

Understanding immune effects of oestrogens to explain the reduced morbidity and mortality in female *versus* male COVID-19 patients. Comparisons with autoimmunity and vaccination

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Epidemiology of COVID-19

infection: sex and age distribution

Several lines of published literature suggest a sex and age distribution of COVID-19 infection.

Firstly, in line with the early Chinese reports, and up to the most recent articles, all confirm that female patients exhibit a lower disease morbidity after the COVID-19 infection and a significantly lower mortality rate compared to male patients (1-3).

Secondly, the COVID-19 infection is age related. For example the vast majority of Chinese cases (87%) based on the data of 72,314 patients infection were adults between 30 to 79 years (2). Equally, analysing the data of 4,226 COVID-19 cases from the US Centers for Disease Control (CDC), 31% of patients was 65 years or older, but 80% of deaths were registered in those 65 years or older (4). Also, a very recent report (April 23, 2020) by the Italian "Istituto Superiore di Sanità" (Health Regulatory Agency), that considered the percentage of lethality (percentage of deaths in 23,740 positive patients by age), attested a significant age related increase of deaths in male compared to female patients (Fig. 1).

Interestingly, the Global Health 50/50 (<http://globalhealth5050.org/covid19>) tracks the sex-disaggregated infection and mortality by COVID-19 data from the 39 most-affected countries.

In short, from this interesting comparison, the COVID-19 infection appears to progress easier and severely until the death in male than in female patients, with a worldwide average sex ratio M/F of 2 (mostly in the 70-89 age group) (Fig. 2).

Also the Public Health Information from the city of New York (nyc.gov),

which has one of the world's largest outbreaks, confirms that men are more likely to be hospitalised and are nearly twice as likely to die.

Lastly, looking at the most critical cases, in a recent and impressive retrospective case series of 1,591 consecutive severe COVID-19 patients referred for Intensive Care Unit (ICU) admission to a coordinator center (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy) of 72 hospitals, 1,304 were men (82%), the median (IQR) age was 63 (56-70) years and 26% died (5).

The key role of oestrogens on immune response in COVID-19 patients

Recently it has been reported that in severe COVID-19 patients, the average of SARS-CoV-2 IgG antibody serum concentrations in women tended to be higher than that of in men in severe status (6).

In addition, the production of IgG seemed to be stronger in female patients in the early phase of the SARS-CoV-2 infection (6).

Previous studies showed that adult women (range 20-89 years) generate greater neutralising antibody titres to the H3N2 and influenza B antigens following seasonal inactivated influenza vaccine (TIV) than men, and men having highest serum testosterone concentrations, tend to have the lowest neutralising antibody titres (7).

Such important biological observation, as mentioned before, should be considered as the consequence of the crucial role played by the female hormone oestrogens, and their receptors (ERs) signalling, in both innate and adaptive immune responses, as well as in tissue

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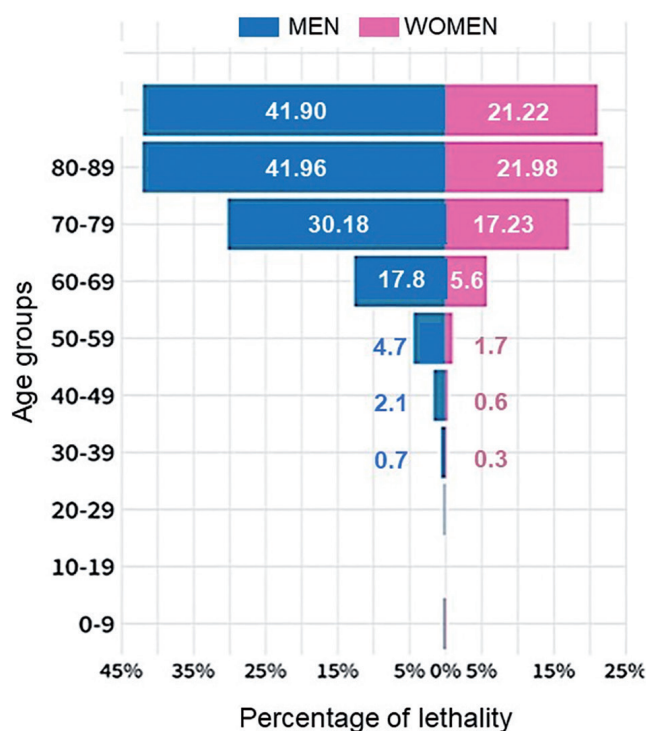


Fig. 1. Percentage of lethality (% of deaths in 23,740 positive patients by age in Italy) related to COVID-19 infection, by sex and age.

Source: data reported on April 23th by the Istituto Superiore di Sanità (Italy) in open access daily report (modified).

