Role of Polycystic Ovary Syndrome in Increasing Susceptibility to COVID-19: A Biochemical and Psychological Approach

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Abstract: *The effect of comorbidities on coronavirus 2019 susceptibility and prognosis is of recent research interest. Polycystic ovary syndrome must be considered one of the comorbidities owing to the influence of hyperandrogenic conditions on increasing expression of viral receptor such as transmembrane serine protease and angiotensin-converting enzyme-2. Obesity and undesirable adipocyte accumulation increase hospitalization rate. Insulin resistance induces abnormal cytokine production and impairs T cell functions. The renin-angiotensin system hyperactivity and neuropilin-1 upregulation increase viral entry. Impaired gastric microbiota and Vitamin D deficiency lead to inflammation. Hypertension, cardiovascular ailment, hair loss, anxiety, and depression are consistent in coronavirus 2019 patients. This review addresses the comprehensive role of biochemical and psychological aspects of polycystic ovary disease on immune functions against severe acute respiratory syndrome coronavirus-2 infection. The study provides knowledge on the up-to-date mechanisms related to coronavirus infectivity on polycystic ovary syndrome women and shall help healthcare professionals to consider inclusive treatment options for such patients. However, there are numerous gaps in the therapeutical and molecular mechanisms involved in polycystic ovary syndrome and its heterogenous role as a comorbidity in coronavirus infection.*

Keywords: COVID-19, Polycystic ovary syndrome, Hyperandrogenism, Immunity, Depression

1. Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by the presence of multiple cysts in the ovarian follicle, anovulation, and hyperandrogenism. The syndrome is common among women of reproductive age, with a prevalence of 6 to 16%, based on the diagnostic criteria [1], [2]. This heterogeneous syndrome is generally associated with oligomenorrhea or amenorrhea, insulin resistance, obesity, low sex drive, chronic inflammation, acne, hair loss, hirsutism, stress, sleep disorders, and reduced fertility [3]. Several comorbidities linked with PCOS have been identified which include metabolic disorders like type 2 diabetes mellitus, cardiovascular diseases, non-alcoholic fatty liver disease, vitamin D deficiency, pregnancy complications, and cancer [4]. In addition, these symptoms and dysfunctions tend to decrease the overall quality of life of women with PCOS in terms of physiological health, mental stability, and social well-being [5]. Furthermore, the comorbidities associated with PCOS correlate with the risk factors for Coronavirus disease 2019 infections [6].

Coronavirus disease 2019 (COVID-19) pandemic is an alarming outbreak of global healthcare emergency with its origin in the capital city of Hubei Province of China, Wuhan [7]. The total number of reported COVID-19 cases in 222 countries is about 190, 459, 848, with a mortality count of 4, 094, 836 as of July 17, 2021 [8]. India has reported 31, 064, 908 cases and 413, 123 fatalities [9]. The causative organism of COVID-19 is the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that has an incubation period of 7-14 days [10]. Major manifestations of COVID-19 include fever, fatigue, anosmia, ageusia, cough, myalgia, headache, rhinorrhoea, and dyspnoea [11]. It is ascertained that this airborne virus transmits by entering the respiratory tract as aerosols (<5 μm) and respiratory droplets (>5-10 μm), thereby triggering the host immune response [12]. The severity of the disease may lead to acute systemic inflammatory response, cytokine storm, multiple organ failure, and acute respiratory distress syndrome (ARDS) [13]. However, most patients recover without the need for hospitalization in about 16 to 34 days [14]. Comorbidities like diabetes, hypertension, chronic respiratory ailments, immunodeficiency disorders, cardiovascular diseases, hepatic diseases, and cancer increase the risk of COVID-19 susceptibility and severity [15].

The coincidence of risk factors between COVID-19 and PCOS renders women with PCOS more susceptible to COVID-19 infection [16]. In addition, it is estimated that women with PCOS are at 52 % increased risk to COVID-19 infection in comparison with non-PCOS women with a risk percentage of 28 % [17].

In this review study, we have attempted to analyse all possible cumulative, metabolic, and psychological effects of PCOS that correspond with COVID-19 vulnerability.

