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## Research Article

# The Immun System Response in Covid-19 Infection in Polycystic Ovary Syndrome

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### Abstract:

COVID-19, globally affecting people's lives, is a respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which reaches the pandemic state. People who are vulnerable and not immunocompromised are known to suffer severe COVID-19 complications and are at a relatively high risk of death. Risk factors include age, male gender, cardiovascular comorbidities including hypertension, history of cardiovascular disease, insulin resistance, diabetes, and obesity. Emerging data also linked the risk of severe COVID-19 to certain factors such as hyper inflammation, low vitamin D levels, and hyperandrogenism. Androgens play a key role in the pathophysiology of this infection. Therefore, women with polycystic ovarian syndrome (PCOS), the most common endocrinopathy among women of reproductive age with a prevalence of 8-13%, who suffer from hyperandrogenism and are characterized by most metabolic diseases, need to be evaluated for risk. In this article, possible pathophysiological mechanisms related to the risk of COVID-19 in women with PCOS will be discussed. More scientific research is needed to understand which women are most at risk of becoming infected or developing complications, what causal mechanisms are possible to intervene, and what the long-term consequences will be.

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**Keywords:** Polycystic ovary syndrome, COVID-19, hyperandrogenism, ACE2, inflammation.

### Introduction:

The new severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) reached a pandemic state in March 2020 with a serious impact on international health systems and the global economy (1). Although the emerging coronavirus disease 2019 (COVID-19) was asymptomatic or mild in most cases, COVID-19 has caused severe illness with increased mortality in high-risk patients. It has led to mandatory quarantine measures and economic constraints worldwide to maintain capacity in health systems and intensive care units (2, 3)

COVID-19 has infected more than 142 million people globally, including the deaths of more than 3 million people currently reported to the World Health Organization (WHO) (4). Numerous large observational studies have shown that those with metabolic risk factors such as diabetes, obesity, and hypertension, and chronic cardio-metabolic

diseases are at higher risk for severe COVID-19 infection (5, 6). Prevention strategies are very important for elderly patients, immunocompromised or pregnant, those with health problems such as diabetes, heart, liver and lung disease who are in the high-risk group for COVID-19 infection. Increasing clinical evidence suggests that the incidence of severe COVID-19 is significantly higher in the elderly than younger adults and in men compared to in women (7, 8, 9,10). While the etiology is likely multifactorial, the physiological effects of androgens are one possible reason that may explain these gender-specific differences in results. Salonia et al suggest that different hormonal environments may have a deeper pathophysiological role in relation to SARS-CoV-2. It suggests that endogenous testosterone makes men more susceptible to the development of other serious complications associated with SARS-CoV-2 infection compared

to women (7). There are at least two plausible mechanisms by which androgens can lead to clinical consequences in COVID-19. The first possible mechanism is linked to the expression of type II transmembrane serine protease, a cellular co-receptor required for SARS-CoV-2 infection (11). The second possibility is androgen-driven immune modulation (12). Androgens play a key role in the pathophysiology of this infection. Therefore, women who suffer from hyperandrogenism and have polycystic ovarian syndrome (PCOS), most of which are characterized by metabolic diseases, need to be evaluated for risk. PCOS is the most common endocrinopathy in women of reproductive age, with an estimated prevalence of 8-13%. Its pathogenesis includes insulin resistance and hyperandrogenism that trigger reproductive (menstrual dysfunction, infertility), metabolic (metabolic syndrome, diabetes, cardiovascular risk factors) and psychological (anxiety, depression, low quality of life) complications (13). After excluding similar disorders (eg hyperprolactinemia, hypothyroidism, and nonclassical congenital adrenal hyperplasia), both ovarian dysfunction (i.e. chronic oligo- or anovulation) and hyperandrogenism (clinical hirsutism and / or biochemical, i.e. increased free testosterone or free androgen index) are key features for diagnosing PCOS. Polycystic ovarian morphology on ultrasound has also been presented as another potential feature for the diagnosis of PCOS according to the Rotterdam PCOS diagnostic criteria (14,15).

