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Polycystic ovary syndrome and risks for COVID-19 infection: A comprehensive review

PCOS and COVID-19 relationship

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Abstract
This comprehensive review aimed to evaluate the relationship between SARS-CoV-2 infection (the cause of coronavirus disease 2019, or COVID-19) and the metabolic and endocrine characteristics frequently found in women with polycystic ovary syndrome (PCOS). In the general population, COVID-19 is more severe in subjects with dyslipidemia, obesity, diabetes mellitus, and arterial hypertension. Because these conditions are comorbidities commonly associated with PCOS, it was hypothesized that women with PCOS would be at higher risk for acquiring COVID-19 and developing more severe clinical presentations. This hypothesis was confirmed in several epidemiological studies. The present review shows that women with PCOS are at 28%–50% higher risk of being infected with the SARS-CoV-2 virus at all ages and that, in these women, COVID-19 is associated with increased rates of hospitalization, morbidity, and mortality. We summarize the mechanisms of the higher risk of COVID-19 infection in women with PCOS, particularly in those with carbohydrate and lipid abnormal metabolism, hyperandrogenism, and central obesity.

Keywords Polycystic ovary syndrome · COVID-19 · Obesity · Hyperandrogenism · Insulin resistance · Dyslipidemia

Abbreviations

ACE2	Angiotensin-converting enzyme 2
ADAM	A disintegrin and metalloproteinase
Ang	Angiotensin
ARDS	Acute respiratory distress syndrome
ATIR	Angiotensin receptor 1
BMI	Body mass index
COVID-19	Coronavirus disease 2019
CVD	Cardiovascular disease
DPP-4	Dipeptidyl peptidase 4
1L	Interleukin
IR	Insulin resistance
LH	Luteinizing hormone
NAFLD	Non-alcoholic fat liver disease
NK cell	Natural killer cell
PCOM	Polycystic ovary morphology
PCOS	Polycystic ovary syndrome
RAS	Renin-angiotensin system
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus virus 2
T2DM	Type 2 diabetes mellitus
TMPRSS2	Transmembrane serine protease 2
USA	United States of America
WHO	World Health Organization

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1 Introduction

Coronavirus disease 2019 (COVID-19) was declared a pandemic in March 2020 [1]. Women and young people were reported to be less affected [2, 3]. COVID-19 might be more severe and carry higher mortality rates in patients with comorbidities, such as hormone abnormalities, diabetes

mellitus, obesity, arterial hypertension, and dyslipidemia [4–9]. Among endocrine conditions, hyperandrogenism, adrenal insufficiency, and hyperthyroidism may facilitate the acquisition of the infection and be associated with more severe clinical forms of the disease. Polycystic ovary syndrome (PCOS), diagnosed in 5% to 20% of women of reproductive age [7, 10], is characterized by hyperandrogenism (70%–80%) and frequently accompanied by obesity (29%–70%), glucose intolerance (30%–40%), insulin resistance (IR) (18%–48%), diabetes mellitus (4%–26%), dyslipidemia (70%–75%), arterial hypertension (5%–25%), non-alcoholic fatty liver disease (NAFLD) (34%–70%), and low-grade chronic inflammation (20%–27%) [11–17]. This spectrum of clinical and laboratory findings in PCOS are major risks for severe COVID-19 [4, 18–20]. Because PCOS is among the most common endocrine diseases in women of reproductive age and is frequently associated with a higher risk of more severe COVID-19, this review updates the current knowledge on the subject. The need for elucidating the mechanisms of this association among the various PCOS phenotypes was also considered.

2 Methods

This narrative review aimed to identify possible connections between COVID-19 severity, PCOS phenotypes, and associated comorbidities. We identified the most relevant publications in the past two years in the English language. We searched PubMed, Web of Science, and Google Scholar to identify studies from December 2019 to November 2021. The search was enlarged by retrieving bibliographic citations from the obtained articles. The following major subject headings were combined: polycystic ovary syndrome and SARS-Coronavirus, PCOS and COVID-19, obesity and COVID-19, hyperandrogenism and COVID-19, IR and COVID-19, dyslipidemia and COVID-19. Abstracts were reviewed, and the most relevant complete publications were used (Fig. 1).

