# SEVEN HILLS TIMES

Volume 4 | Issue No 8 | August 2020

An Official Publication of Department of Pharmacy Practice
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To emerge as one of the premier pharmacy colleges in the country and produce pharmacy professional of global standards.

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- To deliver quality academic programs in Pharmacy and empower the students to meet industrial standards.
- To build student community with high ethical standards to undertake R&D in thrust areas of national and international standards.
- To extend viable outreach programs for the health care need of the society.
- To develop industry institute interaction and foster entrepreneurial spirit among the graduates

## ROLE OF ESTROGEN IN THE MANAGEMENT OF COVID – 19 IN FEMALES


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### Introduction:

Given the rapid spread of the coronavirus disease 2019 (COVID-19) pandemic and its overwhelming effect on health care systems and the global economy, innovative therapeutic strategies are urgently needed. The proposed primary culprit of COVID-19 is the intense inflammatory response-an augmented immune response and cytokine storm-severely damaging the lung tissue and rendering some patients' conditions severe enough to require assisted ventilation. Sex differences in the response to inflammation have been documented and can be attributed, at least in part, to sex steroid hormones. Moreover, age-associated decreases in sex steroid hormones, namely, estrogen and testosterone, may mediate proinflammatory increases in older adults that could increase their risk of COVID-19 adverse outcomes. Sex hormones can mitigate the inflammation response and might provide promising therapeutic potential for patients with COVID-19.

### Covid – 19 in Males Vs Females

Though sex-disaggregated data for COVID-19 show equal numbers of cases between men and women, there seem to be sex differences in mortality rate and vulnerability to the disease. Emerging evidence suggests that more men than women are dying, potentially due to sex-based immunological differences. The possible role of smoking, more frequent in men in China and worldwide, in aggravating the infection has also been proposed. Another possible explanation is the potential role of oestrogens. Viral infections have been recognised to differ between men and women in their prevalence, intensity, outcomes and pathogenetic mechanisms: women are usually less susceptible than men to viral infections, since the immune response in women is more efficient, intense and prolonged, as well as humoral and cell-mediated.

Testosterone exerts an overall inhibitory effect on differentiation of the T helper 1 arm of the immune system, with consequent reduced production of interferon gamma, which may explain the higher susceptibility to viral infections in men compared with women. Moreover, the effect of progesterone on the immune system is similar to that of testosterone, with an immune suppression of both innate and cell-mediated immune responses. It is well known that progesterone suppresses the T helper 1 response and favours T helper 2 cytokine production, inhibits cytotoxic T cells and modulates the function of natural killer cells.

## Coronavirus Disease–2019 Mortality Is Lower In Women Compared To Men:

Since the beginning of the 21st century, 2 previous deadly zoonotic betacoronavirus outbreaks have crossed the species barriers to infect humans and exhibited the same apparent female protection from severe outcomes. The first SARS-CoV outbreak emerged in 2002 in Guangdong province, China, and among 1755 hospitalized patients in Hong Kong the case fatality rates was 13% in women compared to 22% in men. During the ongoing Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak that began in 2012 in Saudi Arabia, among 425 reported cases, disease occurrence was lower among women (38% of cases) and the case fatality rate was 23% for women compared to 52% for men.

The International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) in a prospective observational cohort study of more than 17 000 patients in the United Kingdom reported that among hospitalized patients, women accounted for only 40%, with a 20% lower mortality than in men. Although advancing age is associated with greater risk of mortality in both sexes, female protection remains evident. An analysis of COVID-19 data from Italy, Spain, Germany, Switzerland, Belgium, and Norway reveals that among all age groups older than 20 years, fatality rates are greater for males than females. In contrast, male-female differences in the rate of confirmed SARS-CoV-2 infections are age dependent in all countries, being greater among females age 10 to 50 years and greater among males younger than 10 years and older than 50 years.

Hence for the period of the pandemic, would it not be worth considering this on a case-by-case basis, depending on the patient's other risk factors, including male sex, smoking, immunosuppression, and other comorbidities. Behavioural aspects could also reduce survival in men. Women are more likely to seek medical attention early in the course of an illness compared with men.

- Men should consider reducing their consumption of androgenic steroid supplements. Many protein powders taken by young and older men contain dehydroplandrosterone, an androgenic steroid, and potentially other androgens.
- Postmenopausal women and women taking progestin-only contraceptives may wish to speak with their treating physicians about temporarily using estrogen-containing alternatives, if there are no contraindications.
- Transgender individuals may wish to reduce testosterone supplements or take testosterone blockers, depending on the situation, to reduce testosterone exposure.
- If taking ACE inhibitors or angiotensin II receptor blockers for hypertension, consider switching to another agent during the pandemic.

