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Review Article

Does Estrogen Protect against COVID-19?

Nasser Mikhail* and Soma Wali

Division of Endocrinology, Department of Medicine, Olive-View UCLA Medical Center, David-Geffen School of Medicine, CA, USA

***Corresponding Author:** Nasser Mikhail, Division of Endocrinology, Department of Medicine, Olive-View UCLA Medical Center, David-Geffen School of Medicine, CA, USA.

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Abstract

Background: Emerging data suggest that estrogen could play a protective in women affected with coronavirus disease 2019 (COVID-19).

Methods: PUBMED search until September 23, 2020. Search terms include COVID-19, men, women, mortality, estrogen, pregnancy, safety. Retrospective, meta-analyses and pre-print studies are included.

Results: Women with COVID-19 have lower mortality compared to men with similar age even after controlling for co-morbidities. In premenopausal women, estradiol serum levels above 70 pg/ml were associated with decreased risk of having severe COVID-19. Pre-menopausal women using combined oral contraceptives (COCP) may have decreased risk of COVID-19. In post-menopausal women, one retrospective study from UK showed that hormone replacement therapy may have increased risk of COVID-19. However, another multinational study showed that estradiol use after menopause was associated with significant reduction in mortality from COVID-19. During pregnancy, when circulating levels of estrogen are normally very elevated, the course of COVID-19 is generally similar to that in non-pregnant women.

Conclusion: Preliminary data suggest that estrogen could be protective in women with COVID-19. However, data are sometimes inconsistent and exclusively based on retrospective studies. Nevertheless, available data justify the evaluation of the potential therapeutic role of estrogen in COVID-19 in the context of randomized trials.

Keywords: *COVID-19; Estrogen; Inflammatory Markers; Mortality; Severity; Pregnancy*

Introduction

Accumulating data suggest that men are disproportionally affected by COVID-19 in terms of severity and mortality [1-3]. Jin., *et al*. [1] from China were the first to report that men had more severe COVID-19 than women. They also found that death rates were 2.4 times greater in men than in women (70.3% versus 29.7%; P = 0.016) [1]. More recent data from 7 European countries and Korea showed that overall male to female ratio of mortality per 100,000 population was 1.4 [2]. The ratio varies with different ages as follows: 1.9 in the 40 - 49 years age group, 2.3 in the 50 - 59 group, 2.6 in the 60 - 69 group, and 1.6 in people older than 80 years [2]. Likewise, using data from 6 countries including the USA, Green., *et al*. [3] reported that male to female case fatality ratios were 2.53, 2.92, 2.57, 1.83, 1.57, 1.58 and 1.48 for ages 0 - 39, 40 - 49, 50 - 59, 60 - 69, 70 - 79, 80 - 89 and 90+ age groups. Ding., *et al*. [4] have shown that sex differ-

ences in COVID-19 severity and mortality may depend on menopausal status. Thus, they did not find differences in disease severity and clinical outcomes when comparing post-menopausal women with age-matched men [4]. Yet, significant differences existed between pre-menopausal women and age-matched men, with fewer pre-menopausal women suffering severe form of COVID-19 (46% versus 75% in men, P < 0.01) and death (0% versus 9.7% in men, P < 0.01) [4]. These results suggest that pre-menopausal state, characterized by ample estrogen levels, may have protective effect against COVID-19. Most researchers believe that excess mortality in men relative to women is largely due to higher prevalence of smoking, cardiovascular and lung disease co-morbidities [5]. Using a multinational registry formed of 14,712 patients with COVID-19, Alkhouli., *et al*. [5] found that all-cause mortality was 8.8% in men and 4.3% in women, odds ratio (OR) 2.15, 95% CI, 1.87 - 2.46; P < 0.01). After propensity score matching to control for differences in age and co-morbidities, all-cause mortality was slightly attenuated but remained significantly higher in men than in women, 8.13% versus 4.60%, OR 1.81, 95% CI, 1.55 - 2.11; P < 0.001) [5]. Therefore, there are factors beyond co-morbidities that contribute to excess mortality in men with COVID-19. These factors may include gender differences in immune response to infections and sex hormones, particularly estrogen [6,7]. The purpose of this article is to try to elucidate the implications of endogenous and exogenous estrogen in women with COVID-19.

Relevance of estrogen to COVID-19

Estrogen was shown to exert anti-inflammatory effects with subsequent reduction in pro-inflammatory cytokines such as interleukin-6 (IL-6) and interferon-α (IFN-α) as well as markers of severe inflammation such as C-reactive protein [7]. This anti-inflammatory action could virtually decrease severity of cytokine storm, the main cause of acute respiratory distress syndrome (ARDS) and mortality in COVID-19. Therefore, estrogen could virtually play a possible protective role against COVID-19 in large part due to its anti-inflammatory effect.

