Coronavirus Disease 2019 (SARS-CoV-2) and polycystic ovarian disease: Is there a higher risk for these women?

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A B S T R A C T

The new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with acute respiratory distress syndrome and infected patients have a relatively high risk of death.

Emerging risk factors for poor outcome in this disease include age, male gender, cardiovascular co-morbidities including hypertension, prior cardiovascular disease, diabetes and more recently obesity. To date there are no data relating to SARS-CoV-2 in PCOS women.

The present Clinical Opinion represents a summary of the epidemiological evidence and possible pathophysiological mechanisms regarding PCOS and COVID-19. PCOS women could be more susceptible to infections compared to non-PCOS women. Insulin resistance and the associated hyperinsulinaemia are drivers for enhanced steroidogenesis in women with PCOS. Weight-gain and obesity, through their worsening effects on insulin resistance, thereby drive enhanced steroidogenesis and hyperandrogenism. All these features represent key points to provide an explanation for the possible association between PCOS and SARS-CoV-2. Indeed, androgens may drive clinical results in COVID-19, through the expression of TMPRSS2, a cellular co-receptor necessary for SARS-CoV-2 infection and through androgen-mediated immune modulation.

In women with PCOS the endocrine-immune axis leads to immune dysfunction with a state of chronic inflammation, and hyperandrogenism and IR with compensatory hyperglycaemia could play a determining role in the pathophysiogenesis of the infection. However, it is possible that only specific PCOS phenotypes may be more susceptible.

In addition, vitamin D deficiency and gut dysbiosis are another important factor potentially involved in the increased risk of developing severe forms of COVID-19 in PCOS women.

Further scientific investigations are needed with the aim of understanding which women are most at risk of becoming infected or developing complications, what are the causal mechanisms on which it is possible to intervene with prophylactic and therapeutic measures and what the long-term consequences will be on the health of these patients.

1. Introduction

The new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), previously named 2019-nCoV disease (COVID-19), has been associated with acute respiratory distress syndrome and infected patients have a high risk of death. Recently, it has been also hypothesized that SARS-CoV-2-induced infection may lead to a complex and different disease, much more systemic, termed microCLOTS syndrome (i.e., microvascular SARS-CoV-2-associated lung vessels obstructive thromboinflammatory syndrome). Further data has suggested that human lung, gastrointestinal tract, liver, cardiovascular and urinary systems are also potential targets of SARS-CoV-2 infection [1].

COVID-19 has now infected over 6 million people worldwide, with a death toll of over 390.000 people. Emerging risk factors for poor outcome in this disease include age, male gender, cardiovascular co-morbidities including hypertension, prior cardiovascular disease,

diabetes and more recently obesity [2].

Preliminary published data show a much greater prevalence of male with laboratory-confirmed SARS-CoV-2 referred for intensive care unit admission and severe sequelae in several countries. In this context, males seem to not only be more susceptible to the infection compared to female subjects, at least in western countries, but their mortality rate attributable to SARS-CoV-2 infection is also highest [3]. Although the etiology is probably multifactorial, the physiological effects of androgens are one possible reason that may explain these sex-specific differences in outcomes. Salonia et al. speculate that the different hormonal milieu could have a more profound pathophysiological role in association with SARS-CoV-2, with endogenous testosterone leaving men more susceptible to the development of other serious complications related to infection of SARS-CoV-2 compared to women [4].

There are at least two plausible mechanisms by which androgens may drive clinical outcomes in COVID-19. The first possible mechanism is linked to the expression of TMPRSS2, a cellular co-receptor required for SARS-CoV-2 infection [5]. The second possibility is androgen-driven immune modulation [6].

So, if androgens play a key role in the pathophysiology of this infection, what might happen to women suffering from hyperandrogenism? Is it plausible to speculate that polycystic ovary syndrome (PCOS) women are more susceptible to infections?

PCOS is the most common endocrine and metabolic disorder in premenopausal women with a prevalence ranging from 6% to 20% [7]. Heterogeneous by nature, PCOS is defined by a combination of signs and symptoms of androgen excess and ovarian dysfunction in the absence of other specific diagnoses [8].

