



Hormone Therapy in the Era of the COVID-19 Pandemic: A Review

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The coronavirus disease 2019 (COVID-19) pandemic has impacted the medical, social, and reproductive health of millions of people since its outbreak. The causative virus transmits, reproduces, and manifests through the respiratory tract. COVID-19 can invade any system of the body, including the cardiovascular and endocrine systems, through a secondary immune response. In particular, because the fatality rate is high in those over the age of 50 years, special attention is required during the medical care of this population. However, considering the benefit of therapy and the risk of COVID-19, high-quality evidence regarding individualized management in relation to hormone therapy is still insufficient in the field of gynecology. Furthermore, this review aims to serve as a reference for clinical application by analyzing and summarizing the results of studies reported to date regarding female hormone therapy in the context of the COVID-19 pandemic.

Key Words: Contraceptives, COVID-19, Hormone therapy, Vaccine

INTRODUCTION

As of May 2, 2022, the World Health Organization (WHO) reported a total of 4.37 billion severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection cases worldwide and 5.96 million deaths directly associated with coronavirus disease 2019 (COVID-19), since its first case reported in December 2019. Taking under-reporting into account, the actual number of deaths is estimated to be 2 to 4 times the count [1]. As the Omicron variant of SARS-CoV-2 has been emerged as dominant species, the pattern of outbreak continues to change, and there still remains a possibility that the pandemic will develop into a new way.

SARS-CoV-2 is transmitted through the respiratory tract (Fig. 1). Usually an immune response is induced from the affected lung tissue, resulting in a remission of the infection. However, in some patients, an excessive

immune response known as a cytokine storm occurs, which damages multiple organs throughout the body, including the cardiovascular system. This reportedly occurs more frequently in elderly patients or patients with underlying diseases [2].

From early epidemiologic studies, the infection fatality ratio showed a distinct pattern of consistent increase with aging, especially after the age of 60 [3]. In addition to age, sex was also noted as an important prognostic factor. In fact, differences in the disease course according to sex have been pointed out in the coronavirus outbreak (SARS) in the early 2000s and middle east respiratory syndrome (MERS) in the mid-2010s [4]. In the case of COVID-19, there was a report that the severity differs depending on the expression level of the sex hormone receptor, drawing attention to the role of sex hormones [5].

Although menopausal hormone therapy can ef-

Received: December 17, 2021 Revised: March 12, 2022 Accepted: March 13, 2022

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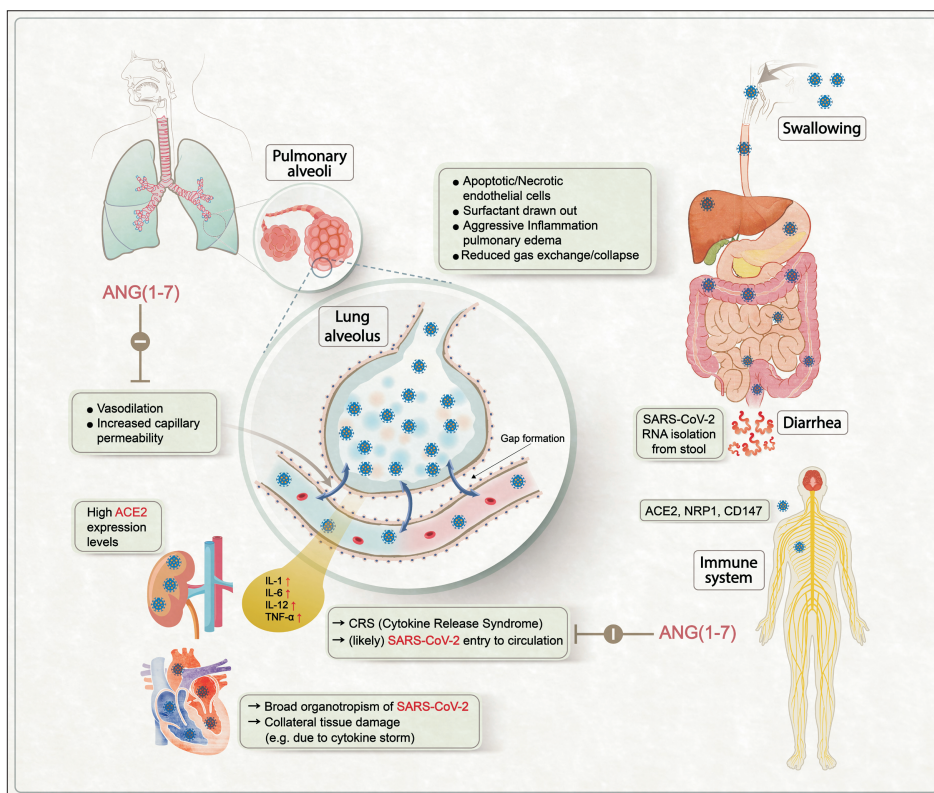


