



**University of diyala  
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**A Review article ;  
Sex hormones in COVID-19 disease**

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**Submitted by ;  
Shahad Jabbar majid  
Supervised by ;  
Asst. Lec. Yasmine sami Nassir**

## **Abstract**

Coronavirus disease 2019(COVID-19) is a rapidly spread respiratory disease that affects healthcare systems and global economy and therapeutic strategies are urgently needed.

The viral infection can affect immune response and lead to severe inflammatory response resulting in damaging of lung tissue. The condition is severe enough to require assisted ventilation.

Sex differences in COVID-19 in response to inflammation have been reported.

Sex hormones play important role in disease severity and susceptibility.

Hormone level varied between different age groups.

In hospitalized men the level of testosterone generally decreases and is associated with adverse outcomes and high mortality. ADT that indicated for Patients with prostate cancer have a favourable outcome. In hospitalized women The level of testosterone is high and associated with pro-inflammatory cytokines.

Premenopausal women that take oral contraceptive pills have a favourable prognosis with COVID-19.

Post-menopausal women that have not taken HRT had a poor prognosis..

Pregnant women had the same course of disease as non pregnant.

## **Keywords;**

**COVID-19, testosterone, estrogen, androgen deprivation therapy.**

## **Introduction**

Coronavirus\_ large family of viruses that are known to cause disease which the severity of it range from common cold to more severe respiratory diseases like Middle East Respiratory syndrome (MERS) & Acute Respiratory syndrome (SARS).

Novel coronavirus disease (COVID-19) was identified in 2019 in Wuhan City, china. Since this outbreak causes severe respiratory disease & leads to more lethal complications. It's spread to more than 196 countries and infected around 2 million patients around the world with over 130,000 deaths.

Death in these diseases occurring due to Acute respiratory distress syndrome (ARDS), Respiratory failure, Coagulopathy, septic shock, metabolic acidosis, arrhythmias, cardiogenic shock..

Accumulating data suggest that men are more commonly affected by COVID-19 in terms of severity and mortality [1-3]. Jin et al. [1] from China reported that men had more severe COVID-19 than women also found that mortality rates were 2.4 times greater in men than in women. While the mortality rate of male/female ratio per 100,000 population in Korea and European countries was 1.4 [2].

This ratio varies with different age groups[2]

1.9 in 40-49 yrs

2.3 in 50-59 yrs

2.6 in 60-69 yrs

1.6 in greater than 80 yrs.

Ding et al. [4] have explained that differences in ratio may depend on menopausal status and they didn't find any differences in severity & outcome of disease when comparing post-menopausal women with age\_matched men [4].

Recent studies show that pre-menopausal women have protective mechanisms against COVID-19 disease.

Most researchers believe that the increase in mortality rate in men relative to women is due to higher prevalence of smoking, cardiovascular disorders and lung disease comorbidities [5].

There are many factors beyond comorbidities that contribute to increased mortality in men with COVID-19.

These factors may include:

- gender differences in immune response to infections.
- sex hormones [6,7].

### **Sex differences in COVID-19**

Recently, several studies in china show differences in detected cases and case fatality between male /female. Which observed that women affected by this disease equally like men but the difference in course, severity and case fatality rate between them.[8,9,10]

