

Letter to the Editor

Gender differences in COVID-19 infection. The estrogen effect on upper and lower airways. Can it help to figure out a treatment?

Dear Editor,

Epidemiologic evidence from the first large-scale studies suggests that males are more severely affected than females by Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-CoV-2). They present worse outcomes, require longer hospitalization time and have a higher mortality rate when compared with women¹. Scientists have speculated that female hormones, especially estrogen, could explain the better outcomes and the higher resistance to the virus observed in women. This higher resistance is due to the systemic and local effect of female hormones on the different cells. In particular, estrogens stimulate the immune system by modulating the function of B cells and improving T-helper 2 cell activity².

It is known that COVID-19 penetrates into the body through the upper respiratory tract, mucosal contact, and eye conjunctiva through droplets in the air or deposited on surfaces spread by coughing or sneezing². Estrogen has an established benefic effect on the upper and lower airways². As first, women's nose responds to the variation of estrogen levels by improving the local immunity response as confirmed in several clinical trials³ and histology studies⁴. The hormone stimulates the reactivity of nasal mucosa³ (Figure 1) by determining turbinates hypertrophy and increased production of nasal mucus which contains mucins, electrolytes, IgA and IgG lysozyme, lactoferrin and oligosaccharides. These substances have anti-viral and antibacterial proprieties

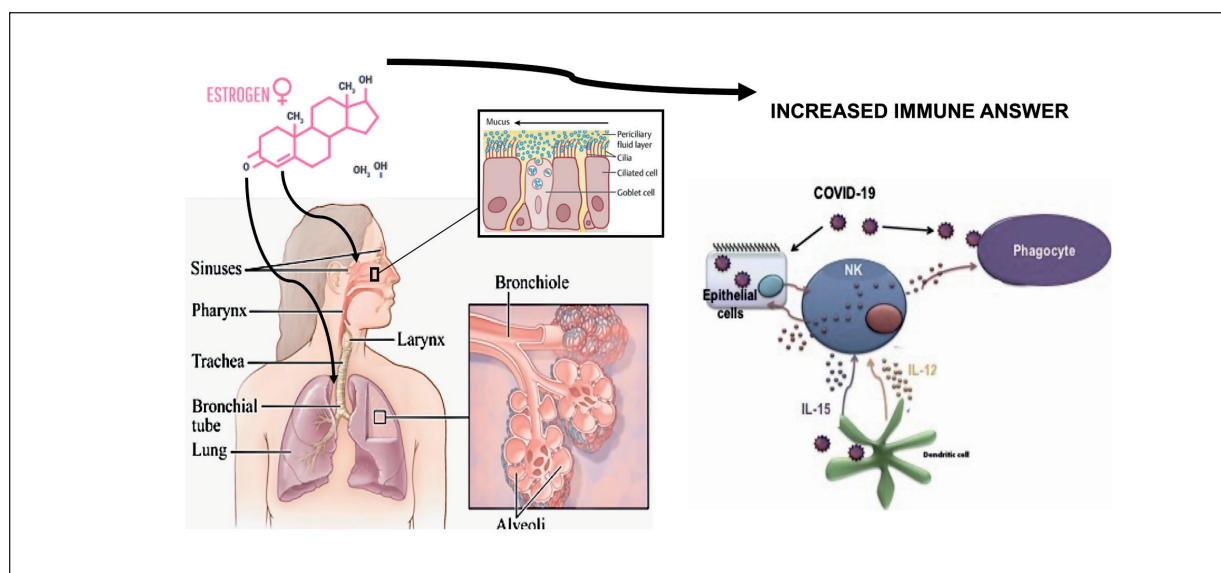


Figure 1. Schematics showing the protective action of estrogen in the upper and lower respiratory tract, and its benefit on the immune response.

actions that are fundamental to contrast upper airway infections. In addition, estrogen stimulates production of hyaluronic acid that maintains a good tropism of the nasal mucosa and nasal cilia^{3,4}. Finally, estrogen stimulates the local nasal immune system acts directly on the nasal immune system by increasing the activity of phagocytes, dendritic cells and natural killers³ (Figure 1). These cells, once active, are able to destroy the virus preventing its diffusion into the lower respiratory tract or reduce the viral charge (virulence)^{3,4}.

In addition to the local effects on nose filter, estrogen ensures good hydration of the mouth through the stimulation of hyaluronic acid production⁴, and improves the function of the lower respiratory tract by acting directly on the bronchial epithelia cells that increase the production of mucous rich in antiviral agents^{5,6}. At this level the positive effect of estrogen is supported by the action of progesterone (PG) which upregulates the epidermal growth factor amphiregulin by inducing a repair of lung structure in case of viral infection; PG also improves the outcome of pulmonary disease^{5,6} when administered to women in menopause.

Although the role of estrogen is intriguing there are still open questions. Menopause causes a drastic drop of estrogen levels which might delete the risk difference between men and women; however, case series show that the gender difference is still present in the elderly. Children suffered less than adults from COVID_19 without gender differences; this could be related to the absence of androgen hormones prevalence on the estrogen hormone in male up to the complete sexual maturity.

Based on this evidence, we hypothesize the potential utility of a local nasal spray with low-dose isoflavones from soya (natural estrogen) suspended in a solution with sodium could stimulate nasal receptor by stopping or reducing the aggressiveness of COVID-19 as already suggested by a previous animal study⁷.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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