In this Clinical Opinion we will try to elucidate why PCOS women could be more exposed to infection, evaluating point by point the most salient features of the syndrome that could explain the predisposition to SARS-CoV-2 infection.

1.1. PCOS and hyperandrogenism

In 2006, The Androgen Excess PCOS Society indicated that PCOS is mainly a hyperandrogenic disorder and that the second criterion essential for the diagnosis could be either chronic anovulation or polycystic ovarian morphology [9].

Emerging data state that testosterone represent a key hormone in the context of COVID-19 pandemic [10]. The first biologic step required for potential infectivity of SARS-CoV-2 is the priming of the spike proteins by TMPRSS2. Although other proteases have been described to activate the spikes in vitro, only TMPRSS2 activity is regarded as essential for viral spread and pathogenesis in the infected hosts. TMPRSS2 may also cleave angiotensin converting enzyme 2 (ACE2) for augmented viral entry because SARS-CoV viruses interact directly with ACE2 via their S domain B to enter target cells [5]. Recently, ACE2 expression levels have been demonstrated to be higher in males than in females, at least in the lungs.

Androgen receptor activity has been considered a requirement for the transcription of the TMPRSS2 gene because no other known TMPRSS2 gene promoter has been described in humans to date [11]. Moreover, the androgen-regulated nature of TMPRSS2 is what permits testosterone or dihydrotestosterone driven oncogene expression in prostate cancer via the androgen receptor (AR) [12]. Nevertheless, it is not known if TMPRSS2 expression in the normal human lung is regulated by androgens in physiological settings. If the answer is yes, and TMPRSS2 suppression impedes viral entry or activation, inhibition of (gonadal +/- adrenal) androgen synthesis or direct AR blockade with prostate cancer therapies should be tested clinically [6].

Hyperandrogenic PCOS women show a higher activation of the renin–angiotensin system (RAS) [13,14]. Indeed, in rat model of hyperandrogenemia, the RAS is activated and angiotensinogen mRNA expression was increased 10 fold in rats. Androgens stimulate intrarenal synthesis of angiotensinogen and ACE synthesis was also increased with

dihydrotestosterone with a greater conversion of Angiotensin II [13]. It could therefore be assumed that if the phenotype of PCOS women with hyperandrogenism expresses higher ACE expression levels, an augmented viral entry TMPRSS2 mediated could occur in this subpopulation of women, as happens in men.

Furthermore, in hyperandrogenic PCOS women the AR activity is greater than in non-PCOS women, and this would lead to a greater transcription of the TMPRSS2 gene.

1.2. PCOS and insulin resistance

PCOS is also associated with metabolic abnormalities such as insulin resistance (IR), impaired glucose tolerance, and diabetes [7]. A bidirectional link between IR and hyperandrogenism is also present in PCOS [15].

Insulin is a key hormone that controls the metabolism of carbohydrates, proteins, and lipids. In metabolic tissues, insulin promotes glucose uptake and favors its conversion into glycogen and lipids for storage, through engaging downstream signaling pathways, including the phosphotidyl-inositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway and the mitogen-activated protein kinase (MAPK) pathway [16]. Upon ligand binding, the insulin receptor (INSR) dimerizes and self-phosphorylates, leading to the phosphorylation and activation of insulin receptor substrates. The regulation of INSR signaling may occur at multiple levels, at the level of insulin availability and surface receptor expression and post-translational modification, as well as at the intracellular level where crosstalks with additional pathways confer further activity and specificity [17]. Interestingly, immune cells, such as macrophages, B cells, and T cells, also express the INSR [18]. INSR signaling exerts critical immunostimulatory effects on T cells upon activation, driving T cell proliferation, cytokine production, and glycolytic and aerobic metabolism, which ultimately result in strengthening host defense against infection. Thus, T cell INSR signaling represents an important link at the crossroads of immunology, endocrinology, and metabolism that promotes optimal adaptive immunity. In a model of severe influenza infection with H1N1, lack of insulin receptor on T cells curtails antigen-specific immunity to influenza viral antigens [16].