While younger age and female gender are typically associated with a lower overall risk of severe COVID-19 infection and mortality, patients with PCOS may represent a different subgroup of women with an above-average risk of adverse COVID-19-related outcomes. Indeed, a cohort study showed that women with PCOS have a 51% higher risk of COVID-19 compared to women without PCOS (16). In this review, we will try to explain why women with PCOS are more exposed to infection and which possible mechanisms may increase the susceptibility to SARS-CoV-2 infection and cause it to be severe.

### **PCOS and hyperandrogenism:**

Hyperandrogenism is present in more than 80% of women with PCOS, and these women have a worse metabolic profile than normoandrogenic women with PCOS (17). SARS-CoV-2 is an enveloped positive sense RNA virus that enters the

body through the interaction between the S-protein on the virus surface and angiotensin converting enzyme-2 (ACE-2) molecules, causing a cellular response. Before interacting with ACE-2, the S-protein is prepared by a type II transmembrane serine protease. ACE-2 and type II transmembrane serine protease have been shown to be present in different concentrations in women and men (18). ACE-2 expression levels have been shown to be higher in men than in women (19). Type II transmembrane serine protease is an androgen-regulated cell surface protease expressed predominantly in the prostate epithelium, spermatogonia and spermatids (20). PCOS is not only a state of hyperandrogenism with higher androgen levels, but also a state of increased androgen sensitivity. Androgens play an indirect role in viral entry through androgen receptor activation (21). When androgen receptor activation occurs, type II transmembrane serine protease is upregulated (21). Type II transmembrane serine protease acts as a primer for the spike protein of SARS-CoV-2, which then interacts with ACE-2 for viral entry. Increased levels and sensitivity to androgens may potentially directly affect susceptibility to COVID-19 in patients with PCOS (21, 22). Therefore, if the phenotype of PCOS women with hyperandrogenism expresses higher ACE expression levels, it can be assumed that an enhanced viral entry mediated by Type II transmembrane serine protease may occur in this female subpopulation as in men (16). Theoretically, patients with PCOS may be at higher risk of being infected by the virus and may require further supervision by specialists. Indeed, a cohort study showed that women with PCOS have a 51% higher risk of COVID-19 compared to women without PCOS (16).

One study found that the frequency of some common clinical symptoms of COVID-19 was significantly more pronounced in hyperandrogenic women than in non-hyperandrogenic women (23). Interestingly, significant androgenic alopecia has been documented as a common feature (71%) in a small cohort of hospitalized COVID-19 patients. [n, 41; mean age (range), 58 (23–79) years]. Accordingly, a potential relationship between androgens and COVID-19 severity appears plausible and may support the hypothesis that anti-androgens may represent an additional potential intervention against severe COVID-19 (24). This hypothesis also becomes relevant in the context of PCOS, as women with PCOS may exhibit hyperandrogenism (eg androgenic alopecia) on the

one hand and be under treatment with anti-androgens (eg spironolactone or finasteride) on the other hand. Currently, data on anti-androgen therapy in women with PCOS in the context of COVID-19 are insufficient; therefore, it is one of the additional aspects of PCOS management that needs to be studied (25).