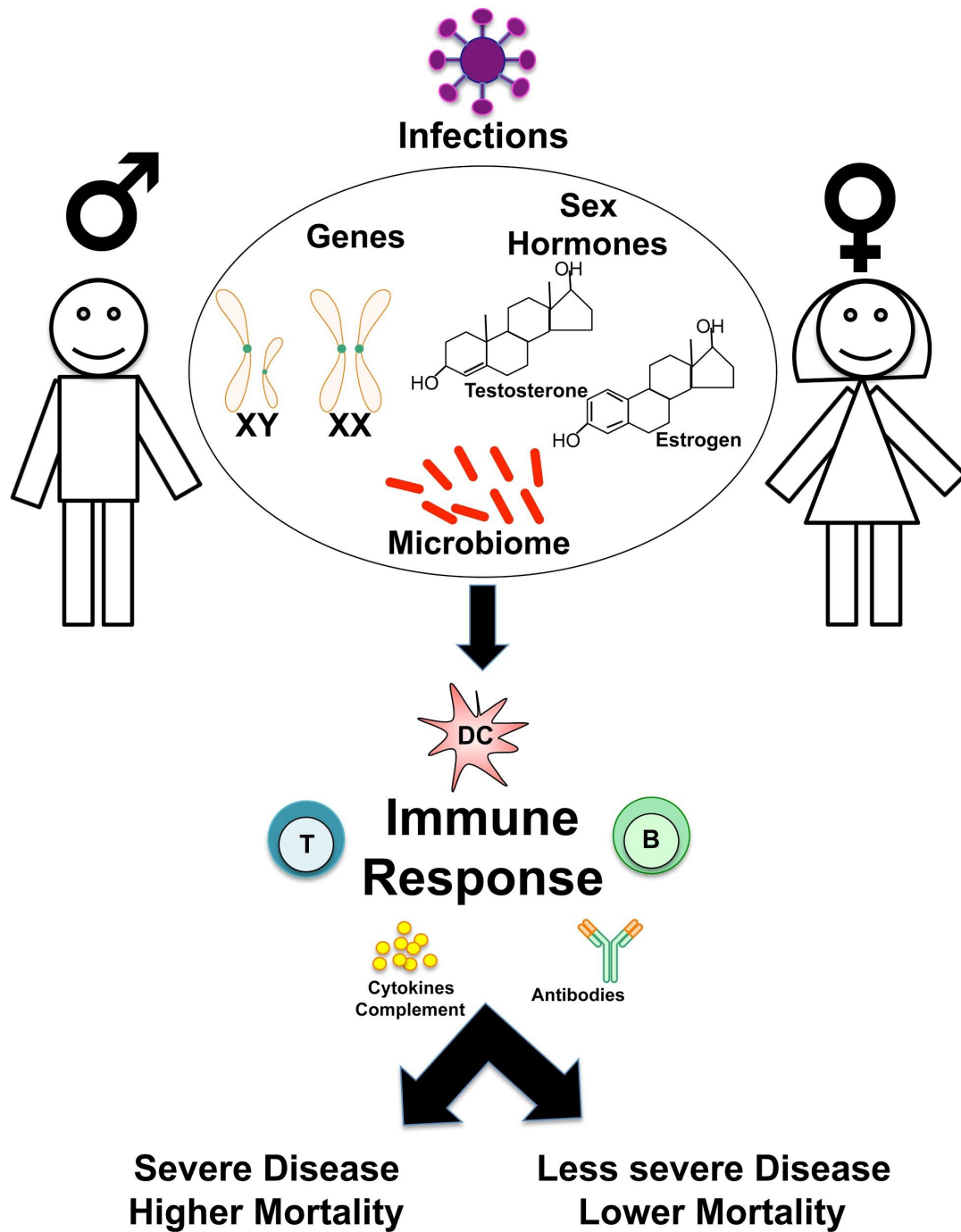
In fact, studies from Switzerland and Germany have recently sampled patients with COVID-19 aged from 60\_69yrs, 70\_79yrs, +80 yrs..

This studies show patients (male) >60 yrs are at high risk of severe complications of disease and death. [11,12]

While other countries like France show there is no difference between male And female in death..

Sex differences mostly observed in European countries due to age\_sex mix of cases and due to national testing strategies.

Novel data show more than 50 % of hospitalized patients and ICU admission are male. So the male affected by 1.5 fold more than women.[13]



. Fig 1 : genes, sex hormones, and microbiome may influence sex-based differences in the immune responses to infection, determining susceptibility, disease course, and clinical outcomes.