Furthermore, relationship between diabetes, of which IR is the underlying cause, and infection has long been clinically recognized [19]. Infections, particularly influenza and pneumonia, are often common and more serious in people with type 2 diabetes mellitus (T2DM) [20]. Nevertheless, the evidence remains controversial regarding whether diabetes itself indeed increases susceptibility and impacts outcomes from infections, or the cardiovascular and renal comorbidities that are frequently associated with diabetes are the main factors involved [21]. Diabetes and uncontrolled glycaemia were reported as significant predictors of severity and deaths in patients infected with different viruses, including the 2009 pandemic influenza A (H1N1), SARS-CoV and MERS-CoV [22].

Diabetes is a chronic inflammatory condition characterized by multiple metabolic and vascular abnormalities that can affect our response to pathogens [21]. Hyperglycemia and IR promote increased synthesis of glycosylation end products and pro-inflammatory cytokines, oxidative stress, in addition to stimulating the production of adhesion molecules that mediate tissue inflammation. This inflammatory process may compose the underlying mechanism that leads to a higher propensity to infections, with worse outcomes in patients with diabetes [21].

Several defects in immunity have been associated with hyperglycemia. Poorly controlled diabetes has been linked to inhibited lymphocyte proliferative response to different kinds of stimuli [23], as well as impaired monocyte/macrophage and neutrophil functions [21]. Abnormal delayed type hypersensitivity reaction and complement activation dysfunction have also been described in patients with diabetes [22]. In vitro studies have shown that pulmonary epithelial cells exposure to high glucose concentrations significantly increases

influenza virus infection and replication, indicating that hyperglycemia may enhance viral replication in vivo [24].

An endocrine-immune axis that controls T cell immunological function should be considered. Understanding that immune dysfunction is associated with hyperglycemia and IR - characteristics also present in women with PCOS - will provide good help in understanding and treating SARS-CoV-2 infections in this group of populations at risk.

1.3. PCOS, adiposity and inflammation

Obesity was not specifically reported in the initial cohort studies of COVID-19 from Wuhan, but regional epidemiological data from the USA suggests that at least 25 % of patients who die have obesity [25]. According to the Intensive Care National Audit & Research Centre (ICNARC) report on COVID-19 in critical care of United Kingdom (March 27th 2020), it was observed that 73.2 % of 3883 patients with confirmed COVID-19 were overweight or obese and that among patients with BMI > 30 Kg/m2 who had undergone intensive care, 54 % of them died [26]. In addition, according to Italian data published on May 7th 2020 by Istituto Superiore di Sanità, an overall prevalence of obesity of 11.0 % was found among 2621 patients died for whom there was the availability of medical records [27].

A small retrospective study of 85 subjects with COVID-19 identified obesity as a risk factor for admission to ICU with patients requiring increased medical attention [28]. Moreover, in the influenza A subtype H1N1 pandemic, obesity was also strongly associated with a worse disease outcome and death [29].

These data raise the question of whether there is link between obesity and disease survival, and whether obesity over its endocrine or cardiometabolic associations might independently contribute to COVID-19 risk. Moreover, most women with PCOS (38 %–88 %) are overweight or obese [30]. Considering that there are close links between obesity and PCOS, another question is whether obese PCOS women are therefore more susceptible to infection.

Obesity could contribute to both diabetic and cardiovascular risk of COVID-19 [31,32]; it is an independent risk for hypoventilation syndrome in ICU patients [33] and could contribute to respiratory failure in patients with acute respiratory distress syndrome [33].