Fig. 1. The mechanism of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) penetration into the body. ANG: angiotensin, ACE2: angiotensin-converting enzyme 2, IL: interleukin, TNF- α : tumor necrosis factor- α , NRP1: neuropilin 1.

fectively control menopause symptoms and prevent related complications, a public objection stands due to safety issues in past large-scale studies related to subject selection. Since the 2000s, < 20% of women in their 50s in Korea received hormone therapy [6]. Despite the very low risk of adverse effects from hormone therapy on carefully selected patients, a survey by the Korean Menopause Society in 2020 showed that more than 75% of respondents still had concerns about the undesired effects.

Besides alleviating menopausal symptoms, female hormones also have physiologic effects such as maintaining homeostasis [7] and modulating immune system [8], and reducing all-cause mortality [9]. There have been studies on pathophysiological and clinical implication in the COVID-19 pandemic. In this review, the authors explored the study results and organization or society recommendations suggested so far to summarize the understanding of the pathophysiology of COVID-19 in relation to female sex hormones and to delineate the potential roles and considerations of female hormone therapy in the COVID-19 pandemic situation.

THE PATHOPHYSIOLOGY BETWEEN FEMALE HORMONES AND COVID-19

There are several reports that indirectly reflect the role of female hormones in COVID-19 disease course. A study conducted in China found that younger women were less severe than younger men, while this gender difference decreased after menopause [10]. A study from Canada also showed that female, especially of reproductive age, had less severe outcomes when several risk factors were adjusted [11]. Similarly, a recent prospective study based on Korea Disease Control and Prevention Agency (KDCA) revealed that in-hospital mortality of female was lower than that of male [12]. These results suggested the possibility of the protective effect of female hormones on disease course of COVID-19. In a related study, estradiol therapy showed no difference in the fatality rate in premenopausal women, whereas in postmenopausal women, the fatality rate of patients on menopausal hormone therapy was lower than women who did not receive menopausal hormone therapy with a hazard ratio of 0.29 [13].

Conversely, there have also been studies investigating the effect of COVID-19 on ovarian function. One

found no significant difference in serum anti-Müllerian hormone level between women of reproductive age with COVID-19 and their age-matched controls [14]. However, after being infected with COVID-19, significant proportion of premenopausal women complained of menopausal symptoms such as hot flush along with changes in the menstrual cycle even after the acute phase, which is presumed to be partly related to disturbances in female hormones production [15].

Among various factors possibly associated with sex difference in severity of COVID-19, female sex hormones seem to play an important role. Estradiol has been well known for its function as an immune modulator [16]. The receptors are distributed not only in the reproductive organs but also in tissues throughout the body, implying that estrogen has systemic functions beyond sex hormones. Particularly in relation to COVID-19, estradiol has recently been shown to act on its receptors α and β , respectively, to inhibit pro-inflammatory cytokine production and cytotoxic T cell activity, and to directly promote production of neutralizing antibody against SARS-CoV-2 (Fig. 2) [17]. Therefore, estrogen may contribute to inducing a healing process rather than systematic inflammation through immunomodulation (Fig. 3).