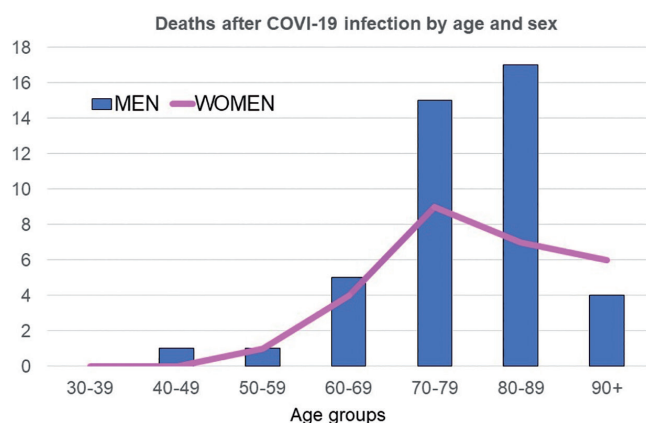


Fig. 2. Deaths after COVID-19 infection by age and sex.

Source: COVID-19 deaths in Australia (last updated April 19, 2020). Personal modification and adaptation of a table from the Australian Government, Department of Health (modified).

repairing processes during respiratory virus infection in COVID-19 patients. Oestrogens activate ERs that, as transcription factors, regulate the development of immune cells and the pathways of the immune system reactivity against infections (and self-antigens), leading throughout the B-cell mediated adaptive immunity to the specific antibody production (8).

However, the innate immunity is the first barrier and is rapid (within hours) and non-specific, representing a frontline defence that is more generalised, targeting any invaders and slowing infection, until adaptive immunity is developed.

During the innate immune response, oestrogen already activates ERs in ac-

cumulated monocytes, macrophages and neutrophils inducing the production of proinflammatory cytokines (IL-12, TNF- α), and chemokine (CCL2) (9).

This leads to activation of lymphocytes and alveolar macrophages with increased the production of type I and III interferon (IFN) which is important for decreasing the virus title production (9, 10).

Shortly after, proinflammatory cytokines (IL-1, IL-6, TNF- α) activate aromatase expression in the affected tissues and promote the conversion of androgens to oestrogens in both male and female patients, by increasing the concentration of oestrogen metabolites, as observed in the synovial tissue of

rheumatoid arthritis (RA) patients (11, 12).

On the contrary, testosterone generally has an immunosuppressive effect and does not exhibit marked influences on inflammatory and reparative immune functions (13). In short, the immune responses to environmental factors like infections are clearly sex-biased.

As consequence, compared to men, women maintain a higher immune reactivity post-viral infections due to higher antibody production, therefore after vaccinations result in higher serum antibody concentrations and more efficient protection (4).

Practically, after COVID-19 infection the majority of female patients react immunologically better and may neutralise earlier the virus, whereas men, in a larger amount, do not mount a similar efficient "virus blockade" via SARS-CoV-2 IgG antibodies, with the final result that the infection further evolves, as already reported for other infections (4).

Oestrogens and autoimmunity: the case of rheumatic autoimmune diseases and COVID-19 infection

Regarding the immune modulatory effects exerted by oestrogens, we should consider what happens into a pathological condition that is different from infections, more specifically in autoimmunity (16).

In autoimmunity, oestrogens facilitate in female subjects the development of immune-pathogenic effects including the occurrence and prevalence of autoimmune systemic diseases like systemic lupus erythematosus (SLE) in presence of other risk factors (average ratio in adults F/M 8:1) (11, 17) (Fig. 3).

The sex ratio in SLE, remains high even after menopause and ageing (F/M ratio 4:1), since oestrogens are decreased after the gonadal latency but are still being synthesised in women by tissue aromatases (11).

Is this autoimmunity protective against COVID-19 infection?

Initial retrospective data from the COVID-19 Global Rheumatology Alliance registry reveal that, of a total number of 110 patients (aged >65 years) with rheumatic diseases who

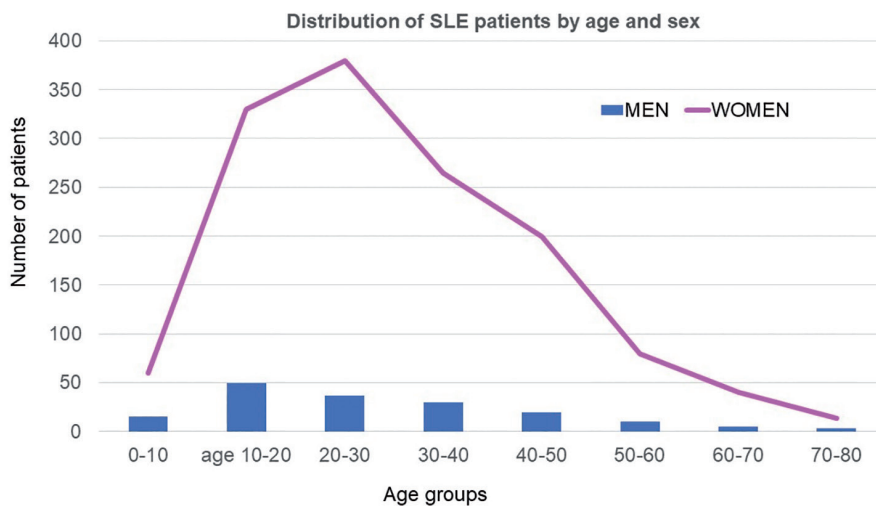


Fig. 3. Distribution of systemic lupus erythematosus (SLE) patients by age and sex.