Hyperandrogenemia

Hyperandrogenemia is an endocrine disorder of excess circulating androgen and it is one of the essential diagnostic criteria for PCOS [18]. Specifically, hyperinsulinemia caused due to insulin resistance reduces androgen binding to its receptor, thereby acting as a major factor in inducing hyperandrogenism [19]. Androgen is found to have direct involvement in the pathogenesis of COVID-19 through several molecular pathways. One such

significant pathway includes the transmembrane serine protease (TMPRSS2) enzyme that favours the entry of SARS-CoV-2 into the lung epithelial cells by activating viral spike protein. The expression of the TMPRSS2 gene is positively regulated by the androgen response element [20]. Moreover, an experimental study with hyperandrogenic female mice proved that elevated androgen levels positively correlate with increasing angiotensin converting enzyme 2 (ACE2) and TMPRSS2 expression in lungs and therefore promoting viral entry [21].

A comparative study highlights that men are 60 % more likely to experience adverse COVID-19 complications than women [22]. Taking account of the high androgen levels in men as well as women with PCOS, androgen-induced upregulation of the TMPRSS2 gene could be the possible determinant in rendering COVID-19 susceptibility in such individuals. However, there could be other mechanisms of pathogenesis and intensification of COVID-19 that employ androgen in eliciting COVID-19 complications.

Obesity and dyslipidemia

Obesity is a driving factor that acts as both cause and effect in PCOS severity. About 30 % of obese women develop PCOS in comparison to 5 % of the lean population. Hyperandrogenemia in such women contributes to increasing body fat deposition and lipolysis in adipocytes leading to obesity, insulin resistance, and increased adrenocorticotropic hormone [23]. Interestingly, peculiarly large abdominal fat muscle cells are found in women with PCOS, proving adipocyte accumulation in the abdominal region [24]. Moreover, the hormone ghrelin involved in appetite is found to be relatively low in PCOS women, thereby ensuring a link between insulin resistance and obesity [25].

Obesity is a significant risk factor in augmenting prognosis and mortality chances of diseases owing to its association with multiple comorbidities. Several studies have concluded the effect of obesity on COVID-19 infection and hospitalization [26]–[28]. One such survey conducted in New York City highlights a positive correlation between obesity and COVID-19 hospitalization with a prevalence of 41.7 % [29].

In addition to PCOS-related comorbidities such as hyperglycemia, insulin resistance, dyslipidemia, cardiovascular diseases, and inflammation, obesity also contributes to respiratory distress [16]. Moreover, increased expression of viral entry receptor protein ACE2 in adipocytes ensures a greater risk of COVID-19 infection in people with obesity [30]. Besides, the effect of pandemic lockdown and work from home is considerably reducing the extent of physical activity in working PCOS women which could escalate fat deposition and further undesirable weight gain.

Hyperglycemia and Insulin Resistance

Resistance to insulin is one of the key characteristics of obese women with PCOS and in few cases of lean PCOS. This resistance is conferred by impaired insulin signalling pathway, wherein constitutive phosphorylation of serine residue of the insulin receptor occurs, coercing them metabolically inactive [31]. Thus, the role of insulin as an endocrine hormone in carbohydrate, protein, and fat metabolism, especially the ability of insulin to favour glucose uptake and glycogenesis is affected. This results in hyperglycemia in women with PCOS.

Several researchers have concluded the relationship between hyperglycemia and COVID-19 prognosis to severe cases [32], [33]. Possible mechanisms of inducing severity include increased furin and ACE2 expression, affected T cell function and increased production of cytokine interleukin 6 [34]. Furthermore, COVID-19 infection is in turn found to induce insulin resistance, and hyperglycemia in non-diabetic patients [35]. Evidently, the triglyceride-glucose index which is one of the key markers of insulin resistance is significantly increased in deceased COVID-19 patients [36].

With the increased prevalence of insulin resistance among PCOS women, there is a greater chance of COVID-19 severity and post-covid induced diabetes. Metformin is one of the beneficial medications in controlling insulin resistance in women with PCOS and type 2 diabetes mellitus [37]. However, maintaining blood glucose level in COVID infected hyperglycemic patients require special care in prescribing case-specific medications as provided in the guidelines issued by international diabetic experts [38].