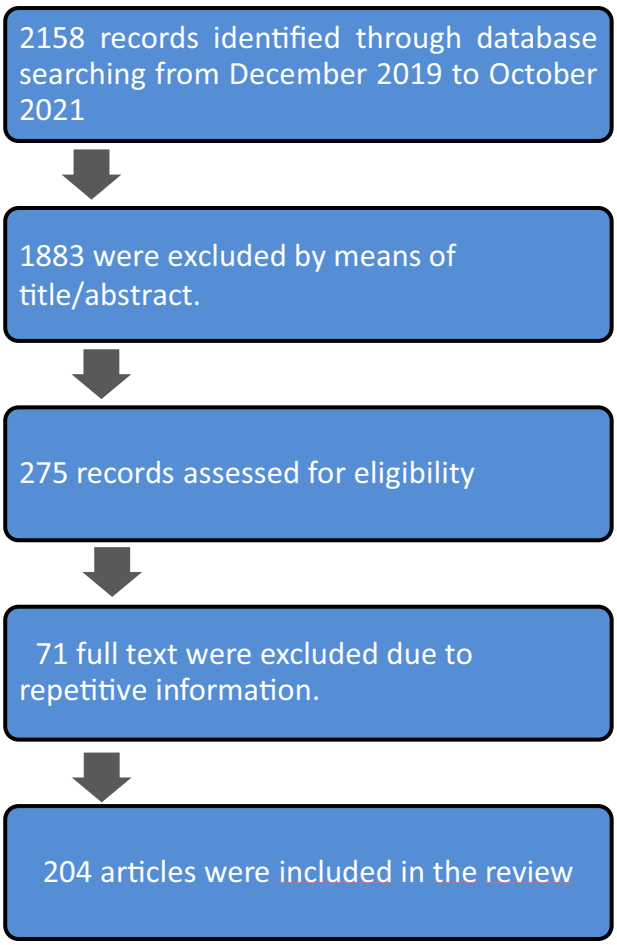

Fig. 1 Flowchart for review of the relationship between COVID-19 and polycystic ovary syndrome

3 COVID-19 prevalence, physiopathology, and risk factors

3.1 Prevalence and clinical manifestations

The pandemic began in December 2019 in Wuhan, China, via zoonotic transmission of a virus from animals to humans [2]. A novel coronavirus was identified that shared substantial homology with SARS-CoV; the new virus was named SARS-Cov-2. Epidemiological data showed that COVID-19 is more frequent in men than in women and older adults than in children [21]. The worldwide case-fatality rate ranges from 2.0% [2] to 7.2% [22–24]. It is currently estimated that COVID-19 occurred in over 258 million individuals worldwide and has resulted in 5 million deaths [25]. Children represent 7% to 27% of all cases of COVID-19 but only 1.2% to 4.2% of hospitalizations [26–29].

Symptoms of COVID-19 range from entirely asymptomatic to those of a common cold to a drop in oxygen saturation, pulmonary dysfunction, and death [29]. Asymptomatic carriage has resulted in poorly defined viral prevalence rates; however, the rate is estimated at 35% [30]. Seropositivity in these subjects had been estimated at 4.6% in the USA (ranging from 1.1% to 14.2%) [31]. Between the ages of 18 to 44 years, about four to five cases are undiagnosed for every diagnosed case of COVID-19 [31, 32]. There is a general sequel rate of 0.30–0.43 and 0.52 among those requiring hospitalization [32]. Older age is associated with a moderately increased risk of persistent symptoms [33], such as fatigue, dyspnea, insomnia, joint pain, and memory problems [32].

3.2 Physiopathology

SARS-CoV-2 infection causes an acute respiratory syndrome called COVID-19 (later broadened to include extrapulmonary manifestations). To enter cells, SARS-CoV-2 spike S protein requires two enzyme receptors, the angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease serine 2 (TMPRSS2) [34–36]. SARS-CoV-2 primarily affects the respiratory system, kidneys, heart, liver, central nervous system, and coagulation system. Involvement of the cardiovascular system may be associated with microvascular obstructive thrombo-inflammatory alterations [37]. The average incubation period lasts 5 to 6 days, and the initial symptoms include fever, dry cough, runny nose, sore throat, headache, dizziness, weakness, anosmia, ageusia, vomiting, and diarrhea [25].

3.3 Risk factors

Many clinical abnormal conditions are thought to facilitate SARS-CoV-2 infection. It may be more frequent and severe, with increased morbidity and mortality in the context of age, gender, metabolic, cardiovascular, and endocrine diseases [5]. Despite having a lower incidence in younger and female subjects, several comorbidities may increase the risk for COVID-19 in these populations [3, 4]. COVID-19 is more severe in patients with hypertension, cardiac disease, pulmonary disease, chronic kidney disease, and liver disease [38–40]. The Center for Disease Control lists about 25 clinical-laboratory abnormalities associated with increased prevalence of COVID-19. These included cancer, diabetes mellitus, immunocompromised state, heart diseases, chronic kindly disease, chronic obstructive pulmonary disease, obesity, pregnancy, smoking, liver disease, and arterial hypertension [41]. Additionally, several endocrine conditions were associated with more frequent COVID-19. Hyperandrogenism may facilitate SARS-Cov-2 infection. For this reason, polycystic ovary syndrome (a hyperandrogenic condition) gives rise to an almost 30% increased risk for COVID-19 compared with controls, even after adjustment for body mass index (BMI), age, and impaired glucose regulation [20].

