



## Invited Editorial

## COVID-19 and hormonal contraception



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Since the beginning of the COVID-19 pandemic, many studies have tried to define what mechanisms are involved in determining the risk of becoming infected and the clinical evolution of the disease. Immediately it became evident that fewer women than men die from COVID-19 [1]. The difference is not due to a different degree of infection but rather to a lower risk of disease progression [2]. In fact, the risk of infection for women is slightly higher than that for men between the ages of 20 and 50, although it then becomes lower than that for men after the age of 60 years. The mortality trend is the opposite: women's mortality rate is 70% lower than that of men between the ages of 20 and 50 but becomes only about 35% lower than that of men after 60 years of age. These epidemiological trends seem to indicate an influence of female sex hormones on the risk of infection and mortality. Complementary experimental studies have shown possible modulatory effects of sex steroids on the mechanisms involved in infection and COVID-19 progression.

The virus' spike protein binds to the ACE2 receptor to enter the cell and infect the body [3]. During this process, ACE2 is internalized and lost from the cell surface. ACE2 also plays an important role in reducing the progression of the disease, by intervening in the conversion of angiotensin II to angiotensin 1–7 and the degradation of other peptides important for vascular function and inflammatory modulation [3]. High concentrations of ACE2 counterbalance angiotensin II-induced inflammatory activation and reduce disease progression [3]. Oestrogens and androgens modulate ACE2 activity differently; moreover, the response direction differs with the experimental conditions. Recent studies have clearly shown that oestrogens stimulate ACE2 activity in the atrial tissue of the human heart [4]. Oestrogen-induced ACE2 activity is in accordance with the epidemiological data that women aged 20 to 50 have a higher risk of becoming infected but a lower risk of disease progression. Aside from its effect on ACE2, oestrogen exerts an inhibitory effect on the renin-angiotensin-aldosterone system by reducing angiotensin II activity and its possible adverse effects [3].

The immune response is different in men and women. In the course of COVID-19, women show less activation of innate immunity and a more

robust adaptive immunity, characterized by increased activity of T and B cells [5]. Sex steroids may be responsible, at least in part, for this different immune response. High levels of oestrogens suppress the production of proinflammatory cytokines by macrophages and prevent monocytes and neutrophil migration in inflamed areas. Furthermore, they stimulate antibody production by B cells [6]. Progesterone reduces the formation of proinflammatory cytokines and, together with high oestrogen levels, stimulates the production of anti-inflammatory cytokines by T-helper cells and enhances increases in the numbers of regulatory T cells [6].

Hormonal contraception (HC) is used to prevent unplanned pregnancies and for its additional benefits. Whether HC should be used during the COVID-19 pandemic and in patients with the disease is a matter of debate. The estrogenic component of HC increases the risk of venous thrombosis due to its ability to boost the coagulation system [7]. This effect is directly related to the potency and the dose of the estrogenic component, and only partially opposed by the androgenic component of some progestins [7]. Based on these considerations, some clinicians have suggested women with COVID-19 discontinue their usual HC, use HC with androgenic progestins, or use progestin-only contraceptives [8]. This prudential attitude could be wrong, and possibly harmful.

The progression of COVID-19 is no worse in individuals at greater risk of venous thrombosis, such as patients with hereditary thrombophilia or pregnant women [6]. Both arterial and venous intravascular coagulation induced by infection is in fact the consequence of a state of marked inflammation, massive endothelial damage, platelet deposit and subsequent activation of the coagulation system. Apart modulation of ACE2 and immunity, oestrogenic activity in reducing platelet adhesion could be useful in decreasing, rather than increasing, clotting activation [9]. The use of androgenic progestins may not be indicated, COVID-19 being less severe in estrogenic than in androgenic environments. Progestin-only contraception may reduce oestrogen levels to insufficient values, a high oestrogen stimulus, as obtained during HC, being

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probably necessary to increase ACE2 expression and modulate immune system activity [3,6]. Therefore, in women with COVID-19, HC with non-androgenic progestins seems preferable to HC with androgenic progestins or progestin-only contraception.

From the start, the recommendation of the Italian Society for Contraception was to continue the administration of HC in women with COVID-19 [10]. Others then followed the same line of thought. A recent epidemiological study found that COVID-19 is less serious in women who use HC [11]. At the moment, no study says otherwise. Therefore, the use of HC in women suffering from COVID-19 seems reasonable and justified by epidemiological, clinical, and research data.

#### Contributors

Angelo Cagnacci was responsible for writing the initial draft.

Ambrogio Pietro Londero contributed to data discussion.

Anjeza Xholli was responsible for the literature search and data discussion.

All authors approved the final version of the manuscript.

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