## Females Generally Exhibit Greater Immune Responses to Viruses

Females generally develop heightened immune responses compared to males. In 1967, Butterworth et al reported that women produce higher levels of circulating immunoglobulins IgG and IgM than men, which was subsequently confirmed by multiple studies. Accordingly, following vaccination against influenza, yellow fever, rubella, measles, mumps, hepatitis, herpes simplex 2, rabies, smallpox, and dengue viruses, protective antibody responses are twice as high in women than in men.

Women also have higher frequencies of CD4+ T helper cells than men. The biological reasons why females develop a more robust immune response than males against pathogens, including viruses, likely explain the observed female protection from COVID-19 fatal outcomes. First, females enjoy the genetic benefit of 2 X chromosomes and being a mosaic of X-linked genes (ie, randomly expressing alleles inherited from their mother or father), including more than 60 immune-response genes. By contrast, males have only one X chromosome inherited from their mother. Several studies show that genetic diseases associated with deleterious X-linked alleles are more frequently observed in males. Generally, there should be no dosage effect associated with position of 2 X chromosomes in females. Incomplete inactivation of immunoregulatory genes on the X chromosome in females, however, can cause a gene dosage imbalance between the sexes, which is implicated in female-biased autoimmune diseases and vaccine efficacy. The Y chromosome also has immunoregulatory functions that are linked to influenza outcomes, at least in mice. Sex steroids are potent immune-modulators and the different concentrations of estrogens, P4, and androgens between women and men, in addition to the genetics described previously, are likely to influence COVID-19 immune responses and inflammatory outcomes. This is especially important because acute and severe illnesses, such as COVID-19, may alter the function of the hypothalamic-pituitary gonadal axis and decrease the endogenous production of estrogens and P4.

Hormones are also amenable to therapeutic intervention. Later, we discuss immunomodulation provided by high physiological serum concentrations of estrogens and P4 as it relates to SARS-CoV-2 infection. This background knowledge is paramount to appreciate the potential benefits that E2 and P4 treatment could provide in the context of SARS-CoV-2–mediated hyperinflammation and acute respiratory distress syndrome.

## Role Of Pro-inflammatory Cytokine Storm In Coronavirus Disease–2019 Outcomes:

Severe COVID-19 outcomes are associated with delayed and exaggerated innate immune responses, including hypercytokinemia and inflammatory cell infiltration in the lungs. Our current understanding of the disease, which is rapidly evolving, is that patients with COVID-19 do not die from damage caused by virus replication, they die from the consequences of a so-called “cytokine storm”. In an attempt to protect the body from SARS-CoV-2, immune cells infiltrate the lungs, causing hyperactivation of monocytes and macrophages, and elevated production of proinflammatory cytokines (eg, interleukin-6 [IL-6], interleukin-1β [IL-1β], tumor necrosis factor α [TNFα]) and chemokines (eg, monocyte chemoattractant protein-1 (MCP-1/CCL2]).

The cytokine storm is also associated with lymphopenia, and a study in 21 patients from Wuhan reported a decrease in CD4+ and CD8+ T cells, as well as suppressed interferon γ production by CD4+ T cells, which was associated with COVID-19 severity. The local outpouring of chemokines and cytokines attracts more inflammatory cells, such as neutrophils and monocytes, into lung tissue, resulting in lung injury. Ironically, the cytokine storm is a result of the immune system responding to infection in an effort to protect the host, but results in acute respiratory distress syndrome and multiorgan failure. Increased production and elevated local and systemic IL-6 is hypothesized to be central to the development of the cytokine storm. Accordingly, therapeutic strategies targeting the inflammatory response such as IL-6 blockade or the transplantation of mesenchymal stem cells to restore immune tolerance are showing promising preliminary results in mitigating the cytokine storm. Here we discuss a paradigm in which therapy with the steroid hormones E2 and P4 could mitigate this virally induced innate immune inflammatory response

## Estrogen Regulation Of COVID-19 Through ACE – Efficient In Females:

The novel SARS-CoV-2 depends on angiotensin-converting enzyme 2 (ACE2) for cell entry and engages the serine protease transmembrane protease serine 2 (TMPRSS2) for priming of the viral spike protein. Therefore, both ACE2 and TMPRSS2 are crucial for the ability of SARS-CoV-2 to cause infection. Here, we sought to determine whether 17β-estradiol ($E_2$), a primarily female sex steroid, can regulate the gene expression of ACE2 and TMPRSS2 in differentiated normal human bronchial epithelial (NHBE) cells.Here we demonstrate that $E_2$-treated NHBE cells expressed lower levels of ACE2 mRNA compared with the vehicle-treated controls. This $E_2$-driven downregulation of ACE2 expression is particularly relevant, as the efficiency of ACE2 usage by SARS-CoV has been shown to be an important determinant of viral replication and disease severity. Furthermore, the levels of TMPRSS2 mRNA were not affected by $E_2$ treatment. Finally, it is confirmed prior reports that undifferentiated NHBE cells express very low levels of ACE2. Therefore, it is critical to use fully differentiated NHBE cells grown at the ALI to accurately study ACE2 gene expression.

