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Commentary

Long COVID risk - a signal to address sex hormones and women's health

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The COVID-19 pandemic has brought health inequalities into sharp focus on an international scale. Vulnerability to and mortality from acute COVID-19 infection is higher in men [1], whereas, Long COVID disproportionately affects women [2]. Why?

A recent review [3] on Long COVID highlights the multi-organ sequalae following infection, articulating a pressing need for greater understanding of the mechanisms in the post-acute phase, to guide research for effective management. Underlying mechanisms include virus-associated pathologies, immunological dysfunction and inflammatory-mediated damage [3]. However, despite the stark asymmetry in risk and outcomes between sexes, sex-specific pathophysiology receives little attention in this review [3].

Sex-specific risk and ultimately outcomes are multifactorial - a function of the complex interplay between biology, behaviour, and the wider determinants of health. Wenham et al. [4] describe important factors which result in disproportionate risk to women's socioeconomic positions and health during the COVID-19 pandemic. These factors set the stage for the disproportionate impact that Long COVID has on women. Female sex and age under 50 years are now acknowledged as risk factors for Long COVID [2]. However, recognised predictors of acute COVID mortality risk [1] (increasing age, chronic comorbidity, male sex) fail to predict poor outcomes in Long COVID.[2] In fact, Long COVID risk appears to be largely unaffected by pre-existing comorbidities or disability [2], making identification of at-risk women more difficult – a problem for both women and clinicians. Despite the already vulnerable socioeconomic positions of women during the pandemic, their ability to return to work is further impeded by the chronicity of symptoms of Long COVID. This situation is likely far more challenging for perimenopausal and menopausal women who already experience significant and additional inequality in the workplace [5].

From a biological perspective, we propose the asymmetry in risk and outcomes between sexes, and an overlap of symptoms of Long COVID [3] with those of perimenopause and menopause [6] point towards sex hormone differences as targets for further investigation. Furthermore, the higher prevalence of Long COVID in women under the age of 50 years [2] is an important and supporting clue as the mean age of natural menopause (in the UK) is 51 years [6].

Oestrogen and androgen receptors are ubiquitous, present in almost all tissues in the body, evidencing the widespread and important roles of sex hormones [7], well beyond their obvious roles in the reproductive system. Viral-induced sex hormone dysfunction resulting in early menopause, menstruation abnormalities and miscarriage are documented in HIV and Hepatitis B and C infections [8]. In the context of viral infections, sex hormone dysfunction may be related to multisystem disruption or due to organ-specific effects [8]. The role of sex hormones in COVID-19 infection are now beginning to emerge. A recent study [9] highlights important clinical and immunological differences between sexes in acute COVID-19 infection; women had lower mortality, lower levels of inflammation, higher lymphocyte counts, and faster antibody responses than men. Specifically, oestradiol may be implicated here [7] owing to its immunomodulatory effects [7] as well as antiplatelet and vasodilatory activity [7]. Observational research [8] highlights transient menstruation abnormalities during acute COVID-19 possibly owing to the expression of the ACE2 receptor proteins in the ovaries [8]. Such findings support a hypothesis of temporary disruption to physiological ovarian steroid hormone production, which could acutely exacerbate symptoms of perimenopause and menopause.

Many symptoms of Long COVID [3] (fatigue, muscle aches, palpitations, cognitive impairment, sleep disturbance) have a significant overlap with the perimenopause and menopause [6], both which can affect women of all ages. Such overlap may create diagnostic uncertainty and requires clinicians to assess for this additional diagnosis as

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it offers an opportunity to treat perimenopause and menopause symptoms with safe and effective hormone replacement therapy (HRT) [6]. Failure to recognise this overlap misses an opportunity to treat many debilitating symptoms affecting both physical and mental health, but also to reduce some women's risk of cardiovascular disease, type 2 diabetes, osteoporosis, obesity and possibly dementia [6] - all of which increase after the menopause. Furthermore, it could lead to women with symptoms of the perimenopause and menopause being misdiagnosed with Long COVID.

Identification of patients at highest risk of Long COVID is now of great importance [2,3]. This allows prioritisation of resources for those in greatest clinical need, along with identifying multi-speciality teams [2]. Clinicians working in Long COVID clinics should receive training in menopause care so perimenopausal and menopausal women can be promptly diagnosed and offered appropriate management. Screening for and diagnosis of perimenopause and menopause is simple and quick, does not usually involve serum sex hormone analysis [6], and should be routinely performed in all women in Long COVID clinics. Changes in menstruation are often early signs of perimenopause [6]; other common symptoms of perimenopause and menopause include hot flushes, memory problems, brain fog, reduced stamina, fatigue, anxiety, low mood, joint pains and headaches [6]. Clinicians should actively enquire about all of these symptoms. Where appropriate, a trial of HRT is a safe and useful treatment option [6] for women and clinicians to consider, as an improvement in symptoms supports a diagnosis of hormone deficiency.

Failure to explore sex-specific risk and outcomes in COVID-19 is unethical [10] and associated with several risks. Firstly, it threatens opportunities for identifying mechanisms and treatment targets, where at present, no treatments exist. Secondly, it threatens global women's health at present and in the future, owing to the risk of misdiagnosing Long Covid instead of the perimenopause and menopause, and failing to implement appropriate treatment strategies. Thirdly, it threatens global economic recovery and future preparedness due to the highly gendered nature of work and female dominated sectors such as health and social care [4]

Looking ahead, there is urgent need for robust research to help understand the epidemiological basis, as well as the underlying biological mechanisms for sex-differences in Long COVID. The deficit in sex and gender-specific outcomes within clinical trials is recognised, with calls for the systematic application of sex-specific methodologies [10]. Sex-disaggregated data underpins this vital research, along with power calculations which consider sex as an analytical variable a priori [10].

Contributors

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Declaration of interests

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