In addition, the gene encoding the ACE2 receptor, which is the route of entry for SARS-CoV-2, is present on the X chromosome [18], while estradiol helps regulate the expression of ACE2 receptor [19]. Although the

physiologic role of ACE2 has not been entirely elucidated, it has been known to have an anti-inflammatory, vasodilatory effect [20]. This can partly explain why the severity of the COVID-19 is lower in female than male despite the incidence of COVID-19 is higher [21]. SARS-CoV-2, after entering to host cell via the ACE2 receptor, downregulates the expression of ACE2 receptor [22], resulting in pro-inflammatory condition of infected host. Again at this point, estradiol promotes ACE2 expression, thereby alleviating the course of COVID-19 [23].

On the molecular level, some researchers also suggested Toll-like receptor (TLR) 7 as one of the key to explain the sex bias [24]. TLR7, encoded on the X chromosome, recognizes single strand RNA derived from the virus and mediates downstream signaling pathway to activate both the nuclear factor kappa B and the type 1 interferon. Therefore, female seems to be more competent than male in viral clearance as they have biallelic expression of TLR7 from both X chromosomes.

CLINICAL IMPLICATION OF FEMALE SEX HORMONES

On this pathophysiological basis summarized above, researchers and clinicians have been trying to verify whether female hormones, of which serum concentration can be a modifiable factor, could have a place in the therapeutic role against COVID-19. A large scale

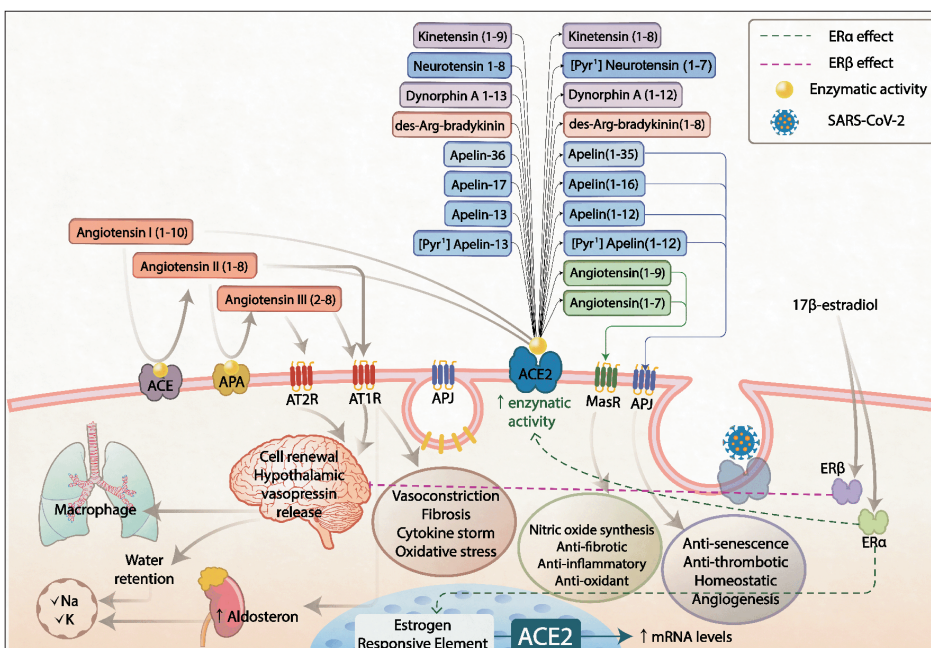


Fig. 2. Effects of estrogen on immune-related cellular pathway and organs through the estrogen receptor. ER α or β : estrogen receptor α or β , SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, ACE: angiotensin-converting enzyme, AT1R or AT2R: angiotensin2 receptor 1 or 2, ACE2: angiotensin-converting enzyme 2, MasR: mitochondrial assembly receptor.