## Repurposing Estrogens and Progesterone To Mitigate Coronavirus Disease–2019 Mortality?

High physiological concentrations of E2 and P4 possibly synergize to mitigate innate immune cells production of proinflammatory cytokines, promote T cells' anti-inflammatory responses and immune tolerance, and stimulate antibody production by B cells (fig 2). In individuals with confirmed COVID-19, acute hormone therapy with E2 and P4 could mitigate the cytokine storm while increasing antibody production. Pandemics such as SARS-CoV-2 provide little time for drug development. Repurposing existing and approved drugs that have already been tested in humans—and for which detailed information is available on their pharmacology, formulation, dose, and potential toxicity—provides an expedited and safe approach for off-label use of potentially life-saving therapeutics.

## Selective Estrogen Receptor Modulators As Possible "Adjuvant Drugs" In Covid-19

Noteworthy, the protective effects evoked by endogenous estrogens are also promoted by drugs belonging to the class of SERMs. These drugs exhibit a complex profile of mixed agonist/antagonist modulators of the ER subtypes and their effects on immune system and immune-mediated inflammatory responses have been described. Indeed, many preclinical and clinical studies demonstrated that SERMs evoke significant anti-inflammatory responses and inhibit the expression of many proinflammatory cytokines, in different conditions of systemic or local inflammation.Concerning coronavirus infections, a single preclinical study investigated the role of sex hormones in single gender – related vulnerability to SARS-CoV. In this study, male and female mice were infected with murine-adapted SARS-CoV. Male mice were vulnerable to SARS-CoV infection compared to female mice. Ovariectomy or treatment of female with an ER antagonist increased mortality, indicating a protective effect for ER signaling in mice infected with SARS-CoV. In contrast, treatment of female mice with SERMs (i.e. tamoxifen) led to increased levels of protection.

## Finally...

Taken together, these data suggest that ER modulation may be a suitable pharmacological approach for preventing/attenuating the cytokine storm and inflammation associated with COVID-19 and particularly, the use of SERMs and/or tissue selective estrogen complex (TSEC, i,e. SERMs and natural estrogen) may provide promising pharmacological results. Such a treatment option would be beneficial in both male and female patients in early phase of disease to prevent progression of disease/infection to severe forms.

## Webinars Conducted in the month of July 2020:

| S No | Webinars | Date Streamed | Speaker | Department Conducted | No of Participants |
|---|---|---|---|---|---|
| 1 | Career Guidance for Pharm D | 3rd July 2020 | Dr Krishna Undela Faculty , Dept of Pharmacy Practice JSS College of Pharmacy, Mysuru | Pharmacy Practice | 1841 |
| 2 | Pharmaceutical Quality System | 11th July 2020 | Mr M Narendira Kumar Associate Director Dr Reddys Lab Vizag | Pharmaceutical Analysis | 1305 |
| 3 | SCIENCE OF COVID-19 & CHANGING NUTRITIONAL DYNAMICS | 25th July 2020 | Dr. Prabakaran Ravichandran Research Scientist - Biology ITC Life Sciences & Technology Center Bangalore | IQAC & Pharmaceutical Chemistry | 1302 |

## e-FDP Conducted in the month of July 2020:

| S No | Theme | Date Streamed | Speaker | Topic Delivered | No of Participants |
|---|---|---|---|---|---|
| 1 | In-Silico Tools for Biopharmaceutics & Virtual Pharmacokinetics | 17th July 2020 | Dr Gowtham Rajan K Professor & Head Dept of Pharmaceutics JSS college of Pharmacy, Ooty. | Simulations in BioPharmaceutical Applications | 1196 |
| | | 18th July 2020 | Dr Raj Kumar Dept General Manager, USV Ltd, Mumbai. | Biopharmaceutics Mechanistic PBBM for Virtual Bioequivalence (Demo on PK-SIM software) | 1108 |
| | | 19th July 2020 | Dr Muralidhara Anandamurthy Academic Ambassador JMP (SAS), Bangalore, Karnataka. | Enabling Statistical Discovery through JMP | 1297 |