### **PCOS- Renin-Angiotensin System:**

In hyperandrogenic women with PCOS, the renin-angiotensin system (RAS) shows a higher activation. Higher renin and lower angiotensinogen levels have been reported, indicating RAS hyperactivation in PCOS (22). RAS plays an important role in the regulation of blood pressure through the regulation of sodium and water balance. RAS overactivation is a risk factor for the development of kidney and cardiovascular diseases (22). RAS overactivity has also been described in metabolic syndrome, type 2 diabetes (T2D) and obesity, all high-risk conditions for COVID-19 infection, and severe diseases (22). PCOS, a cardiometabolic disease that includes metabolic syndrome, insulin resistance and increased risk of T2D, and obesity, as reported in case reports of PCOS women infected with SARS-CoV-2, causes a predisposition to severe COVID-19 disease (26). Neuropilin-1 (NRP1), a protein associated with RAS, is a cofactor that shows minimal viral infectivity when expressed alone, but significantly increases viral infectivity when co-expressed with ACE2 (27). NRP1 is a transmembrane glycoprotein that is expressed in endothelial cells and acts as a receptor for vascular endothelial growth factor (VEGF), and expression of both NRP1 and VEGF is increased in COVID-19 patients (28). Since RAS-associated proteins, NRP1 and VEGF, play a role in the severity of COVID-19, increased risk of severe COVID-19 in PCOS has been attributed to altered soluble NRP1 (sNRP1) and VEGF levels (26).

### **PCOS -Inflammation:**

PCOS is a hyperinflammatory condition that makes patients more prone to activate pro-inflammatory pathways in response to infection, and it has been suggested that it may underlie many cardio-metabolic abnormalities in this disorder (29). Increased levels of circulating pro-inflammatory mediators, including highly sensitive C-reactive protein (hsCRP), tumor necrosis factor (TNF) -alpha, procalcitonin, and interleukin-18 (IL-18), have been reported in women with PCOS. Although it is frequently associated with obesity

with a prevalence rate of 50-80%, these relationships persist even after correction of total fat mass (30, 31). It is also noteworthy that the severity of COVID-19 is the predisposition to develop a cytokine storm syndrome with excessive pro-inflammatory cytokine release (e.g. tumor necrosis factor- $\alpha$ , chemokines and interleukins such as IL-6, IL-7, IL-8, IL-2 and IL-1 $\beta$ ) in infected lung tissue (32). Available data suggest that this syndrome may lead to respiratory and multi-organ failure by inducing self-sustaining hyperinflammatory reactions in a subset of severe COVID-19 patients (32). Remarkably, hyper-cytokemia and activated pro-inflammatory pathways are thought to promote the pathogenesis and cardio-metabolic complications of PCOS, especially when combined with obesity (25). It is now well understood that women with PCOS and obesity exhibit marked adipose tissue dysfunction and irregular adipokine / cytokine secretion that causes a chronic pro-inflammatory state. In addition, women with PCOS often have polymorphisms in genes encoding proinflammatory cytokines such as tumor necrosis factor- $\alpha$  and IL-6 compared to healthy controls. It is known that the androgen receptor, which is closely related to COVID-19 in the lungs, plays a role in adaptive and innate immunity, especially in macrophage and neutrophil uptake (25). Women with PCOS who have been shown to have low-grade inflammation beyond that observed in obesity may be considered to be potentially at risk of serious COVID-19 infection due to this underlying proinflammatory predisposition. It can be assumed that the current inflammatory PCOS condition may more easily trigger a characteristic cytokine storm by exacerbating COVID-19 infection (16).

### **PCOS - Vitamin D Deficiency:**

Another common finding in PCOS and obesity is vitamin D deficiency, which has been reported to increase the risk of systemic infections and impair the immune response. On the contrary, vitamin D supplementation can prevent respiratory infections through various immunoregulatory functions, including reduced production of proinflammatory cytokines by the innate immune system, thus reducing the risk of cytokine storm leading to pneumonia (33). A relatively high prevalence of vitamin D deficiency has been observed among women with PCOS (approximately 67-85% of PCOS women). Compared to the general population, the prevalence of vitamin D deficiency