Source of table: Our modification and elaboration of table from Lalani S et al.: *J Rheumatol.* 2010; 37: 38-44 (modified).

contracted the infection, 19 had SLE (17%) and 40 had RA (36%).

The high prevalence of these rheumatic diseases in COVID-19 patients, from these first data seem to suggest that to be affected by an autoimmune disease would not be protective against SARS-CoV-2. However, the patients were old and under immunosuppressive therapies, making difficult to interpret their complex clinical condition and to draw definitive conclusions (17).

Indeed, a recent report, from an Italian paediatric hospital, showed that children affected by liver autoimmune conditions or transplantations, became affected by the SARS-CoV-2, even if without late pneumonia (18).

Finally, from years it has been demonstrated the apparent safety of vaccinations administered to female patients with quiescent SLE or RA, whereas worsening of SLE in young patients treated with hormonal therapy has been described (19-21).

Therefore, oestrogens appear to act as a double-edged sword, on the one hand, they protect women from diseases like infections, on the other, they potentially favour pathologies like autoimmune rheumatic diseases.

Oestrogens and vaccination: notes and suggestions for the incoming COVID-19 vaccination

We have already underlined that physiologically concentrations of oestradiol,

are significantly lower in postmenopausal than reproductive-age women.

Among women, serum oestradiol concentrations have been found positively correlated with seroconversion in both adult and aged individuals and partially explain reduced vaccine-induced immunity and protection from flu with ageing in female patients (22).

During a recent experimental study to determine the role of sex steroids in vaccine-induced immune responses, adult mice were gonadectomised and gonadal hormones (oestradiol in females and testosterone in males) were replaced in subsets of animals before vaccination. Vaccine-induced antibody responses were increased in females treated with oestradiol and decreased in males treated with testosterone.

In humans, some studies have reported that the use of hormone replacement therapy (oestrogens) in menopausal women is associated with increased numbers of circulating B cells and decreased levels of proinflammatory cytokines (23, 24).

In addition, the development of systemic sclerosis was recently reported in transgender females suggesting that the hormonal modification (oestrogens) as part of gender transition may be relevant in development of this autoimmune rheumatic disease (25).

On the other hand, since age has always been correlated to lower vaccine responsiveness, the significant differ-

ence between younger and older women should be considered regarding the vaccine dosage (22).

An interesting suggestion is that when a COVID-19 vaccine is available, postmenopausal women will need a tailored vaccine dose to contrast their heightened susceptibility to infectious diseases once their oestrogen levels decline.

Use of oestrogens on COVID-19 patients? Recent started trials

As recently synthesised there is currently not an efficient therapy for COVID-19 infection, but just symptomatic treatments to contrast the violent immune-inflammatory reaction (cytokine storm) against the SARS-CoV-2 invasion with all related clinical consequences including high fever, hypercoagulopathy and lung progressive failure (pneumonia) (26).

On the other hand, several approaches with the use of "off label" drugs are underway or included in controlled trials sometimes with high risk/benefit ratio (26, 27).

Very recently, based on the immunomodulating effects of oestrogens, the prevention and therapy of COVID-19 via exogenous oestrogen administration has been proposed for both male and female patients (28).

With this in mind, US clinicians at Renaissance School of Medicine at Stony Brook University and at Cedars-Sinai Medical Center they planed to treat COVID-19 patients of both sexes with female steroid hormones (oestrogens or progesterone) (29, 30).

The Stony Brook trial will include male (18 years and older) and female patients (55 years and older) with confirmed or presumed cases of COVID-19 who develop at least one serious symptom, such as high fever, shortness of breath or pneumonia, but do not yet require mechanical breathing support through intubation (28). Half the participants will be treated with an oestrogen patch placed on their skin for one week, while the other half will receive standard medical care.

On the contrary, participants in the Cedars-Sinai trial will receive progesterone, rather than oestrogen, as progesterone may have anti-inflammatory

properties and could (theoretically) prevent the onset of the “cytokine storm” (29). The study will include hospitalised men with mild to moderate COVID-19 infections. Half of those men will receive two doses of progesterone a day for five days.

During both the oestrogen and progesterone trials the severity of patient illness versus untreated groups will be monitored through time.

Conclusions

The empowering effect exerted by oestrogens on immune responses and protection against infections, can explain the reduced morbidity and mortality in female patients after COVID-19 infection. On the other hand, by considering that COVID-19 vaccines will be soon available, it is suggested that postmenopausal women will need a tailored vaccine dose to contrast their heightened susceptibility to infectious diseases once their oestrogen levels decline.

Finally, all the epidemiological studies confirm that older men are at high risk for more severe morbidity and mortality from SARS-CoV-2 infection, especially in presence of co-morbidities.

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