Hyperactive Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system plays a vital role in blood pressure homeostasis, renal tubule sodium chloride reabsorption, and aldosterone production. One of the significant enzymes involved in this system is ACE2, which acts as a viral receptor in SARS-CoV-2 infectivity [39]. This receptor enzyme hydrolyses angiotensin II to biologically active angiotensin (1–7) which results in vasodilation and conferring lung protection [40].

ACE2 upregulation leads to serious pathological conditions such as organ failure and mortality in COVID-19 infected patients [41]. On contrary, an experimental study reveals a low level of angiotensinogen and ACE2 in PCOS women suggesting the effect of renin-angiotensin system hyperactivity on increasing aldosterone levels and vasoconstriction [42]. In addition, there is a lack of sufficient evidence to draw any conclusive relationship between ACE/ACE2 levels in PCOS women and COVID-19 predisposition. Moreover, the approach of managing COVID-19 mortality with the treatment of angiotensin receptor blockers or ACE2 inhibitors is also found to be insignificant [43], [44].

Neuropilin-1 Upregulation

Neuropilin-1 is a cell surface signalling receptor family, which when co-expressed with ACE2 results in increased SARS-CoV-2 infectivity. Vascular endothelial growth factor (VEGF) is one significant ligand that binds to the neuropilin-1 receptor and aids in tumour proliferation. Moreover, high levels of neuropilin-1 have been reported in blood endothelial cells, olfactory epithelium, diabetic pancreas, respiratory and intestinal tracts. In extreme COVID-19 cases, upregulation of the neuropilin-1 gene and low levels of soluble neuropilin-1 is seen [45]. Interestingly, increased neuropilin-1 expression in the olfactory epithelium and brain olfactory tracts of COVID-19 infected patients suggests a strong influence on neuropilin-1 in inducing anosmia, a distinguished symptom of COVID-19 [46].

High levels of neuropilin-1 are dominant in conditions such as autoimmune encephalomyelitis, demyelinating diseases, rheumatoid arthritis, and asthma [45]. A biochemical study on PCOS women reveals the occurrence of significantly low levels of soluble neuropilin-1 which indicates Renin-angiotensin system hyperactivity and high levels of membrane-bound neuropilin-1 [47]. Hence, women with PCOS are more susceptible to neuropilin-1 induced SARS-CoV-2 infectivity.

Hypertension

The connection between obesity and hypertension is well established by several experimental and survey studies [48]. Specifically, hyperactivity of renin-angiotensin-aldosterone system, increased aldosterone levels and stimulation of sympathetic nervous system in obese conditions are found to directly elevate blood pressure [49].

As revealed by a study in Australia, the prevalence of hypertension in women with PCOS is significantly high compared to the control group [50]. Moreover, PCO-induced rats are found to develop hypertension and increased sympathetic nervous system activity [51]. Certainly, these researches suggest a strong influence of PCOS on abnormal blood pressure levels.

Hypertension is evident comorbidity in COVID-19 infection and severity with 30 % prevalence in COVID-19 patients [52]. In addition, a recent study on the effect of blood pressure on COVID-19 mortality revealed that the prevalence of heart failure-induced death in COVID-19 patients increased with high systolic pressure [53]. Also, conditions such as respiratory failure, sepsis, and hospitalization are seen in COVID-19 patients with grade 1 hypertension [54].

The above-mentioned adverse effects of hypertension make it an ideal risk factor for COVID-19 mortality especially in PCOS women with obesity and hyperglycemia. Moreover, research on the treatment of such comorbidities in COVID-19 infected patients is very limited. Treatment of hypertension with renin-angiotensin-aldosterone system inhibitors in COVID-19 patients are hypothesised earlier but the success of such an approach lacks significant proof [55].

Cardiovascular Ailments

PCOS women are predisposed to cardiovascular disease risk factors such as dyslipidemia, obesity, stress, insulin resistance, and hypertension making them suitable candidates for cardiovascular abnormalities [56]. Moreover, markers for cardiovascular ailments such as C reactive protein and homocysteine are relatively high in PCOS women [57]. A recent systematic review highlights that women with PCOS are at two-fold greater risk of developing coronary heart disease and stroke [58].