Ryan et al. provide a theoretical framework whereby viral systemic spread, entry and prolonged viral shedding in already "inflamed" adipose tissue (AT) may augment immune responses with consequences for cytokine cascade amplification. The authors highlight AT as an abundant source for local and systemic enrichment of cytokines, some already independently associated with increased COVID-19 mortality [34]. As well known, obesity represents a state of low grade chronic inflammation that can contribute to the onset of metabolic diseases (dyslipidemia, IR and T2DM) and can modify innate and adaptive immune responses, making the immune system more vulnerable to infections and less responsive to vaccinations, antivirals and antimicrobial drugs [35].

Obesity-driven chronic inflammation and impaired fibrinolysis contribute to increase the risk of developing thrombosis, which currently seems to be one of the mechanisms potentially involved in worsening lung damage and in death, this justifies the use of heparin for both prophylactic and therapeutic purposes in different protocols used in patients with COVID-19 [36].

Low-grade inflammation is determined by a condition of adipocyte hypoxia and dysfunction, that results in an exuberant secretion of pro-inflammatory cytokines such as tumor necrosis factor α, interleukin (IL) 1β and IL-6 and the recruitment of immune cells macrophage, T-cell and B-cell, creating an auto-regenerating inflammation loop [37].

Obesity have a substantial impact on immunity and pathogen defence, including the disruption of lymphoid tissue integrity; alterations in leukocyte development, phenotypes and activity; and the coordination of innate and adaptive immune responses. In particular, obesity has been shown to impair memory CD8 + T cell responses to

influenza virus infection, resulting in increased mortality, viral titers in lung, and worsened lung pathology [36].

An endocrine-immune axis in which adipose tissue is responsible to immune dysfunction should be considered. IR which plays a decisive role in obesity, contributes to this cascade of events through the mechanisms mentioned above. All of these conditions support our hypothesis that women with PCOS are a risk category for this disease.

1.4. PCOS and vitamin D

Another common finding in PCOS and obesity is vitamin D deficiency (VDD) that has been reported to increase the risk of systemic infections and to impair immune response [38,39]. Conversely, vitamin D supplementation can prevent respiratory infections through several immunoregulatory functions including the decreased production of pro-inflammatory cytokines by innate immune system, therefore reducing the risk of cytokine storm leading to pneumonia [39]. Interestingly, epidemiological data report that Italy is one of the Countries with the highest prevalence of hypovitaminosis D in Europe, with a very high prevalence in subjects with obesity and elderly women with diabetes [39].

A series of studies have demonstrated that VDD might be a causal factor in the pathogenesis of IR and the metabolic syndrome in PCOS [40]. Indeed, a relatively high prevalence of VDD is observed among women with PCOS (approximately 67–85 % PCOS women) and compared with the general population, the prevalence of VDD is relatively higher in PCOS patients [38]. Additionally, positive associations of VDD with some well-known comorbidities of PCOS including T2DM, IR, metabolic syndrome, and cardiovascular diseases, are reported [38]. This is supported by the fact that the vitamin D receptor (VDR) regulates more than 3% of the human genome, including genes that are crucial for glucose metabolism [40].

Vitamin D has multiple roles in the immune system that can modulate the body reaction to an infection. Vitamin D deficiency impairs the ability of macrophages to mature, to produce macrophage-specific surface antigens, to produce the lysosomal enzyme acid phosphatase, preventing them from releasing too many inflammatory cytokines and chemokines and to secrete H2O2, a function integral to their antimicrobial function [41,42]. This might explain, in part, why Martineau et al. have observed that vitamin D was protective in cases of hypovitaminosis [43]. Crucial in the innate immune response are the toll-like receptors which recognise molecules related to pathogens and when activated release cytokines and induce reactive oxygen species and antimicrobial peptides, cathelicins and defensins. Several of the toll-like receptors affect or are affected by vitamin D receptor induction [44].

Therefore, based on the previous considerations it could be hypothesized that VDD could potentially take part to the link between obesity, PCOS and increased susceptibility to complications and mortality due to COVID-19.

1.5. PCOS and microbiota

The ecosystem of the gut and commensal microbiota can both regulate and be regulated by invading viruses, facilitating either stimulatory or suppressive effects. Therefore, it is plausible to consider whether the gut and SARS-CoV-2 interaction may play significant roles in the intensity of the infection and its clinical outcomes.

