ORIGINAL RESEARCH

Long COVID in vaccinated women with Polycystic Ovary Syndrome: A retrospective cohort pilot study

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ABSTRACT

Objective: Long COVID, or the persistence of symptoms after acute COVID-19 illness, can affect individuals with pre-existing health conditions such as polycystic ovary syndrome (PCOS). Long COVID and PCOS may share overlapping pathogenesis which potentially exacerbate one another. The aim of this study was to evaluate the symptoms of long COVID in women with PCOS who have been vaccinated and investigate whether COVID-19 vaccination or infection worsened PCOS symptoms.

Materials and Methods: We carried out a retrospective cohort study on 44 women with PCOS who have been vaccinated and previously diagnosed with COVID-19. Questionnaires were distributed to find out the effect of COVID infection and vaccines in these women, as well as the symptoms of long COVID-19.

Results: Of all participants, 28 women (70%) continued to report persistent long COVID symptoms, with the highest number of complaints being fatigue and hair loss. The results, using Mann-Whitney test, showed that there was no difference in PCOS symptoms before and after COVID-19 vaccination ($p = 0.520$) or after COVID-19 infections ($p = 0.241$). Although this study revealed a substantial prevalence of long COVID symptoms among women with PCOS, an encouraging finding emerged: neither the administration of COVID-19 vaccination nor prior infection with COVID-19 had a significant impact on PCOS-associated symptoms.

Conclusion: This study further underscores the importance of vaccination for all individuals, including women with a history of PCOS. Furthermore, the purpose of COVID-19 vaccination is to mitigate symptom severity, thus potentially diminishing the occurrence of long-term COVID-19 symptoms in future cases.

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Highlights:

1. Among women with PCOS, many still reported persistent long COVID symptoms such as hair loss and fatigue.
2. COVID-19 vaccination does not exacerbate symptoms of PCOS, which further emphasizes the importance of completing COVID-19 doses for women with PCOS to avoid long COVID sequelae.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex reproductive system disorder affecting women of reproductive age. It involves a combination of endocrine imbalances, leading to various health issues such as infertility, insulin resistance, obesity, and cardiovascular problems, among others. PCOS is characterized by a multifaceted nature, involving multiple genes and factors, and it manifests as a systemic, inflammatory, dysregulated steroid state with autoimmune components, often influenced by lifestyle factors.[1] The main contributors to PCOS are disruptions in the liver and ovary functions, leading to elevated levels of androgen, insulin, estrone, LH, and lipids.[2]

COVID-19, caused by the SARS-CoV-2 virus, emerged as a global pandemic in early 2020, challenging healthcare systems and disrupting lives worldwide. While most individuals with COVID-19 experience mild to moderate symptoms and recover within a few weeks, a significant number face prolonged health issues even after the acute phase.[3] This condition is known as Long COVID, or post-acute sequelae of SARS-CoV-2 infection (PASC). Long COVID is characterized by persistent symptoms that persist for weeks or months after the initial infection, affecting individuals of all ages, regardless of the severity of their initial illness. The symptoms of Long COVID can vary widely and may include fatigue, shortness of breath, brain fog, muscle and joint pain, chest pain, and even psychological distress.[4]

The severity and persistence of Long COVID symptoms can vary widely among individuals, regardless of their pre-existing health conditions. Factors that have been associated with an increased risk of Long COVID include the severity of the initial COVID-19 infection, age, and certain pre-existing health conditions, such as diabetes, obesity, and asthma. Recent studies have indicated a potential link between PCOS and an increased risk of developing Long COVID symptoms in women who contract COVID-19. When women with PCOS contract COVID-19, their pre-existing immune dysregulation may contribute to a more pronounced and prolonged inflammatory response to the viral infection. This chronic inflammation can lead to a wide range of Long COVID symptoms persisting well beyond the acute phase of the illness. Furthermore, the hormonal imbalances and insulin resistance commonly observed in PCOS may also exacerbate the impact of COVID-19 on the body's systems.[5,6]