3.3.1 Age

Despite infants and young children having a higher risk of respiratory tract infection, SARS-CoV-2 causes milder symptoms COVID-19 in younger people than in older patients [42, 43]. The reasons for this difference in susceptibility are not clear [2]. Children may carry smaller viral loads. It is also possible that the expression of ACE2 in lung and epithelial cells is lower in younger humans. Young people also present a qualitatively different response to the SARS-CoV-2 virus than adults, with less transition from naive T cells to central memory, effector, and effector memory T cells [44]. It is also possible that the simultaneous presence of other viruses in the lungs and airways in young children can compete with SARS-CoV-2, limiting its proliferation and cell invasion [2, 45]. Finally, combining these possibilities may explain why young people have a lower risk of COVID-19 than older people.

3.3.2 Gender

It appears that the likelihood of acquiring COVID-19 is similar in both sexes or is slightly higher in males; nevertheless, the severity of the disease is less pronounced in women than in men [3, 46–48]. Immunological and hormonal differences between men and women may explain this phenomenon [36, 49–51]. Despite identical susceptibility, severity and probability of death are higher in men, independent of age [3]. The effects of androgen levels via the expression of ACE2 and TMPRSS2 may explain the sex-specific differences in the disease severity [46, 48, 51–58]. Conversely, estradiol (and possibly progesterone) may protect women [53, 59]. Estrogens promote the production of anti-inflammatory cytokines (interleukin-10) and increase helper T and B cell numbers, thereby increasing antibody production. Estrogens suppress the production of proinflammatory cytokines and the migration of macrophages and monocytes into infected tissues [53]. Estrogens may also enhance vitamin D activity, reducing cytokine production [60, 61]. Moreover, women mount more robust immune responses than men in clearing viral loads [62, 63]. When vaccinated, women produce overresponses that can be twice as strong as men's [49, 64, 65]. Finally, the presence of two X chromosomes accounts for a more robust immune system that more effectively fights infections [65, 66].

3.3.3 Metabolic abnormalities

Obesity**,** dyslipidemia, IR, and diabetes mellitus also worsen COVID-19 [67, 68]. Obesity is characterized by adipose tissue hypoxia resulting in a chronic state of increased proinflammatory cytokines. Adipose tissue is also a target and reservoir of SARS-CoV-2 [69, 70]. The increased risk of severe COVID-19 in "Obesity" is well established [71–75]; the risks are higher for hospitalization and death [73, 76, 77]. The risk was estimated to be three-fold higher than normal-weight individuals [78]. Dyslipidemia is one of the most common comorbidities that worsen COVID-19. However, it remains a matter of debate whether dyslipidemia significantly influences COVID-19 outcome [79]. Two meta-analyses found that even when controlling for age and sex, dyslipidemia increases COVID-19 severity [40, 79]. Furthermore, treatment with statins may reduce severe disease and mortality in patients with dyslipidemia, mediated by their immune-modulatory effects [80–82].

Patients with diabetes mellitus have increased susceptibility to infections [83, 84] because of impaired immune function [85–87]. Despite SARS-CoV-2 infection in diabetic subjects being associated with adverse outcomes, it appears that the infectivity is not increased in the context of diabetes itself [88]. The hyperglycemic state participates in the pathogenesis and outcomes of respiratory infections [88–90]. Therefore, these findings suggest that patients with diabetes may experience higher viral loads when infected with respiratory viruses [87, 88].

3.3.4 Endocrine diseases

Endocrinological conditions such as thyroid dysfunction, adrenal dysfunction, and hyperandrogenism are related to increased susceptibility to acquiring COVID-19 and disease severity [9, 91, 92]. There is a direct effect of coronavirus on the thyroid gland [8]. Studies indicated that lower levels of triiodothyronine and thyroxine were found in SARS infections than controls, attributed to the destruction of follicular and parafollicular thyroid cells [91, 92]. There are few data regarding the relationship between COVID-19 infection and thyroid dysfunction [91, 93–95]. Clinical thyroid dysfunction was reported in 11% of subjects hospitalized with COVID-19: thyrotoxicosis in 94%, overt hypothyroidism in 6%, and subclinical thyroid dysfunction in 14% [91]. Based on thyroxin stimulating hormone levels, hyperthyroidism was identified in 20% and hypothyroidism in 5% of hospitalized patients [91]. Thyrotoxicosis in COVID-19 was associated with high proinflammatory interleukin-6 (IL-6) levels and a high prevalence of thromboembolic events [91]. Thyroiditis is accompanied by hyperactivation of the Th1/Th2 response with overproduction of proinflammatory cytokines [23, 92, 96], a pattern like the one that occurs in abnormal conditions such as COVID-19. Abnormal thyroxin stimulating hormone levels were associated with more prolonged hospitalizations and higher in-hospital mortality, primarily in women with thyrotoxicosis [91]. Regarding patients with a previous diagnosis of hyperthyroidism who were taking antithyroid medications, the risk of agranulocytosis overlapped with COVID-19, and complete blood count sare recommended if the infection is suspected [92].