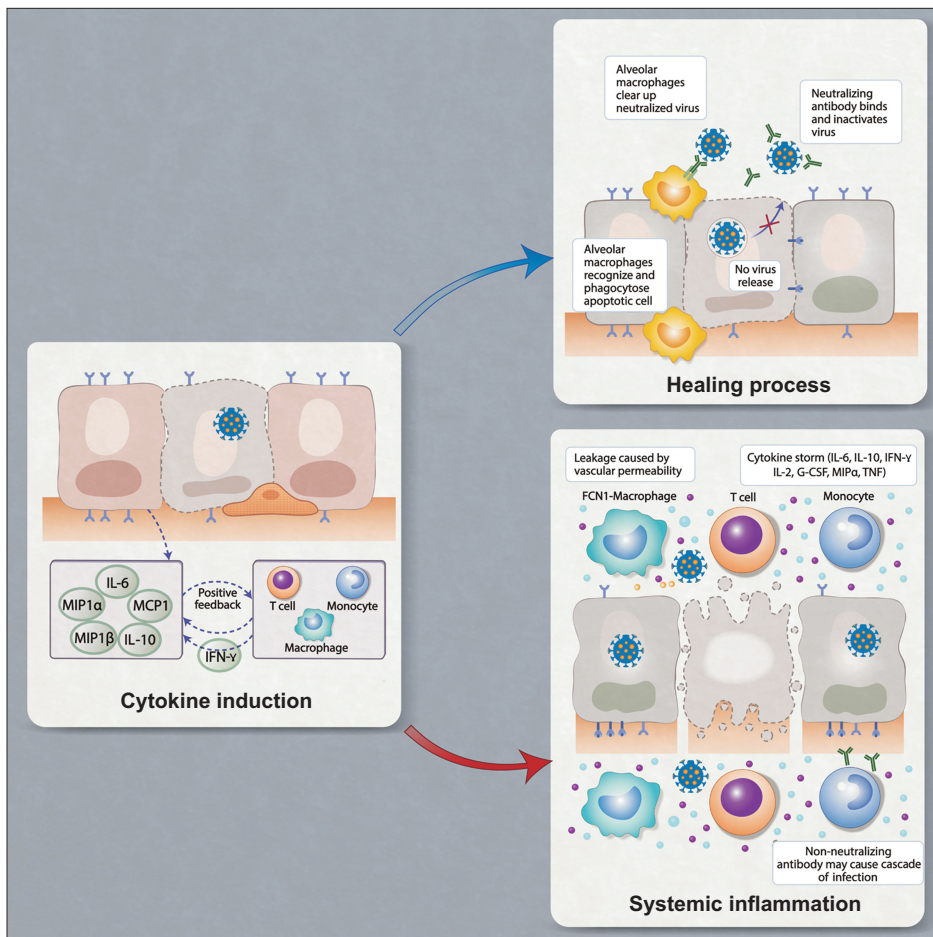


Fig. 3. Changes in the course of infection through immune-modulation by estrogen. IL-2, 6, or 10: interleukin-2, 6, or 10, MIP1 α or β : macrophage inflammatory protein-1 alpha or beta, MCP1: monocyte chemoattractant protein-1, IFN- γ : interferon gamma, FCN1: ficolin-1, G-CSF: granulocyte-colony-stimulating factor, TNF: tumor necrosis factor.

cohort study performed in Sweden revealed that estrogen supplementation in postmenopausal women is associated with decreased mortality [25]. In this study, an adjusted odds ratio of death following COVID-19 was 0.47 (95% confidence interval, 0.34 to 0.63) for women receiving estrogen replacement therapy. However, there is limitation of retrospective design and the possibility of healthy-population bias. To draw a more firm conclusion, a clinical trial is also underway (NCT04539626); the trial is designed to observe the effect of applying ethinyl estradiol 0.6 mg and norelgestromin 6 mg to non-severe COVID-19 patients. Although the optimal dosage to have a therapeutic effect has not yet been established, it has a pro-inflammatory effect at a low dose while promoting an anti-inflammatory cytokine production at the physiologic E2 level [26]. On the other hand, the application of high-dose transdermal estrogen therapy to severe cases has been proposed [27], but additional research is needed accordingly.