On the other hand, recent literature suggested that long COVID or even COVID-19 vaccination may also exacerbate PCOS symptoms such as metabolic syndrome, weight gain, and menstrual irregularities. Infection with SARS-CoV-2 may worsen insulin resistance which is already experienced by PCOS patients. The virus can bind to its receptors on pancreatic islet cells, causing temporary damage and insulin deficiency. The infection also raises inflammatory markers, which may destroy pancreatic fat cells and trigger insulin resistance through ketogenesis and adipocyte dysregulation.[7,8] Chronic inflammation due to long COVID has also been found to disrupt the hypothalamic-pituitary-ovarian (HPO) axis, which is essential for normal function of the ovaries and their responsiveness towards estrogen and progesterone. The inflammatory cytokines released may interfere with follicle development, ovarian angio-genesis, hormone production, timing of ovulation, and corpus luteum formation that all occur within the ovaries.[9] The aim of this study was to evaluate the symptoms of long COVID in women with PCOS who have been vaccinated and investigate whether COVID-19 vaccination or infection also affected PCOS symptoms.

MATERIALS AND METHODS

Study design and participants

This retrospective study was conducted on PCOS patients in Cipto Mangunkusumo Hospital medical record admitted from 2021 to 2023, involving 40 women with PCOS who have been vaccinated and previously diagnosed with COVID-19. Criteria for inclusion comprised women aged 18 years or older and diagnosed with PCOS according to Rotterdam criteria (oligo/anovulation, hyperandrogenism features, polycystic ovaries on ultrasonography). PCOS patients who were also diagnosed with other reproductive endocrinology disorders were excluded. The ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia, with protocol number 24-02-0201 (KET-467/UN2.F1/ETIK/ PPM.00 .02/2024; approved 25 March 2024). We designed a special questionnaire to inquire about the current health status of patients and their persistent symptoms in the post-COVID period, as well as their PCOS symptoms before and after 3 months following COVID-19 infection, and contacted all eligible patients. All research subjects included in this study had given their informed consent.

Content of survey

The information included in the questionnaire were age, weight, height, comorbid diseases, obstetric history, characteristics of acute COVID-19, history of hospita-

lization (disease severity, length of hospital stay, need for respiratory supports, and need for intensive care unit [ICU]), long COVID symptoms, COVID-19 vaccination, and their PCOS symptoms before and after 3 months following COVID infection.

Statistical analysis

All analysis were performed using IBM SPSS software version 27.0. The analysis was conducted using SPSS software version. Descriptive statistics were reported as mean ± standard deviation (SD) or medians with quartiles. Student t-test was utilized to compare continuous variables with normal distribution, while the Mann–Whitney U test was employed for non-normal distribution. The $\chi 2$ test was used to compare categorical variables under parametric conditions. A p-value below 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

From the study, a total of 40 women were followed up. We investigated the long COVID symptoms in women with PCOS who had been vaccinated, as well as their PCOS symptoms during the acute COVID-19 infection compared to the chronic infection >3 months after being confirmed positive. We found that there was no difference in PCOS symptoms before and after COVID-19 vaccination (p = 0.520) or after COVID-19 infections (p = 0.241).

Out of the 40 respondents, 28 of them (70%) still complained of long COVID symptoms to time of survey. The most frequently experienced symptom was fatigue, with a total of 17 individuals reporting it (42.50%). The second most common complaint was hair loss, with 10 out of 28 respondents experiencing it (25%). This was followed by other complaints such as tingling sensations, shortness of breath, concentration difficulties, as well as disturbances in the sense of smell and taste, of which each of the symptoms was experienced by 5 respondents (12.5%). Other complaints included joint pain (10%), chest pain (2.5%), palpitations (2.5%), and cough, allergies, and skin rashes, each reported by 7.5% (Figure 1).

All respondents were asked about their PCOS symptoms shortly after being infected with COVID or during the acute onset (<3 months) as well as during the chronic onset (>3 months). During the acute onset, a total of 11 out of 40 respondents had already received the COVID vaccine. Among them, 26 reported weight gain (65%), 34 experienced infertility (85%), 15 had acne breakouts (37.5%), 25 experienced hair loss or balding symptoms (62.5%), 15 had hirsutism (37.5%), 7 had amenorrhea for more than 6 months (17.5%), and irregular menstruation was reported by 33 respondents (82.5%) (Figure 2).

