*Review / Derleme*

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# Are women with polycystic ovary syndrome more vulnerable to COVID-19 infection?

## *Polikistik over sendromu olan kadınlar COVID-19 enfeksiyonuna daha mı hassaslar?*

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**Abstract**

Severe acute respiratory syndrome-coronavirus-2, the causative virus of Coronavirus disease-2019 (COVID-19), penetrates into the hosts' tissues via binding of its spike protein to the angiotensin converting enzyme-2 (ACE-2) receptors after activation of the hosts' protease enzymes. The most prominent effect is observed when the virus binds to the ACE-2 receptors of the alveolar epithelium and endothelium. Testosterone exhibits an immunosuppressive effect, and androgens play a modulatory role on protease enzymes. It is known that various comorbidities, including obesity; pregnancy; diabetes mellitus (type 1 or type 2); hypertension; cancer; chronic kidney, liver, and lung diseases; cerebrovascular disease; heart conditions; human immunodeficiency virus infection; immunologic disease; and immune suppression; affect the severity of COVID-19 infection. Polycystic ovary syndrome (PCOS) affects 5-10% of reproductive aged-women. Hirsutism is observed in 70-80% of the patients, while increased testosterone levels are detected in more than 50% of the women with PCOS. This syndrome is also associated with hyperandrogenism, insulin resistance, increased renin-angiotensin system activity, diabetes, and metabolic syndrome in a remarkable number of cases. PCOS also manifests a chronic pro-inflammatory state. Hyperandrogenism through hyperinsulinemia causes adipocyte hypertrophy and dysfunction that result in increased secretion of pro-inflammatory adipokine, which culminates in the creation of a chronic inflammatory state. In light of the metabolic and hormonal changes observed in women with PCOS, which make them more susceptible to severe COVID-19 infection, health care givers should provide special care and detailed counseling services.

**Keywords:** COVID-19, polycystic ovary syndrome, hyperandrogenism

**Öz**

Şiddetli akut solunum sendromu-koronavirüs-2, spike proteinin konakçının proteaz enzimleri ile aktivasyonu sonrası anjiyotensin dönüştürücü enzim-2 (ACE-2) reseptörlerine bağlanır ve hücre içerisine girer. En önemli etkiler virüsün alveol epiteli ve endoteldeki ACE-2 reseptörlerine bağlanmasından sonra ortaya çıkar. Testosteronun immün sistemi baskılayıcı etkisi vardır ve androjenler proteaz enzimleri üzerinde düzenleyici rol oynar. Obezite, gebelik, diabet (tip 1 veya tip 2), hipertansiyon, kanser, kronik böbrek, karaciğer ve akciğer hastalıkları, serebrovasküler hastalıklar, kalp hastalıkları, insan bağışıklık yetmezliği virüsü enfeksiyonu, immünolojik hastalıklar, immünosüpresyon başta olmak üzere eşlik eden diğer hastalıklar Koronavirüs hastalığı-2019 (COVID-19) enfeksiyonunun ciddiyetini artırmaktadır. Polikistik over sendromu (PKOS) üreme çağındaki kadınların %5-10'unu etkiler, hastaların %70-80'inde hirsutizm, %50'den fazlasında ise artmış testosteron düzeyleri saptanır. Bu sendrom hastaların önemli bir kısmında ayrıca hiperandrojenizm, insülin rezistansı, artmış renin-anjiyotensin sistemi aktivitesi, diyabet, metabolik sendrom ile ilişkilidir. PKOS ayrıca kronik pro-enflamatuvar bir durum gösterir. Hiperandrojenim hiperinsülinemi yoluyla adipositlerde hipertrofi ve fonksiyon bozukluğuna neden olarak pro-enflamatuvar adipokin sekresyonu ve kronik enflamatuvar bir duruma yol açar. PKOS'li kadınlarda onları ciddi COVID-19 enfeksiyonuna daha duyarlı hale getiren hormonal ve metabolik değişikliklerin ışığında sağlık hizmet sunucuları özel bir bakım ve ayrıntılı bir danışmanlık hizmeti sunmalıdır.

**Anahtar Kelimeler:** COVID-19, polikistik over sendromu, hiperandrojenizm

## Introduction

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), infects multiple organs, especially the alveolar epithelium, thereby causing severe acute respiratory distress. Various factors are involved in the pathophysiology and course of the infection, which mainly include high initial viral load, lung damage resulting from the infiltration of increased inflammatory monocyte macrophages (IMMs), neutrophils, and pro-inflammatory cytokines. Thus, severe acute respiratory distress

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develops, which is accompanied by the activation of endothelial cells that cause pulmonary thrombosis[1]. Replication of the virus results in massive inflammatory mediator release, and an increased inflammatory response is related to the severity of the disease.

SARS-CoV-2 is a single-stranded RNA virus. The spike (S) protein, which is among the four structural proteins, including S, envelope, membrane, and nucleocapsid proteins, has an affinity for the angiotensin converting enzyme-2 (ACE-2) receptors on human cells. This enables the binding and penetration of the virus into the human cells after priming of the S proteins by host proteases, such as transmembrane serine protease 2 (TMPRSS2), furin, and cathepsin L. Increased affinity and increased expression of the ACE-2 receptor allows greater transmission of the virus into the host[2,3]. The binding of CoV-2 to the ACE-2 receptor leads to the downregulation of this receptor and detoriates its protective effect against cardiovascular disease and acute respiratory distress[4]. The most prominent effect is observed when the virus binds to the ACE-2 receptors of the alveolar epithelium and endothelium.