Progesterone is another sex hormone and also known as an immune modulator, as the lower the serum progesterone concentration, the more Th1-dominant immune response is induced, leading to a cytokine storm [28]. Improvements on the outcome of moderate to severe COVID-19 male patients with progesterone supplement were successfully made with regard to clinical status score and shortened period of oxygen treatment and hospitalization [29]. There is also ongoing clinical trial on the efficacy of estradiol cypionate 5 mg/mL and progesterone 200 mg oral capsule in addition to standard of care for improving clinical outcomes of COVID-19 (NCT04865029).

Meanwhile, estrogen itself has a thrombogenic property by activating coagulation factors [30]. Menopausal hormone therapy (MHT)-related venous thromboembolism occurs mainly in the presence of risk factors such as old age and overweight [31]. COVID-19 induces a 49% risk of a thrombosis in patients admitted to intensive care unit (ICU), which is higher than 28%

of non-COVID-19 ICU patients [32]. Studies have focused on the risk assessment of menopausal hormone therapy in the context of the COVID-19 pandemic as thrombotic risk of adenoviral vector vaccine has been observed [33]. In this regard, Centers for Disease Control and Prevention (CDC) analyzed thrombosis cases related to Janssen vaccine inoculation and pointed out that systemic estrogen therapy was a risk factor. There is currently no specific evidence-based recommendation or guideline for a COVID-19 vaccine during menopause hormone therapy. However, based on the CDC data that recommended vaccination during pregnancy [34], and even with a history of thrombosis [35], both of which the thrombotic risk is higher than that of MHT, Korean Menopause Society stated that the benefit of vaccination is significantly higher than the risk, so it can be safely used in healthy postmenopausal women. The reports presented so far on how to select patients and type of medicines, routine of administration, duration of treatment, and timing of initiation to minimize thrombotic risk while maintaining the benefits of hormonal therapy will be introduced below.

HOW TO APPLY HORMONE THERAPY IN THE ERA OF COVID-19 PANDEMIC

Thrombotic risk of COVID-19 and hormone therapy

When MHT is first started, the absolute risk for venous thromboembolism (VTE) is 2 per 10,000 people per year, which is a relative risk of 2 compared to the control population, but the risk becomes minimal after 1 year [36]. If there are risk factors such as old age or obesity, VTE can be prevented through prophylactic measures such as lipid-lowering agent and low-dose aspirin [37]. Furthermore, it is known that transdermal estradiol does not elevate VTE risk [38].

Based on these facts and protective effect of estradiol against COVID-19, a review published in the Journal of the European Menopause and Andropause Society [39] suggested that MHT can be started in symptomatic menopausal women and should be continued even though a postmenopausal woman previously receiving

MHT contracted COVID-19 because hormone withdrawal may worsen the course of COVID-19. In case of progression to severely-ill condition, anticoagulation with heparin and/or conversion to transdermal estradiol should be considered. In addition, it was expected that transdermal route of administration would be advantageous when hormonal therapy was resumed.

A recommendation published in the same journal [40] suggested that all patients hospitalized for COVID-19 should be administered low molecular weight heparin (LMWH), stopped systemic MHT, and applied transdermal MHT if the risk of thrombosis is not high. Even in patients who do not require hospitalization, systemic MHT was recommended to be switched to transdermal therapy, with one exception of tibolone maintained as oral therapy. LMWH is recommended when COVID-19 symptoms persist. Usual dosing regimen of LMWH agents for thromboprophylaxis are given in Table 1 [41].

Regarding the formulation of hormonal agents, transdermal estrogen and oral/vaginal micronized progesterone or levonorgestrel-releasing intrauterine device are suggested as preferable regimens because of favorable adverse effect profile [42].