Adrenal insufficiency may increase the risk of COVID-19 [97] through impaired immune function and defective neutrophil and natural killer (NK) cell activity [97]. Whether the COVID-19 outcome is worsened in adrenal insufficiency is controversial [98]. It appears that COVID-19 promotes degeneration and necrosis of adrenal cortical cells through a cytopathic effect of the virus [99]. It also appears that, in the SARS-CoV-2 infection, specific amino acid sequences mimic sequences of adrenocorticotropic hormone [98]. In the case of suspicion of SARS-CoV-2 infection in patients with adrenal insufficiency, the hydrocortisone dosage might be immediately adjusted [100]. Of note, achieving physiological cortisol concentrations in patients with adrenal insufficiency and COVID-19 is challenging. Patients with Cushing's disease may also be at higher risk of COVID-19 and severe manifestations [9, 101].

As mentioned earlier, sex differences in COVID-19 suggest that men are more susceptible and have worse outcomes and mortality than women in all adult age groups [22, 50]. SARS-CoV-2 spike proteins are primed by ACE2 and TMPRSS2 enzymes, which themselves are upregulated by testosterone levels [50]. Androgens may increase the risk and severity of COVID-19 [102, 103]. Nevertheless, it appears that a higher susceptibility to SARS-CoV-2 infection does not imply a higher risk of death [103]. In general, the compromised antiviral immune response to SARS-CoV-2 in men has been attributed to androgen levels [104]. Otherwise, in women, hypoestrogenism by ovariectomy or treatment with anti-estrogens increased morbidity and mortality, suggesting a protective effect of estrogen [105]. In summary, there are conflicting findings regarding the role of testosterone in COVID-19; however, testosterone modulates the transcription of the TMPRSS2 gene, inhibiting the expression of the protein required for viral entry into cells [30, 106]. Conversely, there is also evidence that low testosterone levels might worsen COVID-19 outcomes [107, 108].

4 COVID-19 and PCOS

In women of reproductive age, the prevalence of PCOS ranges from 5 to 20% [7, 10], depending on age, ethnicity, and criteria used for making the diagnosis [18]. The Rotterdam criteria with the sub-classification of PCOS phenotypes are currently recommended [109]. Women with PCOS present four phenotypes according to the presence or absence of hyperandrogenism, oligo/anovulation, amenorrhea, and polycystic ovary morphology (PCOM) by ultrasound.

The phenotypes may be associated with varying proportions of comorbidities such as obesity (38%–88%), arterial hypertension (5%–25%), glucose intolerance (30%–40%), IR (30%–70%), dyslipidemia (70%–75%), NAFLD (24%–55%), and non-alcoholic steatohepatitis (44%). Nevertheless, the most important clinical features of PCOS are hyperandrogenemia, visceral obesity, and IR [110–112].

A clear explanation of PCOS pathophysiology is lacking. The heterogeneity of PCOS reflects several possible pathophysiologies. An increased frequency and amplitude in luteinizing hormone (LH) pulses may be found in most patients. Higher LH levels are accompanied by increased testosterone production by theca cells. The resulting hyperandrogenism may be associated with IR and hyperinsulinemia. Furthermore, a multigenic polymorphism and steroidogenic enzyme defects can be found in some women with PCOS [113, 114].

Epidemiological studies suggest that PCOS women are more susceptible to infections than women without PCOS. The

crude incidence of COVID-19 was 18.1 per 1000 person-years among women with PCOS and 11.9 per 1000 person-years among those without [19, 20]. A population-based study in the United Kingdom (including more than 21,000 PCOS patients with an average age of 39 years) suggested that PCOS subjects have a 51% higher risk of COVID-19. This risk decreased to 28% after adjusting for age, BMI, and other confounding variables [19]. Despite being young and female, PCOS patients have the disadvantage of frequent comorbidities that may increase the risks of severe COVID-19 [115] (Table1).

IR associated with hyperinsulinemia, weight gain, and obesity enhances steroidogenesis and hyperandrogenism. Taken together, these features that are frequent in PCOS explain the association between PCOS and more prevalent SARS-CoV-2 infection [116] (Fig. 2). Additionally, endocrine and immune features of PCOS lead to immune dysfunction and a low-grade chronic inflammatory state [117]. Vitamin D levels are low and negatively associated with various comorbidities in PCOS. These low levels are also associated with COVID-19 [118–121].

4.1 COVID-19in PCOS phenotypes and associated comorbidities

The clinical relevance of PCOS phenotypes is based on anovulation, hyperandrogenemia, obesity, hyperinsulinemia, and low-grade chronic inflammation, with varying increased risk for type 2 diabetes mellitus (T2DM), dyslipidemia, and cardiovascular disease (CVD); the prevalence of these conditions varies across populations [18, 122]. In other words, the clinical relevance of COVID-19 in women with PCOS might be associated with phenotypes.