Likewise, COVID-19 patients exhibit elevated levels of cardiovascular ailment biomarkers such as troponin1 and brain-type natriuretic peptide and among COVID-19 deceased cases, about 40 % expressed cardiac damage. The possible mechanisms of such cardiac damage include viral infiltration in cardiac cells, inflammatory response, and hypoxia-induced cardiac stress. Moreover, COVID-19 mortality due to cardiovascular diseases is higher compared to other comorbidities like hyperglycemia, age factor, or pulmonary ailments [59].

With the advent of cardiovascular ailment biomarkers in PCOS patients, the COVID-19 induced risk of cardiovascular disease and heart failure could possibly increase the mortality rate several folds in such patients.

Vitamin D Deficiency

Vitamin D deficiency is diagnosed with low levels of serum 25-hydroxyvitamin D, which is one of the common occurrences in women with PCOS [60]. Vitamin D ligand-receptor complex is known to regulate about 300 genes involved in carbohydrate and lipid metabolism, thereby governing insulin resistance. Deficiency of vitamin D also has a link to type 2 diabetes mellitus, chronic inflammation; increased blood lipids lead cardiovascular disorders, and hypertension [61].

A high frequency of vitamin D deficiency is found in PCOS women with a prevalence of about 67 to 85 % in comparison to the normal population [62]. Moreover, there is a positive correlation between the severity of insulin resistance and vitamin D deficiency [60]. Increased expression of inflammatory biomarkers such as CXCL5, CD163, and MMP9 was found in PCOS obese women who could increase susceptibility to infections [63]. However, the exact mechanism of adverse effects of vitamin D deficiency in instilling comorbidities in PCOS women is unclear.

The effect of sunlight-derived vitamin D is an important factor influencing immunity. It was found that COVID-19 cases were high in the countries of the northern hemisphere during winter than in the southern hemisphere. The primary reason for such variation is the vitamin D derived immunity in people of the southern hemisphere which was induced by increased sun exposure

[64]. Moreover, the primary mechanism of vitamin D in suppressing over expression of cytokines, reducing inflammation, preventing acute respiratory distress syndrome, and promoting antiviral effector pathways are troubled by vitamin D deficiency [6].

