on the immune response to the SARS-CoV-2 virus (Fig. 1). Future research should continue to consider the relationship between estrogen and the immune response, and whether women or men should use exogenous hormones (such as estrogen replacement therapy) when infected. Finally, it is recommended that clinicians, epidemiologists, and basic biomedical scientists who interpret data on the pathogenesis of COVID-19 should consider the effects of estrogen on the immune responses of patients or animals.

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### DISCLOSURES

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### AUTHOR CONTRIBUTIONS

Q.M. and Z.-W.H. drafted manuscript; Q.M., Z.-W.H. and Y.-F.W. edited and revised manuscript; Q.M. and Y.-F.W. approved final version of manuscript.

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