Table 1 Comparable comorbidities that increase the risks for COVID-19 disease in women with and without polycystic ovary syndrome

Subjects	Comorbidities
Non-PCOS	
	Hyperandrogenism
	Obesity
	Arterial hypertension
	Insulin resistance
	Hyperglycemia
	Dyslipidemia
	Liver disease
	Kidney disease
	Pulmonary disease
PCOS	
	Hyperandrogenism
	Obesity
	Arterial hypertension
	Insulin resistance
	Dysglycemia
	Dyslipidemia
	Non-alcoholic fatty liver disease
	Non alcoholic steatohepatitis
	Low-grade chronic inflammation

4.1.1 Hyperandrogenism

Testosterone levels, frequently increased in PCOS subjects, inhibit immunity and controls the expression of TMPRRS2 and ACE2, facilitating viral penetration into cells of various tissues [50, 56, 58, 104, 108, 123, 124] (Fig. 3). Women with PCOS and hyperandrogenemia have a worse metabolic profile than normoandrogenemic women with PCOS [15, 16, 125]. As previously stated, androgens favor SARS-CoV-2 infection [52, 56–58, 126–130]. Studies of these phenomena in humans are supported by animal models [123]. In addition to higher susceptibility to the SARS-CoV-2 virus, women with hyperandrogenic PCOS phenotype have more pronounced symptoms than women with PCOS and normal androgen levels [131]. The role of hyperandrogenemia in COVID-19 severity is supported by the benefit of anti-androgens against severe manifestations of COVID-19 [4, 50].

4.1.2 Obesity

The major contributing factors for more severe clinical forms of COVID-19 in obesity are associated respiratory dysfunction [132, 133], overexpression of ACE2 in adipocytes, chronic systemic inflammation**,** and immune system hyperactivation [62, 134, 135]. Subjects with a BMI over 30 kg/m^2 have a greater risk of death by COVID-19 [72, 75, 136], even after controlling for age and sex [71, 137]. In addition, obesity is associated with IR, leading to immune dysregulation characterized by amplified immune responses [138, 139], making the immune system more vulnerable to infections [140]. Increased levels of proinflammatory cytokines, NK cells, and mucosal-associated invariant T cells in obesity are also implicated in the pathogenesis of COVID-19 [73, 141, 142]. Additionally, higher proinflammatory dipeptidyl peptidase4 (DPP-4), and consequent hyperinsulinemia independently increase the risk of COVID-19 in obesity [143]. DPP-4 might interact with the S1 domain of the viral spike glycoprotein of SARS-CoV-2, allowing the virus to enter cells [144]. Obesity is also associated with a higher thrombosis risk relevant to coronavirus infection [145–147].

Concurrent hypoventilation and obstructive sleep apnea associated with obesity may compromise respiratory function [146, 147]. Overall, obesity might increase the risk of comorbidities such as diabetes, cardiovascular disease, and