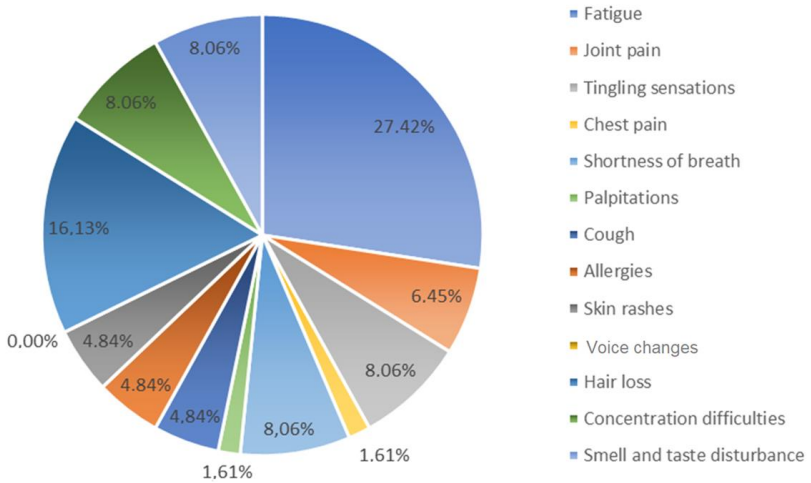

Figure 1. Long COVID symptoms reported among PCOS patients.

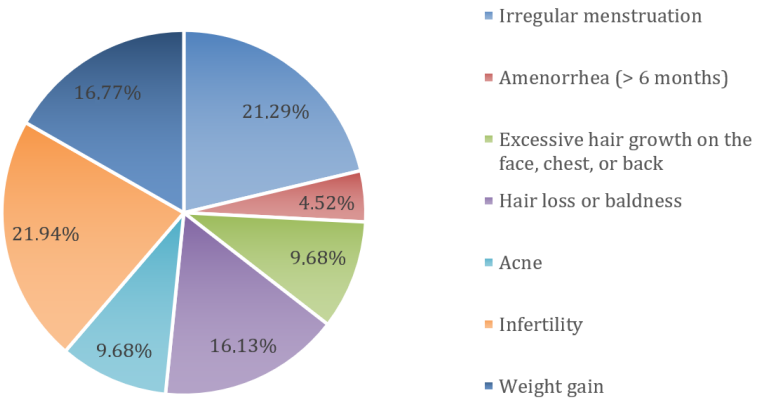

Figure 2. PCOS symptoms shortly after COVID-19 infection.

During the chronic onset of COVID infection (>3 months), they were re-evaluated regarding the PCOS symptoms they experienced. All respondents had already received the COVID vaccine. Only 17 out of 40 individuals reported weight gain (42.5%), 20 experienced infertility (50%), 6 had acne breakouts (15%), 22 had hair loss or balding symptoms (55%), 9 had hirsutism (22.5%), 8 had amenorrhea (20%), and irregular menstruation was reported by 23 respondents (57.5%) (Figure 3, Table 1).

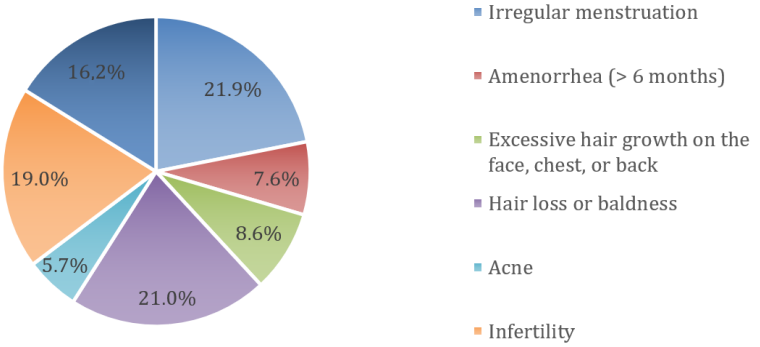

Figure 3. PCOS symptoms 3 months or more after COVID-19 infection.

Table 1. Association between PCOS symptoms reported and onset of COVID-19 infection.