Hence, for the above very reason, vitamin D deficiency not only increases susceptibility to COVID-19 infection but also could worsen the disease progression by contributing to the development of comorbid conditions. Indeed, low levels of external vitamin D exposure during the pandemic lockdown could also add to the existing frailty [6].
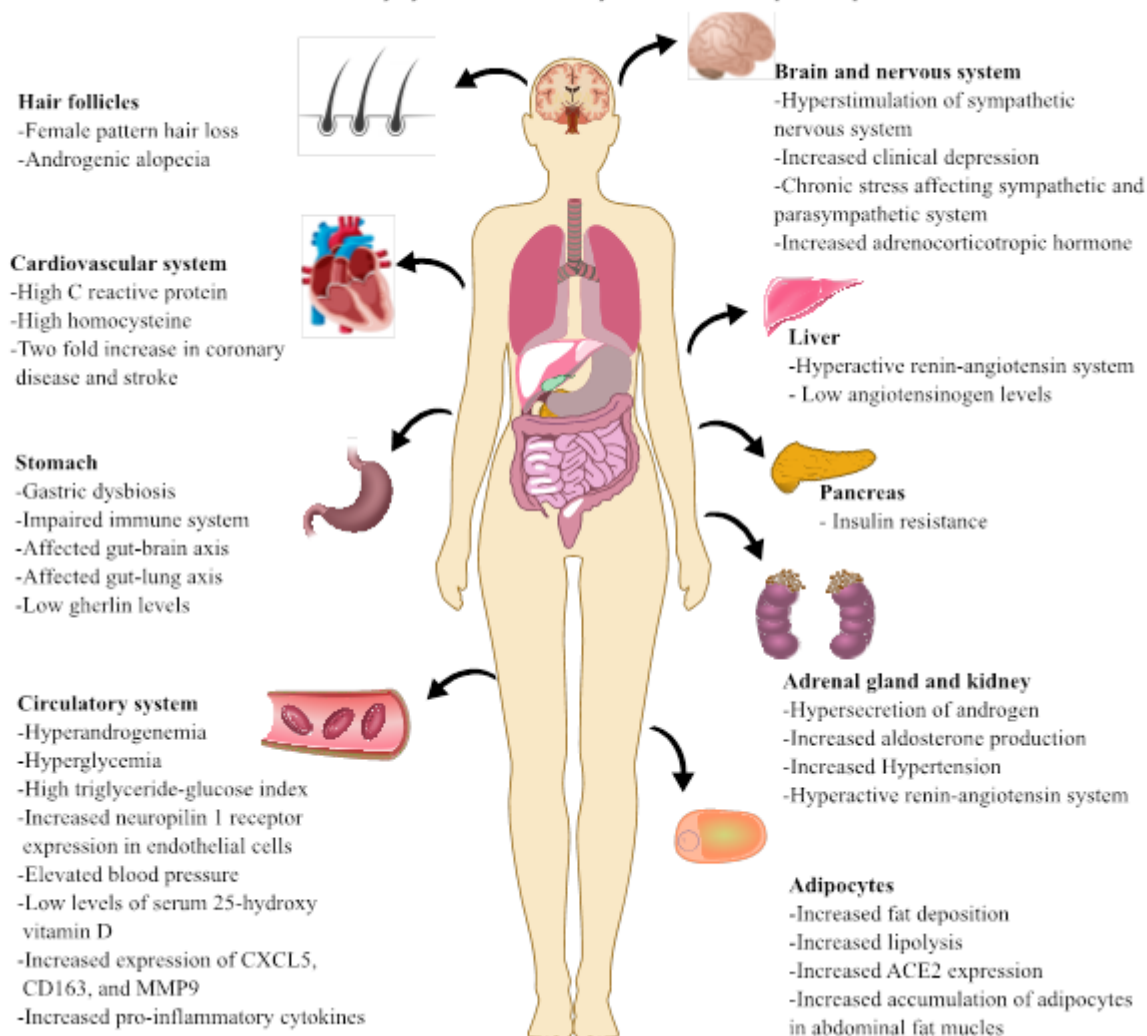

Figure 1: An overview of risk factors in women with Polycystic Ovarian Syndrome that play a critical role in increasing susceptibility to COVID-19 infection. (Created with Inkscape)

Impaired gastric microbiota

Gut microbial biota has known to influence the host immune system, endocrine, and metabolic activities through the gut-brain axis. This diversity of microbial biota (10^{14} microbes) in the gastrointestinal tract is highly host-specific and is subjected to modification by internal and external factors. Moreover, the connection between the diversity of the gastric microbiota and host immunity has been firmly established. A healthy gut microbiome is said to prevent invading pathogens through stimulating host antimicrobial peptides, developments of T cells, and competitive exclusion by demanding nutrition and space [65].

Gastric dysbiosis is of common occurrence in women with PCOS which could be caused due to a diet rich in fats and carbohydrates. Several experimental pieces of research on animal models prove gut microbiome disruption in PCO conditions. Moreover, pilot studies on women with PCOS ensured an increased prevalence of gut dysbiosis in obese PCOS women than in non-obese PCOS women. Such dysbiosis may lead to inflammation, obesity, hyperandrogenemia, hyperinsulinemia, and also affecting psychological health through the gut-brain axis. However, the cause-and-effect relationship between gut microbiota and PCOS is elusive [66].

Interestingly, the gastric microbiota is also found to influence the respiratory tract through the gut-lung axis [67]. However, gut dysbiosis induced inflammation,

psychological distress, and its effect on overall immune health renders such patients more susceptible to SARS-CoV-2 infection. Nevertheless, maintaining healthy diversity of gastric microbiota through probiotics and a healthy diet can aid in improving immune system functions in PCOS women and other patients with metabolic disorders [16].

