By mid-2022, more than 500,000,000 people worldwide have had confirmed Covid-19, caused by infection by the SARS-CoV-2 virus, according to the World Health Organization (WHO) [1]. Following the acute phase of Covid, some patients have persistent or new symptoms. The patients with the post-acute sequelae of Covid-19 (PASC), also known as “Long Covid”, have a spectrum of physical, psychological, and cognitive health problems after their initial Covid infection [2-6]. This newly described Long Covid is a condition that may have a significant public health impact on the care of Women’s Health patients in the near future.

Long Covid patients have heterogeneous signs and symptoms such as shortness of breath, fatigue, memory loss, cognitive impairment or “brain fog”, gastrointestinal issues, and other symptoms for several weeks or months following the start of the acute Covid symptoms and which evolve over time and have varying prevalence based on sex, age, and race [2-6]. The WHO clinical case definition was created by a Delphi consensus and published in 2021: “Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction, and others and generally impact everyday functioning. Symptoms may be new-onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time.”[2] The US Centers for Disease Control and Disease Prevention (CDC) defines Long Covid, PASC, as the following: “Some people who have been infected with the virus that causes COVID-19 can experience long-term effects from their infection, known as post-COVID conditions (PCC) or long COVID.” [3]. The CDC definition applies to individuals with symptoms experienced four or more weeks following the initial SARS-CoV-2 infection [3]. The UK National Institute for Health and Care Excellence (NICE) guidelines classifies “Post-COVID-19 syndrome” as persisting clusters of symptoms beyond 12 weeks after initial Covid disease onset, which is not explained by alternative diagnosis [4]. The US CDC recommends that in the evaluation of the patient for Long Covid, a broad-based approach to the review of symptoms be used, given that the patient may present with symptoms in the cardiovascular, pulmonary, dermatologic, endocrine, neurologic, psychiatric, reproductive and other organ systems [3]. For laboratory testing, the CDC recommends CBC, electrolytes, renal function testing, liver function testing, inflammatory markers (c-reactive protein, ESR, ferritin), thyroid function tests, and testing for Vitamin D and Vitamin B12 levels [3]. Additional testing and imaging studies are recommended if warranted by history or laboratory findings. Given the numerous proposed definitions for Long Covid, it is not surprising that a commonly agreed upon incidence of Long Covid is still being characterized [5, 7-9]. The range is relatively wide, with studies reporting the incidence of Long COVID ranging anywhere from 7.5% to 89% of Covid patients [5, 7-9]. A machine-learning artificial intelligence algorithm is being employed by the ongoing trans-NIH RECOVER initiative in the US, which applies machine learning models to identify Long Covid predictors from data collected from over 8 million patients with over 92% accuracy [9]. The mechanisms by which the initial infection by the SARS-CoV-2 virus results in Long Covid are still unknown. Three hypotheses about the etiology of Long Covid include an increased tendency to form blood clots, the persistence of the Covid infection and for the patient’s immune system to be dysfunctional [10-14]. Additionally, there are alternative hypotheses, such as perturbances in the microbiome of patients with Covid [14]. Although there are major gaps in the characterization of the biological and immunological basis of PASC, longitudinal studies consistently highlight female sex as a factor associated with higher risk of developing Long Covid [15-18]. In a recent literature review, it appears in their analysis of published sex-disaggregated data that the risk of having Long Covid is 22% higher in females than in males (OR 1.22; 95% CI 1.13-1.32) [18]. The possible role of estrogens and other female hormones having an etiologic basis or an accentuating role in Long Covid in females has been considered and needs further investigation [19-21].

GAPS THAT NEED TO BE ADDRESSED

For women, a number of unknowns need to be addressed. The following should be studied to better understand Long Covid in women and to be able to adequately manage these patients. Gap 1: Is Long Covid a new and separate chronic disease that is separable from the initial acute Covid episode? How different are the manifestations of Long Covid in women compared to men? Why does it appear that more women are affected by Long Covid? Gap 2: What diagnostic criteria should be used to diagnose a patient with Long Covid? Are there patients with “subclinical” Long Covid? What may cause exacerbations of the symptoms? Are neurological/mental health symptoms sufficient to make the diagnosis? Gap 3: What are the direct manifestations of Long Covid (the effects on the patient’s normal physiologic function)? If the etiology is inflammation, is Long Covid due to new acute secondary inflammation or due to chronic inflammation from the original infection? Gap 4: What are the secondary effects of Long Covid on women’s health problems, such as premenstrual syndrome (PMS), endometriosis, fibroids, infertility and menstrual irregularities? Gap 5: What are the effects of Long Covid on pregnancy? Are there maternal effects of the condition? What are the short-term effects on the fetus and long-term effects on the child if the mother has Long Covid? Gap 6: What is the relationship between the etiology and symptoms of Long Covid and hormones, especially female reproductive hormones? Gap 7: In the 5% of the patients with recurrent Covid (re-infection 90 days or more after the initial SARS-CoV-2 infection), what are the risks of Long Covid in these patients? Gap 8: What treatment options are available for women? Is it
symptomatic relief only, or are there treatments to be created that could completely cure Long Covid? Gap 9: Could Long Covid be prevented? Are the prevention measures different in women compared to men?

CONCLUSION

Long Covid is a condition that is only beginning to be understood. A key aspect of Long Covid is how it affects Women’s Health, ranging from pre-menarche to reproductive age to postmenopausal women. At this moment, many additional studies are required to define the condition, understand its interactions with other women’s health conditions, and determine how to best treat Long Covid. As Long Covid may affect a large number of the world’s women, it requires acute attention.

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