COVID-19 vaccine and hormone therapy

On April 2021, European Medicines Agency announced that a vaccine using an adenoviral vector can cause thrombosis [43]. The incidence of cerebral venous sinus thrombosis and splanchnic vein thrombosis between 5 and 16 days after vaccination was 6.5 per million people, which is 1.4 times higher significantly than the previously known natural incidence.

Later, another report explained the possibility that the autoantibody to platelet (anti-platelet factor 4 antibody) response to platelets may be involved in the mechanism by which the vaccine induces thrombosis [33]. After temporary suspension of the vaccination due to safety issues, vaccination was resumed according to expert opinion [44] and society recommendation [34] to recommend vaccination based on risk-benefit analysis.

On May 2021, CDC reported on the synergistic ad-

Table 1. Widely used low molecular weight heparin and dosing regimen

	Dosage	Route	Remarks
Enoxaparin	1 mg/kg twice a day or 1.5 mg/kg once daily	Subcutaneous or intravenous	Reduce to 30 mg once daily if CrCl ≤ 30 mL/min
Dalteparin	200 units/kg daily	Subcutaneous	UFH if CrCl ≤ 30 mL/min

CrCl: creatinine clearance, UFH: unfractionated heparin.

verse effects of adenoviral vector vaccination and hormonal therapy. Among 28 cases of thrombosis after 8.74 million Janssen vaccinations there were two cases of concomitant use of combined oral contraceptives and one of transdermal estradiol [45].

According to the KDCA's analysis, which compared the benefit of vaccine-induced death prevention with the risk of death from vaccine-induced thrombosis, the benefit-risk ratio was 10.7 times for those in their 50s and 42.1 times for those in their 60s, indicating that vaccination is significantly more advantageous in the postmenopausal age group. The National Health Service (NHS) of United Kingdom has also recommended continuing adenoviral vaccination, citing research findings that the risk of developing thrombosis from COVID-19 itself is significantly higher than that from vaccines [46].

Considering the rare incidence of vaccine-induced thrombotic thrombocytopenia, the preventive effect of vaccines on the morbidity and mortality of postmenopausal patients with COVID-19 and the protective effect of estrogen therapy, the combination of the female hormone therapy and SARS-CoV-2 vaccinations seems to be safe as long as there is no specific risk factor.

For the mRNA vaccine, no specific consideration or precautions regarding the concurrent administration of hormone therapy have been indicated so far.

CONCLUSIONS

For most carefully selected cases, the benefits of menopausal hormone therapy outweigh the risks even in the situation of COVID-19 pandemic and vaccination. Caution is needed in relation to the risk of thrombosis, but in view of the results so far, if MHT is performed with careful patient selection and individualizing the type of drug, route of administration, timing and duration, the benefit seems to outweigh potential risk even in the context of the COVID-19 pandemic.

However, considering that the long term combined effects of COVID-19/vaccination and MHT has not yet been confirmed, SARS-CoV-2 variant is emerging, and the efficacy and side effects of the vaccine are being updated, continuous data collection and analysis are needed.

Aside from the clinical trials and studies currently in progress, there still remain unanswered questions. First, the effect of physiologic hormonal fluctuation on the course of COVID-19 may give us a clue to under-

stand the dynamic relation between sex hormones and COVID-19. Actually, there have been several reports of changes in COVID-19 symptoms according to the menstrual cycle.

Second, late-phase sequelae of COVID-19, so-called as "long COVID" should be investigated as the main symptoms consist of fatigue, muscle ache, and sleep disturbance and can mimic the symptoms of menopause. Particularly, the therapeutic role of estrogen in the management of long COVID-19 can be explored because the disturbance in hormone physiology may be one of the major axis in the condition.

Finally, long term consequences of COVID-19 on reproductive health, such as the onset of menarche or menopause, childbearing potential, and offspring effect, should be monitored. Considering that being infected with SARS-CoV-2 is unavoidable for many people, it will be most important to understand the long-term outcome of COVID-19 as well as the treatment itself and discuss reasonable strategies.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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