Alopecia

Female pattern hair loss and androgenetic alopecia are some of the most common effects of PCOS which affects psychological health and decreases the quality of life of hyperandrogenic women. Also, a study conducted in women with hair loss highlighted that 84 % of such women exhibit hyperandrogenemia. Other factors like genetic influence and scalp inflammation may also contribute to hair loss [68].

A recent study on 41 COVID-19 infected Caucasian men revealed that about 71 % experienced androgenetic alopecia whereas hair loss prevalence among normal men of such population was about 31 to 53 % [69]. In addition, several cases of alopecia in male and female COVID-19 infected patients were identified [70]. For instance, an observational study on COVID-19 patients shows that approximately 79 % male and 42 % female exhibit androgenetic alopecia [71].

Androgenetic alopecia is also considered as one of the risk factors for COVID-19 susceptibility [69]. Rather than alopecia influenced COVID-19 susceptibility, cumulative effects on hair loss can be seen in PCOS women infected with the virus. The possible mechanism favouring viral entry in such women is the hyperandrogenic condition resulting in upregulation of TMRPSS2, which in synergy with ACE 2 aids in viral reception. However, the research on the relationship between alopecia and COVID-19 is still primitive with a smaller sample size and fewer studies to draw any conclusive statement [72].

Anxiety and Depression

Depression, anxiety, stress, and sleep deprivation are some of the common terms often associated with PCOS. A study conducted by Nese Cinar laid out the possible relationship between PCOS in affecting the psychological health of women. It was identified that about 28.6 % of PCOS women suffer from clinical depression in comparison to 4.7% of the health women population and the level of depression is higher in obese women with PCOS than in lean women with PCOS [73].

An experimental study by McCook (2002) attempts to identify the mechanism behind depression in PCOS women and revealed that increased androgen levels were found to be insignificant in promoting depression [74]. Therefore, the causation of such depression could be due to secondary factors rather than primary factors. For instance, PCOS-related concerns such as overweight, underweight, acne, acanthosis nigricans, hirsutism [75], alopecia, and infertility causes body dissatisfaction and lower body image thereby contributing to depression [74].

Effect of depression on the immune system is a long-studied niche that supports the upregulation of pro-inflammatory cytokines, especially interleukin 6 results in increasing adrenocorticotropic hormone and cortisol which in turn affects immune response [76]. Chronic stress also has an effect on the immune system by affecting the sympathetic and parasympathetic pathways [77].

With depression manifestation in PCOS women, a survey study by Chris Kite highlights that the COVID-19 pandemic lockdown has intensified depression, anxiety, and sleep disturbances in women with PCOS [78]. Thus, a weakened immune system synergises COVID-19 infectivity in women with PCOS. The pandemic has also inflicted stress on health care professionals, particularly endangering PCOS women in the health care sector who are highly susceptible.

Moreover, this influential relationship between stress and pathogenesis of COVID-19 is bidirectional. Therefore, most patients recovered from COVID-19 are found to be diagnosed with psychopathological disorders like anxiety, insomnia, depression, and post-traumatic stress disorder [79].

2. Conclusion

Given the above-mentioned risks and potential cumulative consequences, we imply that women with PCOS are far more susceptible to SARS-CoV-2 and should be considered as high-risk category. The chances of severe progression of SARS-CoV-2 in PCOS women are also high, owing to the upregulation of TMPRSS2, ACE2, and neuropilin-1, and lowered immunity.

The current medical emergency has incurred a lot of stress on women in the health care profession. With the influence on psychological health on hormones, recent pandemic stress could also pay the way for high cases of PCOS in the near future. Metformin has been successful in controlling hyperglycemia and insulin resistance in PCOS conditions. However, the medical concern should be directed towards dealing with other effects like obesity, hypertension, vitamin D deficiency, and most importantly psychological health.

Activities like meditation, yoga and exercise, considerable sun exposure, and taking probiotics will help improve anxiety, obesity, vitamin D deficiency, and gut-induced immunity respectively. Moreover, there is a compelling need for research on the medical diagnosis and curative measures for PCOS-related secondary ailments. Also, special treatment for COVID-19 infected PCOS women should be ensured by the development of a specialized protocol addressing all related comorbidities.

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