Symptoms	Category	< 3 months (Acute onset)	> 3 months (Chronic onset)	*p*-values
Weight gain	Yes	26 (65.0)	17 (42.5)	0.035
	No	14 (35.0)	23 (57.5)	
Infertility	Yes	34 (85.0)	20 (50.0)	0.000
	No	6 (15.0)	20 (50.0)	
Acne	Yes	15 (37.5)	6 (15.0)	0.022
	No	25 (62.5)	34 (85.0)	
Hair loss / Baldness	Yes	25 (62.5)	22 (55.0)	0.508
	No	15 (37.5)	18 (45.0)	
Hirsutism	Yes	15 (37.5)	9 (22.5)	0.070
	No	25 (62.5)	31 (77.5)	
Amenorrhea	Yes	7 (17.5)	8 (20.0)	1.000
	No	33 (82.5)	32 (80.0)	
Irregular menstruation	Yes	33 (82.5)	23 (57.5)	0.002
	No	7 (17.5)	17 (42.5)	

Long COVID, which is defined by the persistence of symptoms after the acute phase of COVID-19, has become a subject of significant interest in recent research. Previous research indicated that women with PCOS may have a heightened risk of contracting COVID-19 and experiencing more severe clinical manifestations of the disease.[5] A comprehensive review by de Medeiros et al. predicted that PCOS patients had 28-50% higher risk of contracting COVID-19 infection.[5] A large-scale cohort study among the British population by Subramanian et al. also found that the incidence rate of COVID-19 infection was higher in women with PCOS (18.1 per 1000 person-years) compared to that in healthy women (11.9 per 1000 person-years).[10] Hence, many have suggested that PCOS should be considered an independent risk factor for COVID-19. On the other hand, past epidemiological studies found that lockdowns and anxiety related to risk of COVID-19 infection were negatively associated with the wellbeing of PCOS patients.[11,12] Up to present, however, there is a lack of evidence from clinical studies regarding how COVID-19 infection might affect the severity of PCOS-related symptoms. The potential mechanisms underlying the association between PCOS and long COVID symptoms are not yet fully understood, but there are several hypotheses based on recent research.[5]

PCOS is associated with chronic low-grade inflammation, which may contribute to the development of long COVID symptoms. Long COVID is also characterized by chronic inflammation, which may be exacerbated in PCOS patients.[13] Previously, it has been found that as many as 30% of all PCOS patients have chronic low-grade inflammation. The key components that constitute low-grade inflammation in PCOS include over-production of pro-inflammatory cytokines, endothelial cell dysfunction, and leukocytosis, and all of this likely stem from hyperandrogenism.[14] Excessive androgen level stimulates monocytic infiltration inside the ovaries and increased production of inflammatory factors such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α).[14,15] Other pro-inflammatory factors that have been found to be higher in PCOS patients than in healthy women include interleukin-17 (IL-17), interleukin-18 (IL-18), interleukin-1B (IL-1B), C-reactive protein (CRP), monocyte chemoattractant protein-1 (MCP1), soluble intercellular adhesion molecule (sICAM), and soluble endothelial leukocyte adhesion molecule (SE selectin).[16,17] Low-grade chronic inflammation in PCOS may then act as a prerequisite to the incidence of various metabolic diseases such as dyslipidemia and diabetes. It also impairs how the innate and adaptive immune system respond to pathogenic triggers, allowing infection to take over.[18,19] Therefore, a low-grade prolonged inflammatory state is integral to the pathophysiology of poor COVID-19 symptoms.[5] The inflammatory state is more pronounced in PCOS patients who are also obese, since adipose tissue can act as a reservoir for SARS-CoV-2 spread, shedding, activation of immune system, and cytokine cascade amplification, further contributing to a state of cytokine storm.[20]

Moreover, women with PCOS have been shown to have immune dysfunction, which may make them more susceptible to COVID-19 infection and more likely to develop long COVID symptoms. 19 PCOS is characterized by hyperandrogenism, which may play a role in the pathophysiology of COVID-19 infection and long COVID symptoms. Previous research has shown a correlation between gender and COVID-19 mortality or morbidity, in which men tend to be more susceptible compared to women. The immune dysregulation in men is likely due to higher androgen levels, as testosterone can regulate the transcription of TMPRSS2 gene which helps facilitate entry of virus into the cells.[5,21,22] The levels of androgens inside the body are also correlated with the number of ACE2 receptors, which are the main receptor for SARS-CoV-2 in target cells.[23] In women with PCOS, the resulting immune susceptibility towards COVID-19 may also be explained by the higher levels of testosterone. Nevertheless, the role of testosterone in COVID-19 is still widely debated as other studies found that it can also be a protective factor in certain conditions. Low testosterone level has been linked with poorer outcomes following COVID-19 infections.[24] Recent evidence has pointed out the beneficial role of testosterone against COVID-19, which lies upon its ability to inhibit inflammatory signalling cascade, endothelial dysfunction, and oxidative stress. These conflicting findings on testosterone's role can be made clearer through future studies that measure the concentration of testosterone before, during, and after a COVID-19 infection.[24,25]