Hormone	Immune Cell/Cytokine	Effect	Relevance to COVID-19
Estrogen	Type 1 IFN	Promotes synthesis	Proinflammatory, beneficial early on but harmful when delayed
	IL-12	Promotes synthesis	Th1 cytokine, proinflammatory
	IL-6	Promotes synthesis	Pro-inflammatory (cytokine storm)
	IL-1 $\beta$	Promotes synthesis	Pro-inflammatory (cytokine storm)
	Neutrophils	Delays apoptosis	High recruitment and subsequent apoptosis are found in severe patients
	B cells	Promotes activation, maturation, differentiation, Ig antibody production	Beneficial IgG response but cytokine response is higher in women
	CD4 +	Promotes activation, Th1 differentiation	Different T cell types are needed for successful infection control
	Th17	Suppresses response	Th17 is proinflammatory, decreased levels means less host damage
	CD8 +	Increases activity	High levels early on may confer benefit
	Tregs	Increases FoxP3 expression and Treg production	Tregs suppress Th1 and Th17 responses and are anti-inflammatory
Progesterone	IL-10	Promotes synthesis	Anti-inflammatory, suppresses cytokine synthesis and MHC expression
	IL-1 $\beta$	Suppresses activation	Th1 cytokine, pro-inflammatory
	TNF	Suppresses activation	Pro-inflammatory, neutrophil and endothelial cell immune activation
	T cells	Decreases proliferation	May control T cell responses and cytokines
	IL-4	Increases production	Th2 cytokine, promotes Ig response controls T cell proliferation
	Tregs	Increases production	Tregs suppress Th1 and Th17 responses and are anti-inflammatory
	Th17	Decreases production	Protects the host from adverse immune response
	CD8 +	Reduces IFN- $\gamma$ production and cytotoxicity	Allows higher numbers of these cells without excess proinflammatory cytokines
Testosterone	TNF	Decreases production	Pro-inflammatory, neutrophil and endothelial cell immune activation
	IFN- $\gamma$	Decreases production	Pro-inflammatory, activates macrophages and increases antibody response
	IL-10	Increases production	Anti-inflammatory, suppresses cytokine synthesis and MHC expression

*Table summarizes the role of sex hormones on immune cells and cytokines and the potential relevance to the SARS-CoV-2 infection.*

## **Sex hormones in COVID-19**

Sex hormones act like biological factors that play important role in immunity response to infection and can affected on disease course, severity and outcome [14,15,16]

Level of sex hormones Varying throughout the lifespan as in pregnancy, puberty, sex hormones therapy, aging/menopause.

In general,estrogen has a protective effect against the infection by stimulating the innate and adaptive immunity response. Whereas testosterone is immunosuppressive which leads to higher susceptibility and disease severity in men [17]

Sex hormones control both ceullar and humoral immunity response.

Each cell in immunity system have receptors for sex hormones include:

- Estrogen receptors (ER)
- Androgens receptors (AR)
- Progesterone receptors (PR)

Sex hormones bind to these receptors and regulate gene and proteins expression to influence development, maturation, activation of immunity system.

Overactive response to infection can seen in certain respiratory virus like (SARS-COV, MERS, COVID-19) lead to severe infection and damage of organs and severe outcome.

hypothesized that the disease outcomes are a combination of the immune response and degree of host tissue damage [18,19]

## **Estrogen**

- Estrogen stimulating both innate myeloid cells ( monocytes, neutrophil, lymphoid cells) [20]

Also stimulate the synthesis of type1 INF and TLR-7 activation in women than men.

Lower physiological concentration enhanced pro-inflammatory cytokines (IL-12,IL-6,IL-1B) activation. While higher physiological concentration diminish their level and allow IL-10 regulatory cytokines. [20]

- Estrogen stimulating adaptive immunity by enhanced T Cell development, activation and differentiation.

Estrogen - ER signaling was shown to be necessary for thymic size and development. Also estrogen known to promote extrathymic T cell differentiation in the liver.

There are many studies mad on 78 premenopausal women hospitalized for COVID-19.Ding et al. [20]they found the level of estradiol >70 pg/ml associated with decrease the risk and severity of COVID-19 infection.