The integrity of the gut microbiome (the collective genomes of the diverse microbiota that reside in the gastrointestinal tracts of humans) could conceivably be disturbed by SARS-CoV-2, causing gut dysbiosis in the host as with other infectious diseases [45]. Scarce data are available on the effect of COVID-19 on intestinal microbiota. A small case series from China revealed that some patients with COVID-19 showed microbial dysbiosis with decreased Lactobacillus and Bifidobacterium [46]. Lactobacillus species, as result of carbohydrate fermentation, can produce lactic acid, and consequent pH changes inactivate different viruses

[47]. The intestinal epithelial cells' functionality relies largely on the luminal presence of butyrate as energy source, and butyrate-producing bacteria in the gut belongs to the phylum Bifidobacterium. The intestinal epithelial barrier dysfunction and altered intestinal permeability represent a major factor contributing to the predisposition to inflammatory diseases [48]. To date, no study has been reported to identify the microbiota species that interact with SARS-CoV-2 [46].

On the other hand, gut dysbiosis is a common features underlying health problems that are associated with inflammation and other disorders, such as diabetes, obesity and PCOS. These conditions are associated with an altered composition of gut microbiome which in turn is fundamental for the regulation of the host's immune system and for protection from infections. In addition, gut microbiome plays a role in mitigating the damage resulting from infections. Direct suppression or promotion of viral infection by the altered microbiome can occur via various mechanisms, such as genetic recombination, alteration of virion stability, driving the proliferation of cells, simulating attachment to permissive cells, and contributing to viral replication suppression; promotion of viral infection may occur by inducing systems' immunoregulatory and perturbing local immune responses [47].

Women with PCOS had a dysbiotic gut mirobiota with reduced alpha diversity, increased beta diversity as well as changes in bacterial composition. Moreover, the altered gut microbiota of PCOS is associated with sex-hormones, anthropometric parameters and metabolic parameters, which may contribute in part to the abnormal glucose metabolism and hyperandrogenism [49].

Reduced alpha diversity has been observed in several diseases, like T2DM, cardiovascular disease and obesity that represent risk factors for SARS-CoV-2 [49]. Lower alpha diversity of gut microbiota could contribute to chronic low-grade inflammation and it is expected that COVID-19 could further exacerbate inflammation exposing patients to higher levels of circulating inflammatory molecules. This may explain the increased risk of severe complications of COVID-19 for subjects with dysbiotic gut microbiota. The use of probiotics to maintain the balance of intestinal microecology and thus indirectly strengthen the immune system should be considered in the management of SARS-CoV-2.

2. Conclusion

We speculate that PCOS women could be more susceptible to infections compared to non-PCOS women. IR and the associated hyperinsulinaemia are drivers for enhanced steroidogenesis in women with PCOS. Weight-gain and obesity, through their worsening effects on IR, thereby drive enhanced steroidogenesis and hyperandrogenism. All these features represent key points to provide an explanation for the possible association between PCOS and SARS-CoV-2. In PCOS women the endocrine-immune axis leads to immune dysfunction with a state of chronic inflammation, and hyperandrogenism and IR with compensatory hyperglycaemia could play a determining role in the pathophysiogenesis of infection. However, it is possible that only specific PCOS phenotypes may be more susceptible.

In addition, VDD and gut dysbiosis are another important factor potentially involved in the increased risk of developing severe forms of COVID-19 in PCOS women.

Our scientific hypothesis has some limitations related to the lack of scientific evidence produced so far due to the recent onset and rapid spread of the pandemic and it must be confirmed by clinical and epidemiological studies. Another limitation of our hypothesis is represented by the fact that women with PCOS are young, of childbearing age and that this disease mainly affects older populations.

There is an urgent need for novel research activities in this area, with the aim of understanding which women are most at risk of becoming infected or developing complications, what are the causal mechanisms on which it is possible to intervene with prophylactic and therapeutic measures and what the long-term consequences will be on the health of these patients.

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