The COVID-19 pandemic has affected more than 150 million people worldwide, causing more than three million deaths; however, a separate data for women and men has not been reported for most countries. Gender has been proposed as one of the risk factors in COVID-19 infection because there is a remarkable difference between men and women in terms of mortality and morbidity[5]. A national Danish study revealed a 50% increased risk of mortality and severe morbidity related to COVID-19 infection in men as compared with women, regardless of age and presence of comorbidities[6]. Studies from China, South Korea, and the United States reported similar or sometimes higher prevalence in women, depending on the criteria applied for COVID-19 testing, whether it is a community testing or symptomatic peoples' testing[7,8]. However, it has been reported that the incidence of severe disease and death was higher among men.

Various studies have shown that comorbidities and health conditions that affect the severity of COVID-19 infection include obesity; pregnancy; diabetes (type 1 or type 2); hypertension; cancer; chronic kidney, liver, and lung diseases; cerebrovascular disease; sickle cell disease or thalassemia; dementia or other neurological conditions; Down syndrome; heart conditions; human immunodeficiency viral infection; immunological disease; immune suppression; smoking; and substance use[8-10]. The differences between male and female ACE-2 receptor expression is questioned in order to understand different clinical outcomes in women and men during COVID-19 infection[11] besides other factors such as differences in immunological response and the effect of sex steroids on the immunological response[12,13]. Testosterone suppresses immune response, and androgens have a modulatory effect on proteins that facilitate the entry of SAR-CoV-2 into hosts' tissues.

Wambier and Goren.[14] mentioned that the hyperandrogenic phenotype in men, which manifests itself in form of androgenic alopesia, acne, and oily skin, increasingly makes the chest and face hair more vulnerable to COVID-19 infection. In an animal study, male and female mice were infected with SARS-CoV-2 and it was found that the male mice had higher mortality and increased accumulation of IMMs and neutrophils in the lungs. Moreover, gonadectomy or antiandrogens did not improve mortality in male mice. However, increased IMMs were encountered in ovariectomized or antiestrogen-treated female mice[15]. Increased IMMs cause elevated lung cytokine/chemokine levels, vascular leakage, and impaired T-cell response[15].

Polycystic ovary syndrome (PCOS) affects 5-10% of reproductive aged-women, and hirsutism is observed in 70-80% of the patients[16], while increased testosterone levels have been detected in more than 50% of the women with PCOS[17]. Hirsutism in PCOS is associated with both elevated levels of androgen, which is mainly secreted from the ovary, and increased sensitivity of the pilosebaceous unit to androgens[18]. Hyperandrogenism through hyperinsulinemia causes adipocyte hypertrophy and dysfunction that result in increased secretion of proinflammatory adipokine and creation of a chronic inflammatory state. PCOS is also associated with insulin resistance, central obesity, metabolic syndrome, and diabetes mellitus[19]. Obesity accompanies PCOS in a remarkable proportion of the patients. A study comparing the association of obesity with the severity of COVID-19 infection in men and women revealed that class II and III obesity (35-39.9 kg/m$^2$ and ≥40 kg/m$^2$, respectively) were independent risk factors of in-hospital deaths in men and in women that was observed only in class III obesity. In-hospital deaths were also found to be associated with IL-6 levels in obese patients[8]. This might be related to the different fat distribution between men and women, considering that men had an androgenic distribution of fat, which is mainly a central adiposity, the type encountered in women with PCOS. Adipocyctes secrete pro-inflammatory cytokines that facilitate chronic inflammatory response.

The risk of venous thromboembolism increased up to 1.5-fold in women with PCOS[20]. Androgens modulate proteases, mainly the TMPRSS2, furin, and cathepsin L, which play a major role in the binding and penetration of the virus into hosts' tissue[21]. Huffman et al.[18] investigated the effects of androgens on SARS-CoV-2 viral entry proteins in hyperandrogenic female mice treated with dihydrotestosterone (DHT) after detecting androgen receptors in the lung, kidney, brain, left ventricle, gastrointestinal system, and tibialis anterior of the untreated female mice. This study demonstrated the upregulatory effect of androgens in hyperandrogenic female mice on COVID-19 priming proteins and the authors suggested that this mechanism might explain the aggravated cardiac, renal, and gastrointestinal symptoms in COVID-19-infected women with PCOS. Subramanian et al.[22] conducted a population-

based study in England and reported that the crude COVID-19 incidence among 21,292 women with PCOS was 18.1, whereas this rate was 11.9 per 1.000 persons/year among 78,310 women without PCOS after age and body mass adjustment. Adjusting women with PCOS were found to have an increased risk of 28%. Morgante et al.[23] stated that besides the presence of insulin resistance linked to hyperandrogenism, another risk factor in hyperandrogenic women with PCOS was higher activity of androgen receptors and renin-angiotensin system. Hyperglycemia, obesity, and chronic inflammatory state were other risk factors besides the high incidence of vitamin D deficiency in women with PCOS[24]. Vitamin D plays an important role in immunoregulatory mechanisms due to its pivotal role in decreasing cytokine storm by decreasing the secretion of pro-inflammatory cytokines[25].

The overlaping risk factors for PCOS and COVID-19 infection should be considered because women with PCOS are at a higher risk for contracting severe COVID-19 infection. Therefore special care and detailed counseling should be provided for women with PCOS.

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