is relatively higher in PCOS patients (33). Potential links between low vitamin D levels and COVID-19 severity have been reported. Moreover, while current evidence suggests that vitamin D deficiency may contribute to acute respiratory distress syndrome (ARDS), mortality associated with COVID-19 is increased by both advanced age and cardio-metabolic comorbidity, which shows positive associations with lower vitamin D levels (25). Recent cross-sectional analysis of vitamin D levels and COVID-19 morbidity / mortality data showed negative correlations between mean vitamin D levels and both the number of COVID-19 cases and COVID-19 mortality in each country (34). Vitamin D is a well-known pleiotropic hormone that modulates adaptive and innate immune responses, regulates the activity of macrophages, and suppresses the pro-inflammatory cytokine response of respiratory epithelial cells against various viruses (35). In one study, obese subjects with PCOS showed a basal pro-inflammatory macrophage-derived protein profile with vitamin D deficiency associated with decreased T-cell regulatory proteins compared to controls (26). However, all these features explained that obese PCOS subjects may be at risk for more severe COVID-19 disease, and the effects of vitamin D on macrophage-related proteins cannot be considered independent of obesity (26). Especially increasing data support an inverse relationship between vitamin D and the severity of multiple PCOS symptoms, including hyperandrogenism, infertility, insulin resistance, and cardio-metabolic disease (25). Additionally, meta-analysis data show that vitamin D supplementation in women with PCOS can significantly lower circulating levels of total testosterone and CRP and increase the level of total antioxidant capacity (36). Taken together, these data suggest that women with PCOS may be at potentially higher risk for severe COVID-19 due to low vitamin D levels, which can be exacerbated by reduced sun exposure due to COVID-19-related quarantine measures.

### **Conclusion and Recommendations:**

Our study shows that women with PCOS are at increased risk for COVID-19 infection, and many factors can directly or indirectly affect it. Weight gain and obesity increase steroidogenesis and hyperandrogenism due to their worsening effects on insulin resistance. All these features represent key points to provide an explanation for the possible relationship between PCOS and SARS-

CoV-2. In women with PCOS, the endocrine-immune axis leads to immune dysfunction with chronic inflammation and hyperandrogenism may play a decisive role in the pathophysiology of infection.

Due to the overlap between risk factors for severe COVID-19 and common PCOS characteristics, some plans and close follow-up may be necessary for this female patient population during the pandemic. Therefore, clinicians treating women with PCOS, regardless of their specialty, should evaluate the risk profile of these patients associated with COVID-19. Depending on the outcome of the risk assessment regarding coexisting comorbidities that may predispose to the serious course of COVID-19, practical recommendations for treatment changes / optimization as well as related advice on issues such as protection and self-isolation should be provided.

The pandemic state of this infection, quarantine conditions, fear of death and the ensuing economic and social impact may have caused dramatic changes in individuals' daily living activities, including physical activity, sleep and eating habits. Considering these conditions, it is seen that the clinical presentation of chronic diseases such as PCOS and failure to comply with the treatment recommendations can cause severe consequences. Because (PCOS) is a lifestyle disease and all these conditions can be a detrimental factor in the development of PCOS management. Increased physical inactivity and unhealthy habits during the SARS-CoV-2 epidemic lead to short-term and long-term effects on different aspects of their health.

Additionally, SARS-CoV-2 may have a trigger for the occurrence of mental health disorders and emotional disorders. Thus, it can be argued that the change in lifestyle affects the clinical picture of PCOS and leads to an increase in the poor hormonal and metabolic profile in women with PCOS. For this reason, severe symptoms of menstrual irregularity, weight gain and dermatological changes such as acne, hair, and hirsutism may occur during the pandemic. This crisis should be turned into an opportunity, and lifestyle improvements should be continued by taking appropriate treatment or preventive measures according to the risk profile. Regular sleep and balanced nutrition profile should be provided by avoiding unhealthy habits. Body weight should be controlled by giving importance to physical activity at home. Motivation should be increased with activities that will reduce stress and

anxiety. As a result; Women with PCOS should be particularly encouraged to adhere to recommended infection control measures during the COVID-19 outbreak. New research is needed in this area in order to understand which women or even which PCOS phenotype are at the highest risk of

becoming infected or developing complications, what are the causal mechanisms that can be intervened, and the long-term consequences on the health of these patients.

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