In conjunction with higher androgen levels, there is also overactivation of the renin-angiotensin-aldosterone (RAAS) system in PCOS. Overactivation of the RAAS system results in excess angiotensin II, which causes disassociation of ACE2 from angiotensin II receptor type 1 (AT1R) that allows angiotensin II to bind to AT1R instead. Excessive angiotensin II stimulation leads to increased vascular permeability, severe inflammation, pulmonary fibrosis, pulmonary edema, and eventually acute respiratory distress syndrome (ARDS). In addition, the detachment of ACE2 from AT1R allows more virus entry into lung pneumocytes.[5,26]

Vitamin D deficiency is common in PCOS patients and has been associated with an increased risk of severe

COVID-19 infection. The role of vitamin D in innate and adaptive immunity has been thoroughly studied. Low vitamin D levels in the body contribute to higher serum levels of proinflammatory cytokines that are released from macrophages. Furthermore, PCOS is often associated with comorbidities such as obesity, diabetes, and hypertension, which are also risk factors for severe COVID-19 infection and long COVID symptoms.[5,13,19] While the provided references do not specifically discuss long COVID symptoms in PCOS patients, they provide valuable insights into the overall understanding of long COVID and the association between PCOS and COVID-19. Further research is needed to explore the specific symptoms and impacts of long COVID in PCOS patients.

Finally, we also need to consider the impact of COVID-19 pandemic on lifestyle changes of women with PCOS. PCOS symptoms may be influenced not only by the COVID-19 infection itself but also by the stress and lifestyle changes that accompany it. A survey by McGowan et al. found that women with PCOS tended to exercise less, increase sugar intake, and gain more weight during the COVID-19 2020 pandemic era.[27] In addition to the infection itself, these unhealthy habits can lead to worsening of PCOS symptoms. However, there are limited long-term studies that track lifestyle adjustments in years after the post-COVID era and their association with PCOS symptoms.

Overall, this study presented several strengths that can be highlighted. Firstly, this study underscored women with PCOS as a vulnerable group at risk of developing persistent long COVID symptoms due to overlapping pathogenesis pathways. Several key pathogenesis pathways such as chronic low-grade inflammation, immune dysregulation, excessive androgen level, overactivation of RAAS system, and vitamin D deficiency, have been elaborated above in the context of PCOS and COVID-19. Moreover, this study proved that COVID-19 vaccination does not exacerbate PCOS-associated symptoms, which further emphasizes the importance of completing COVID-19 doses for women with PCOS to avoid persistent long COVID symptoms. Findings from this study can be used as a foundation for future research, for example to investigate whether lean PCOS patients also exhibit similar long COVID-19 risk with their obese counterparts. Nevertheless, despite the novel insight presented in this study, there remain some limitations. Our sample size is limited since many of our PCOS patients were not advised to come to the hospital for medical consultation unless for emergency at the time of pandemic, especially during lockdown periods. Additionally, since we used a survey to ask about long COVID symptoms and PCOS symptoms experienced by the patients, recall bias to some extent might have occurred.

CONCLUSION

Women with PCOS are considered a high-risk group for experiencing long COVID symptoms. Chronic low-grade inflammation and immune system dysregulation associated with PCOS are likely to contribute to the persistence of long COVID symptoms. Even among PCOS patients who had been vaccinated, some women still reported lingering long COVID symptoms. Therefore, vaccination is essential to potentially reduce the severity of these symptoms. It is reassuring to note that COVID-19 vaccination does not worsen PCOS symptoms. However, further studies are needed to explore the potential relationship between PCOS, long COVID, and vaccination to gain a better understanding of their interactions. Understanding the relationship between PCOS and COVID-19 also opens new research avenues on the link between PCOS and respiratory infections or even other infections.

DISCLOSURES

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Conflict of interest

The authors declare that they have no competing interests.

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Author Contribution

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript. R. M., G. P., A. K. H.; Conceptualization, Methodology, Validation. R. M., K. S. M. M.; Project Supervision. V. S., B. W., A. H.; Administration. A. B., A. A. F.; Formal Analysis, Writing - Original Draft,

Data Curation. E. C. Y., A.N.I; Writing - Review & Editing, Visualization.

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