A study from the UK called The COVID Symptom Study Smartphone Application “app”, Costeira et al. [21]] show the post-menopausal women at highest risk for developing serious disease of COVID-19 compared to pre-menopausal women.

Also the women that used oral contraceptive pills are less likely to developing severe COVID-19 infection.[21]

Ma et al. [22] they mad studies on 81 young males hospitalized for COVID-19 show that estradiol level was normal.



While Schroeder et al. [24] studied a group of median aged 62 years hospitalized patients and the studies show the estradiol level was increased 52 to 185 pg/ml.

### **Testosterone in patients with COVID-19**

Ma et al. [22] they did studies on 81 young men hospitalized for COVID-19 and compared serum level of them with 100 healthy individuals, they found serum level of testosterone lower in COVID-19 patients also (LH) values were higher in COVID-19 patients compared with control individuals.

Testosterone /LH ratio (marker of testicular function) also lower in COVID-19 patients. [24]]

Schroeder et al. [24] measured testosterone in 35 patients with COVID-19 admitted to ICU found that 68% had low serum testosterone and 54% had very low serum testosterone level below 141 ng/dl [23]. 32% of all men and 16% of men with low serum testosterone level had LH level high. [13]

Schroeder et al. [24] observed that male patients with low serum testosterone had increased mortality rate compared to normal individuals.

Rastrelli et al. [25] found that total serum testosterone were negatively associated with the severity of COVID-19.

Ghazizadeh et al. [25] show direct association between free androgen index [ $=100 \times \text{total testosterone} / \text{sex hormones}$ ] and severity and susceptibility of COVID-19.

Wang et al. [27] found that ACE2 receptors of COVID-19 are present in many testicular tissue (Leydig cell, Sertoli cell and spermatogonia).

No orchitis have been seen in patients with COVID-19. While hypogonadism is more commonly to occur in COVID-19 patients. Also COVID-19 are occur in patients with severe underlying disease.

In female,

Schroeder et al. [24] found that 6 of 10 hospitalized females with COVID-19 had elevated serum testosterone levels more than 46 ng/dl.

High level of testosterone in females are correlated with inflammatory cytokines in women.

Ghazizadeh et al. [26] failed to find a significant association between free androgen index and COVID-19 susceptibility and severity in the female patients with COVID-19.

### **Role of androgen deprivation therapy and COVID-19**

Androgen deprivation therapy (ADT) could inhibit viral cellular binding and subsequent infection.

There are two studies suggesting that ADT may play an important role in protection and decrease the severity and susceptibility of COVID-19.

Montopoli et al.[28] reported that only 4 of 5273 patients with prostate cancer treated with ADT had COVID-19.

But all 4 patients they not died from the COVID-19.

Patel et al. [29]] found that usage of ADT in 22 patients with prostate cancer were associated with lowering the risk of COVID-19 infection and hospitalization.

These two studies suggested that low serum testosterone can achieved by ADT.[28]

## **COVID-19 in pregnancy**

As we know pregnancy is associated with increased levels of hormones especially estrogen. So the pregnant mother act as a good tool to examine the protective effect of estrogen against COVID-19.

But the recent data suggest there is no difference between pregnant and non pregnant women.

Chen et al.[30] Studies that were done on 118 pregnant women show 6 of 9 pregnant women got a worse outcome when the level of estrogen decreased.

## **Conclusions**

The effect of sex hormones observed in COVID-19. In men, low testosterone level which is associated with increased inflammatory markers and lead to bad prognosis. whether low testosterone level in men is cause or consequence in COVID-19 is still unclear. Observations showed a good prognostic effect when men taking ADT.

In women estrogen play important role in protection from COVID-19 infection. Premenopausal women are higher protected against covid 19 especially received oral contraceptive pills.

Post menopausal women at highest risk for lethal complication of COVID-19 especially not taking HRT.

High serum level of estradiol in pregnancy associated with less severe infection.

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