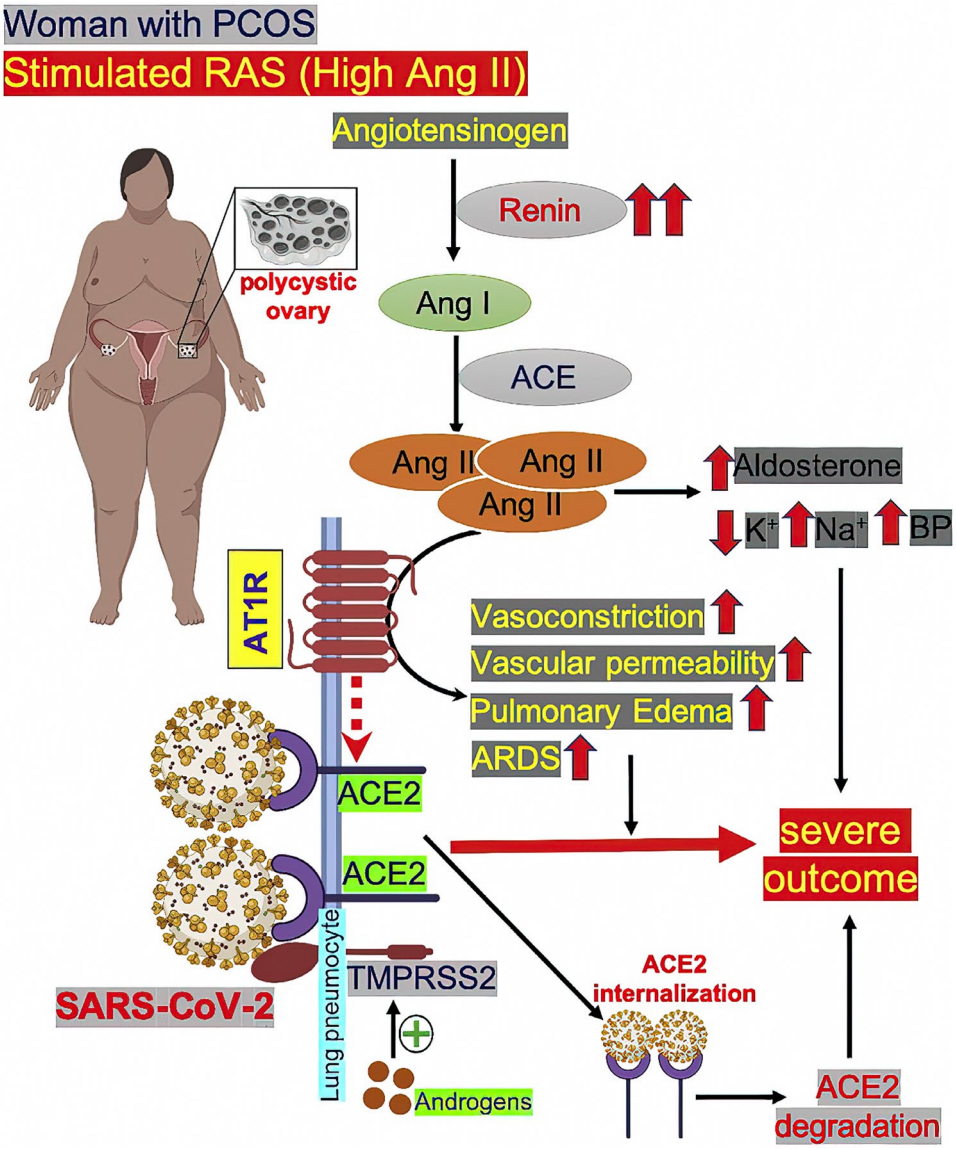

Fig. 2 In women with polycystic ovary syndrome (PCOS), plasma renin levels are high, and the renin-angiotensin system (RAS) is overactivated, leading to high amounts of Ang II. Excess Ang II causes ACE2 to dissociate from the angiotensin receptor 1 AT1R (AT1R) and bind to AT1R. The binding of angiotensin II to AT1R results in vasoconstriction, increased vascular permeability, pulmonary edema, and acute respiratory distress syndrome (ARDS). When ACE2 becomes detached from AT1R (indicated by broken red arrow), it increases the entry point for SARS-CoV-2 into pneumocytes. The viral infection might also be facilitated by overexpression of androgen-induced expression of TMPRSS2 in PCOS, as the androgen levels are higher. Upon binding with ACE2, the SARS-CoV-2–ACE2complex becomes internalized and undergoes proteasomal degradation of ACE2 inside the cell. This may cause the reduction of ACE2 levels in lung cells. High Ang II levels also stimulate the adrenal gland to increase aldosterone level, which, in turn, decreases potassium and increases sodium levels, ultimately causing increased blood pressure. Taken together, these mechanisms could result in severe outcomes inCOVID-19-infected women with PCOS (from Moin et al. [116]; Metabolism Open [115], with permission of CC-Creative Commons License Deed)

thrombosis risk in the context of COVID-19 [148, 149]. Consequently, obesity (a common clinical feature of women with PCOS) is frequently associated with greater severity, poor outcome, and increased death rates from COVID-19 infection in these women [22, 146, 150]. The expression of ACE2 is also higher in subcutaneous and visceral adipose tissue in PCOS, permitting the cellular entrance of SARS-CoV-2 [149, 151, 152]. Visceral adipose tissues in PCOS also overexpress proinflammatory cytokines, worsening COVID-19 outcome [117, 153, 154].

