COVID-19 pandemic has far-reaching consequences on people with comorbidities like Diabetes Mellitus (DM), asthma, cardiovascular disease, and cancer. What seems unusual is an isolated observation that emerged from several independent studies worldwide. Postmenopausal females seem to suffer from severe COVID symptoms. Few of them also show an extended COVID symptom, also "long COVID." Though the association appears strong, there are not enough credible studies to pin it down to the exact cause. We explored the possibility to see if postmenopausal females are at a higher risk for severe COVID and unravel this observation’s molecular pathogenesis.

Research performed at King’s College London found that as estrogen levels in females drop in pre-menopause and menopause, they become vulnerable to COVID19 infection, suggesting that high estrogen levels may have a protective effect against the severity of COVID-19. This concept originated from the immune-modulatory and immune suppressive role of estradiol. Although both male and female sex steroids act primarily on the reproductive tissues and modulate their functions, increasing evidence suggests that sex steroids can also work on non-reproductive tissues like the CNS, immune systems, cardiovascular and skeletal systems, etc. Further, estrogen has an enormous effect both on the innate (macrophages/monocytes, neutrophils, NK cells, complement systems, APC-like dendritic cells (DC)], as well as on the adaptive (B and T cells) immune system. There are reports that estrogen may exhibit a pro-inflammatory response, whereas testosterone counteracts it. This could possibly be through an estrogen-mediated production of inflammatory cytokines like IFNγ, interleukin (IL) 6, TNF α. However, estrogen also has a profound anti-inflammatory effect. We need to remember that many of these observations are context and cell-type-specific with a delicate balance between pro and anti-inflammatory responses. There needs a deeper understanding of the reproductive events in females. Perimenopause, menopause, and postmenopause define the end of a woman's reproductive years. These are the time when her monthly period stops. Whole perimenopause marks the beginning of this process, starting 8-12 years before menopause. Menopause is the stage when her menstrual periods completely ceases for at least 12 months. Postmenopause is the stage after menopause that continues thereafter. Starting from perimenopause, menopause is marked by declining levels of estrogen ([estrone (E1), 17β-estradiol (E2), estriol (E3)], and progesterone. However, there are complex hormonal and cytokine undercurrents to this rather simplistic profile. LH and FSH, however, seem to surge during this period. It currently not know what this LH/FSH surge means for the immune system. With the approach of menopause, there is the release of extracellular vesicles containing inflammasomes, which may be responsible for low-grade systemic inflammation. This cascade may build up significantly and contribute to a hyper-inflammatory environment.

According to a survey by Global Health 50/50, though an equal number of males and females were tested positive for COVID-19, the males were largely presented with severe symptoms, thereby implying that the female hormones may have a protective role in the pathophysiology of COVID-19. Further clinical studies performed on the females showed that pre-menopausal females have a relatively mild disease, while menopausal females had moderate to severe illness. The menopausal group also has significantly more requirements for oxygen, ventilation support, and progression-to-severe disease with a prolonged hospital stay and mortality.

This is further reinforced by the fact that estradiol modulates the immune cells, which could play an essential role in explaining why a lower incidence of COVID-19 is observed among women than in men. Even been a nuclear hormone, estrogen has cytoplasmic targets. The cytoplasmic activity
of estrogen-activated ERα leads to PI3K induction.30 This, in turn, prevents the nuclear shuttling and transport of NF-κB, resulting in reduced inflammation.27 The estrogen axis for inflammation is enormously complex, riddled by the different receptor types usage and post-receptor events. The presence of estrogen receptors (ESR), ERα and ERβ, is of prime importance since the net outcome depends on ER subtypes in use.28 It seems that a preferential engagement of EBrbeta promotes inflammation while ERalpaha dampens it.29 It was further demonstrated that hypoxia, associated with inflammatory conditions, could also downregulate the expression of ERα, tipping the balance in favor of inflammation.29,30 Then there are interferon genes that cross talk with (Estrogen receptor) ESR signaling.31,32 Estrogen can also polarize toward a TH2 response eliciting a protective humoral response33 in addition to its capacity for activation of NK cells.34-36 Further, a wide variety of immune-modulatory roles is under estrogenic control. This involves the antigen-presenting dendritic cells, CD4+ and CD8+ T cell modulatory roles is under estrogenic control. This involves the antigen-presenting dendritic cells, CD4+ and CD8+ T cell populations.37,38 Other than estrogen, progesterone also has a profound influence on the immune system.39,40 Progesterone was found to have an antiviral effect against SARS-CoV-2 in vitro.31,42 Mature NK CD56dimCD16+ KIR+ cells overexpress the progesterone receptor and thus are hormone-sensitive.43 Though there are conflicting reports regarding the association of disease severity and mortality with estrogen levels, it seems that a preferential engagement of EBrbeta promotes inflammation while ERalpaha dampens it.29

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