Circulating estrogen levels in patients with COVID-19

In 78 pre-menopausal women hospitalized for COVID-19, Ding., *et al*. [8] found that estradiol levels greater than 70 pg/ml were associated with decreased risk of having severe COVID-19, hazard ratio 0.30 (95% CI 0.09 - 1.001; P = 0.05) after adjustment for age, phase of menstrual cycle and co-morbidities. In addition, there was inverse correlation between estradiol levels and the cytokines IL-6, IL-8 and TNF-α [8]. Hence, these results are consistent with estrogen anti-inflammatory effect in women with COVID-19. In a study from UK called The COVID Symptom Study Smartphone Application "app", Costeira., *et al*. [9] reported that post-menopausal women had a higher rate of predicted COVID-19 compared with pre-menopausal women (OR 1.22, 95% CI 1.07 - 1.39; P = 0.03) [9]. Likewise, women using combined oral contraceptives (COCP) had a lower rate of predicted COVID-19 (OR = 0.87, 95% CI 0.64 - 0.97; P = 0.023) compared with age-matched women not taking COCP [9]. Conversely, women aged 50 - 65 years using post-menopausal hormone replacement therapy had higher predicted COVID-19 than age-matched women not taking such therapy (OR = 1.32, 95% CI 1.16 - 1.49) [9]. The authors mentioned that co-morbidities, duration and use of postmenopausal hormone therapy might explain the unexpected increase in predicted COVID-19 in this group of post-menopausal women [9].

Estrogen and COVID-19 mortality in women

In a retrospective study of a large international cohort of patients with COVID-19 spanning 17 countries, Seeland., *et al*. [10] examined the effect of use of exogenous estrogen on mortality from COVID-19 in pre-menopausal (aged 15 - 49 years) and post-menopausal (> 50 years-old). In the pre-menopausal group, mortality was similar among women using ethinyl estradiol (n = 2,078) as oral contraceptives and age-matched female patients were not using estrogen (n = 16,814) [10]. Meanwhile, in the post-menopausal group, women using estradiol (n = 439) had significantly lower mortality from COVID-19 compared with age-matched women not using estradiol (n = 16,278), 2.3% and 6.6%, respectively; OR 0.33 (95% CI, 0.18 - 0.62) [10]. These results suggest that, in post-menopausal women, estradiol intake may confer a low mortality risk from COVID-19. The authors attributed the lack of significant mortality benefit in pre-menopausal women to the fact that endogenous estrogen levels are already elevated in pre-menopausal women, thus diluting the effect of exogenous ethinyl-

estradiol administration [10]. The points of strength of this study included its large number of subjects from different countries and the control for age difference between the 2 groups of women who were using and not using estradiol [10]. However, it is limited by the lack of control for other factors that could modify risk of death such as prevalence of diabetes, cardiovascular disease, obesity, and smoking [10].

COVID-19 in pregnancy

Since pregnancy is characterized by extremely high levels of circulating estrogen, evaluation of susceptibility and clinical severity of COVID-19 in pregnant women may be a useful tool to examine the possible protective effect of estrogen. In general, available data suggest that severity of COVID-19 in pregnant women may not be different from non-pregnant women [11,12]. This notion is limited, however, by the lack of direct comparison with age-matched non-pregnant women with similar co-morbidities. Meanwhile, a possible protective effect of estrogen was suggested in the study of Chen., *et al*. [11] including 118 pregnant women hospitalized for COVID-19. In this study, 6 of the 9 pregnant women whose condition deteriorated did so following delivery, i.e. when serum estrogen levels rapidly declined.

Clinical trials underway of estrogen therapy for COVID-19

One trial (NCT04539626) is comparing clinical and biochemical outcomes of transdermal ethinyl estradiol 0.6 mg/norelgesetronin (a progestin) 6 mg weekly patch versus conventional treatment for 3 weeks in hospitalized female patients with non-severe COVID-19 [13]. All patients will receive anti-coagulants (Noxaparim) [13]. A second trial (NCT 04359329) is comparing 7-day course of transdermal estradiol with standard care to relieve symptoms of COVID-19 [14]. The trial outcomes also include rates of hospitalization, of intensive care unit transfer, intubation, and deaths [14]. Interestingly, this study will include men aged 18 years or more in addition to women 55 years or more [14].

Safety concerns about estrogen therapy for COVID-19

COVID-19 has caused thrombosis in both venous and arterial beds [15,16]. This coagulopathy may be in part due to increased platelet activation [17]. Meanwhile, estrogen therapy is known to increase risk of thrombosis [18]. For instance, use of combined oral contraceptives was associated with 2- to 6-fold increase in venous thromboembolism [18]. Although risk of thrombosis may decrease with the use of transdermal estrogen, there is still some residual risk [19,20]. Therefore, extreme caution should be exercised in giving estrogen therapy ton COVID-19 having risk factors of thrombosis, e.g. smoking, immobilization. Nonetheless, it is somewhat reassuring that estradiol administration in the trials underway is relatively of short duration ranging from 1 to 3 weeks [13,14].

Conclusion and Current Directions

Preliminary data derived from retrospective studies suggest that estrogen may have a beneficial effect in women with COVID-19 in terms of severity and mortality. This concept is based on the following observations: higher serum estradiol levels (> 70 pg/ml) are associated with less severe COVID-19 and lower serum levels of pro-inflammatory markers [8], pre-menopausal women may have lower predicted risk of COVID-19 compared with post-menopausal women [9], decreased risk of COVID-19 in pre-menopausal using COCP [9], and decreased mortality in post-menopausal women using ethinyl estradiol [10]. On the other hand, one study showed increase predicted COVID-19 in post-menopausal women using hormonal replacement therapy [9]. In addition, the elevated circulating estrogen concentrations in pregnancy do not seem to confer a milder course of COVID-19 in pregnant women compared to non-pregnant women [11,12]. Nonetheless, the balance of evidence is in favor of possible beneficial effects of estrogen in COVID-19 and justifies the conduct of randomized trials to further investigate this issue. Such trials are underway to evaluate efficacy and safety of estrogen not only in women, but also in men with COVID-19.

Conflict of Interest

The authors have no conflict of interest to declare.

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