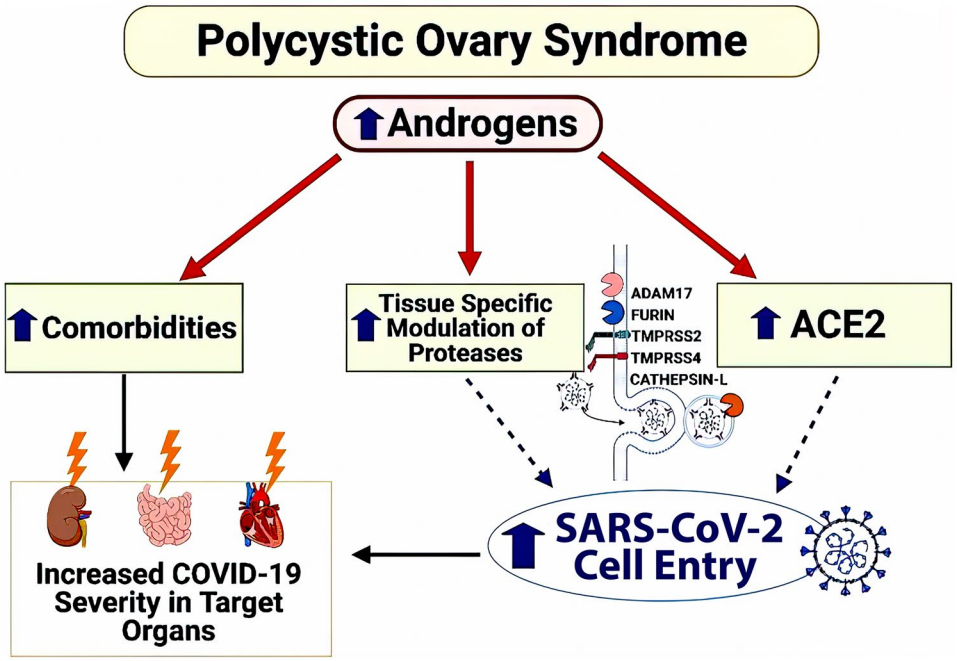

Fig. 3 Postulated mechanism of increased SARS-CoV-2 infection and worsened clinical outcomes in PCOS. In PCOS, elevated androgens upregulate the SARS-CoV-2 receptor ACE2 and modify host proteases to increase SARS-CoV-2 viral entry into tissues. The Up arrow signifies increase(s); the lightning bolt represents injury (from Lizneva et al. [122, 123], with permission of CC-Creative Commons License Deed)

4.1.3 IR/diabetes mellitus

Elevated serum glucose levels in diabetes are associated with seven-fold higher morbidity and mortality from COVID-19 [85, 86, 89, 138]. Overall, IR and diabetes mellitus type 1 and 2 are risk factors for SARS-CoV-2 infection [86, 155–157]. Previously, higher expression of ACE2 in pancreatic islets was associated with diabetes mellitus [158]. Although the prevalence of COVID-19 in diabetic women does not appear to be different from that of the general population, morbidity and mortality are more significant in patients with diabetes [22, 159–163].

There are several mechanisms by which dysglycemia increases the susceptibility to severe COVID-19. These include higher affinity or more favorable cellular binding of SARS-CoV-2 to ACE2 receptors, facilitating cell entry of SARS-CoV-2 by increased expression of ACE2 through reduced ADAMTS 17 activity as a consequence of hyperinsulinemia [164]. There is also reduced viral clearance, upregulation of ACE2 through blockade of the renin-angiotensin system, and reduced T-cell function through defective phagocytosis by neutrophils, monocytes, and macrophages [26, 85, 86, 165–167]. There is also increased susceptibility to hyperinflammation [138, 168] and increased levels of DPP-4, which degrades glucagon-like peptide 1 [144]. Dysglycemia also activates plasmin and thrombin, leading to a hypercoagulable state [169, 170]. Finally, the binding of SARS-CoV-2 to the ACE2 receptor may damage β-pancreatic cells, overwhelming the protective effect of the renin-angiotensin system, causing IR and increased SARS-CoV-2 internalization [158, 171]. The immune response is altered in hyperglycemic states, mediated by inhibiting lymphocyte proliferation and the impairment of macrophage and neutrophil functions [172, 173].

Because IR/diabetes mellitus is found in 30%to70% of women with PCOS, they are clinical biomarkers of more severe COVID-19 in these women [174]. In PCOS, IR is associated with increased proinflammatory cytokines and higher expression levels of ACE2 [175–177]. It appears that metformin, frequently used in PCOS women with IR, has antiviral effects mediated by activation of the adenosine monophosphate-activated protein kinase pathway, modifying the ACE2 receptor, and blocking the entry of SARS-CoV-2 into cells [177, 178]. It must be noted that, in the presence of marked dehydration and renal insufficiency in severe COVID-19, metformin must be discontinued [95, 165]. In the association of PCOS with type 2 diabetes mellitus and COVID-19, DPP4 inhibitors may be used; however, insulin is the treatment of choice [163, 179]. Of note, glucocorticoid treatment should not be used because it may aggravate glucose and metabolic homeostasis [95, 165].

4.1.4 Dyslipidemia

Dyslipidemia increases the severity and mortality of COVID-19 [40, 180]. Lower levels of high-density lipoprotein cholesterol preclude the stimulation of reverse cholesterol transport from the peripheral compartments to the liver, immune system modulation, and infection control. Studies have shown that lower levels of total cholesterol and low-density lipoprotein cholesterol were associated with increased COVID-19 severity [181, 182]. Investigators reported that hypercholesterolemia stimulates inflammatory

responses and increases COVID-19 mortality [83, 84]. More robust studies are needed despite several publications supporting the higher risk of COVID-19 in dyslipidemic patients [180].

Women with PCOS have an increased risk of hyperlipidemia, non-alcoholic fatty liver disease, and central obesity, tightly associated with hyperandrogenism [18, 40, 153, 181, 182]. These conditions are associated with frequent hospitalization for COVID-19 [183]. In about 5% of patients with COVID-19, hyperlipidemia was present [184]. Previous reports associated different SARS infections with dyslipidemia [12]. Interestingly, statin (used to treat dyslipidemia) exerts pleiotropic effects on inflammation and modulates the immune response [183]. There are reports of the effectiveness of statin treatment in some viral infections [185–187]. Whether statins may treat COVID-19 infection in dyslipidemic women with PCOS remains a hypothesis to be tested.

4.1.5 Arterial hypertension

Despite limited data, hypertension is considered one of the most critical risk factors for COVID-19. The loss of ACE2 through binding of SARS-CoV-2 may shift the system to higher angiotensin II and lower angiotensin (1–7) expression, activating the resin-angiotensin aldosterone system with vasoconstriction, sodium retention, oxidative stress, fibrosis, and increased baseline angiotensin levels (1–7) [50, 188, 189]. The rate of hypertension in patients with COVID-19 ranges from 10 to 34% [190]. Women with PCOS have higher blood pressure than non-PCOS women, particularly in the reproductive years and those with increased serum androgen levels [18, 191–194] and activation of the renin-angiotensin system [128, 190, 191]. Patients with arterial hypertension with or without PCOS have a 3–fourfold higher risk of death by COVID-19 [15, 192, 193]. In women with PCOS and COVID-19, renal complications are commonly mediated by upregulated renal ACE2 mRNA [128]. Of note, ACE blockers attenuate the risk of COVID-19 in hypertensive patients [194, 195].

4.1.6 Low-grade chronic inflammation

The risk of COVID-19 is exceptionally high in individuals with pre-existing conditions that impair immune response and amplify proinflammatory responses. Therefore, any condition involving a chronic inflammatory state may predispose a patient to acquire SARS-COV-2 and suffer a poor COVID-19 outcome [196]. Inflammation may accompany elevated BMI, obesity, hypertension, diabetes, and outcomes [197]. In summary, inflammation may facilitate severe COVID-19. The pre-existing inflammatory condition in PCOS renders patients more susceptible to activating proinflammatory pathways in response to infections [198], irrespective of total fat mass [199]. Central obesity in PCOS with dysfunctional adipocytes correlates with marked adipose tissue overproduction of cytokines [17] and the chronic inflammatory state [18], favoring COVID-19 in women with PCOS [200].

4.1.7 Vitamin D deficiency

Vitamin D influences innate and adaptative immune responses that regulate IL-6, and it inhibits the release of proinflammatory cytokines from macrophages in response to various viruses [118, 119, 201]. Lower vitamin D levels have been associated with an impaired immune system and a higher risk for COVID-19 [202]. Because about 60% of women with PCOS have vitamin D deficiency [203], it is expected that a decrease in vitamin D levels will lead these patients to a higher risk of severe COVID-19 [201]. In PCOS, decreased vitamin D levels are associated with factors related to systemic macrophage-derived cytokine panels [117, 118, 204]. Additionally, vitamin D supplementation was shown to reduce the risk of COVID-19 via impairment of macrophage maturation and decreased serum levels of proinflammatory cytokines [118, 119].

5 Concluding remarks

COVID-19 has been consistently reported to be more severe and fatal in the presence of comorbidities. Young age and female sex appear to be protective factors. Obesity, type 2 diabetes mellitus, and arterial hypertension are significant predisposing factors. The low-grade chronic inflammatory state is the core component linking these underlining conditions to poor COVID-19 outcomes. Some endocrinological dysfunctions also facilitate SARS-CoV-2 infection and COVID-19 severity, particularly hyperandrogenism and thyrotoxicosis. Considering that a chronic inflammatory state is found in nearly 30% of PCOS patients, COVID-19 therapy must be tailored for women with PCOS. The hyperandrogenism present in 80% of PCOS patients inhibits immunity and controls the expression of TMPRRS2 and ACE2, facilitating viral prescription into cells. Prescription of antiandrogens appears to have a beneficial effect on COVID-19 manifestations.

Obesity (the major contributing factor for severe COVID-19) is associated with amplified immune responses, increased proinflammatory cytokine levels, higher levels of DPP-4, and hyperinsulinemia. Because obesity is found in 30%–70% of women with PCOS, SARS-CoV-2 infection in PCOS requires specific management of concurrent IR. The prescription of metformin for these patients appears to modify the ACE2 receptor and block the entry of SARS-CoV-2 into cells. Hypercholesterolemia appears to increase

the severity of COVID-19 infection and dyslipidemia, which is found in two-thirds of women with PCOS and is closely associated with hyperandrogenism, NAFLD, and central obesity (conditions frequently associated with PCOS). Hypercholesterolemia stimulates the inflammatory response and increases COVID-19 mortality. Statins may modulate inflammation and immune responses; their use in COVID-19 in women with PCOS needs to be investigated. It is plausible to conclude that the association between COVID-19 infection and PCOS syndrome results in more severe clinical manifestations. Specific protocols for caring for these patients must be developed.

Declarations

Conflict of interest The authors declare there are no financial or other conflicts of interest that could be perceived as prejudicing the impartiality of this study.

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