



## Menstruation and Sex Hormones in Covid-19: Effects in Women of Child-Bearing Age

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**ABSTRACT:** Numerous studies have examined the effects of the COVID-19 pandemic on women's mental health and menstrual cycles. However, most of these studies only included outpatients with COVID-19, whereas information on hospitalised women is minimal. ACE 2 is essential for the SAR-CoV2 virus to enter human cells and the human ovary. Since it stimulates steroid secretion, aids in follicle development and oocyte growth, influences ovulation, and maintains the corpus luteum, it stimulates steroid secretion and aids in follicle development and oocyte growth. Hospitalised female COVID-19 patients exhibit menstrual changes and heightened symptoms of mental health disorders. Length of isolation was the most influential factor in overall menstrual changes and mental health in female COVID-19 hospitalised patients. Infection with COVID-19 may affect the menstrual cycle in females. Further prospective research is required to confirm these findings and determine the duration of these menstrual irregularities.

**KEYWORDS:** ACE2, COVID-19, Follicle development, Menstrual cycle, Sex hormones.

### INTRODUCTION

The coronavirus illness first appeared in 2019 and quickly spread over the world. It rapidly became a burden on the health system and patients [1]. Concerns about female fertility emerged as a result of atypical observations in the menstrual cycle, including altered monthly duration, frequency [2, 3]. Women's reproductive health is essential as the epidemic is far from over and new concerns about the female reproductive system, especially fertility issues are constantly emerging [4]. The infection is considered to spread by direct or indirect contact, social isolation is the best preventative approach [5, 6]. Although the possibility of semen transmission is still open to discussion, a recent systematic review found no evidence to support the notion that COVID-19 is a sexually transmitted disease (STD) [7]. Menstruation affects are incredibly harmful and the cause of problematic menstruation can lead to anemia, significantly lower quality of life, and a considerable economical burden on women, their families, the healthcare system, and society as a whole [8]. The International Federation of Gynecology and Obstetrics (FIGO) has established standard guidelines for normal menstruation in terms of menstrual frequency, duration, regularity, and volume; any variation from these guidelines may indicate irregular uterine bleeding [9, 10].

Menstruation affects are incredibly harmful and the cause of problematic menstruation can lead to anemia, significantly lower quality of life, and a considerable economical burden on women, their families, the healthcare system, and society as a whole [11]. For instance, irregular and protracted menstrual cycles have been linked to an increased risk of premature death, and irregular or missing menstruation may indicate decreased fertility, which is linked to a number of chronic diseases [12]. Discussions on altered menstrual duration, frequency, regularity, and volume (heavier bleeding and clotting), as well as increased dysmenorrhoea and worsening premenstrual syndrome, have been accumulating on social media and blogs since the start of the COVID-19 epidemic [13, 14]. Recent anecdotal reports of menstruation alterations following COVID-19 vaccination have increased vaccine reluctance or refusal [15, 16].

### A. Covid-19 and reproductive system

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) encloses a spike protein (S protein) allowing viral binding to the angiotensin-converting enzyme (ACE) 2, which acts as a viral receptor and is also widely expressed on the surface of various organs and tissues [12]. In order for the virus to gain entry into the cell and bind to ACE 2, cleavage of the S protein is necessary, which is facilitated by the transmembrane serine protease 2 (TMPRSS2) [17, 18]. SARS-CoV-2 does not only invade the lungs but also attacks other organs with high ACE2 expression, including cardiac, renal, intestinal, and endothelial cells [19]. The testis, ovary, vagina, uterus, and placenta are involved [20]. Considering the above, female reproductive organs may be affected



by SARS-CoV-2 infection, as the oocytes and ovarian tissue express medium–high levels of ACE 2 receptor [21]. No significant difference has been observed in the ACE2 / transmembrane serine protease 2 (TMPRSS2) expression rate between young and old ovaries and low and high ovarian reserve [18, 22].

Cleaving of the S protein could be achieved by other proteases, which are currently under investigation for increasing SARS-CoV-2 infectivity, such as TMPRSS4 in the gut epithelial cells, cathepsins B and L (CTSB and CTSL, respectively) in TMPRSS2- cells [23].

FURIN in epithelial layers of several mucosal tissues and MX dynamin-like GTPase 1 (MX1), which modifies the protein S by neutrophil elastase [24]. Angiotensin II (Ang II) promotes vasoconstriction of the spiral arteries and consequently induces menstruation [25, 26]. The myometrial activity might be influenced by the relationship between Ang II and Ang 1–7 [12, 27]. Therefore, an alteration in the function of Ang II and ACE 2 may determine irregularities of the menstrual cycle, heavy periods, and hyperplastic endometrium [25]. Moreover, high levels of stress have been linked to menstrual cycle changes [28]. For this reason, we feel the need to investigate whether COVID-19 infection can induce menstrual cycle alterations, bearing in mind that infertility is already a stress inducer [29].

ACE 2 has a pivotal role in the ovary: it promotes steroid secretion, helps follicle development and oocyte growth, influences ovulation, and maintains the function of the corpus luteum [18, 30]. Both ACE2 and BSG were found in oocytes, depending on the maturity grade. ACE2 protein was present only in immature oocytes, whereas BSG protein was present in all oocytes, independent of the maturity grade [31]. Potential ways of infecting the oocytes during the IVF process might be: through the blood flow, during the staff handling, or by adding infected semen [28]. Trophectoderm cells of a day-6 embryo have the highest co-expression of the ACE-2 and TMPRSS2 [32]. Researchers collected trophoctoderm cells from blastocyst-stage embryos donated to research after exposing them to the SARS-CoV-2 virus (infection by spinoculation with GFP-reporter pseudotyped virions) and discovered that the cells from the embryos expressed ACE2 receptor and TMPRSS2 protease are susceptible to the infection through the ACE2 receptor [33]. The oocytes and embryos are therefore susceptible to the SARS-CoV-2 infection [34, 35]. This observation helps draw special attention to ‘*in vitro*’ (IVF) procedures and embryo transfers [36].

## ***B. Sex hormones and menstruation in female participants***

Several viruses impact the female endocrine and reproductive system. Menstrual problems are common in women with HBV or HCV infections, and reproductive dysfunction in the form of miscarriage or infertility has also been identified [2, 34]. In women infected with the human immunodeficiency virus, menopause begins at a younger age [37]. In animal tests, it has been proven that continuous hantavirus infection impairs female fertility [38]. However, no prior research has studied the effect of COVID-19 on female sex hormones, menstruation, or fertility [39]. It is believed that this is the first study to focus on clinical and laboratory results, particularly sex hormones, menstruation, and ovarian reserve, in women of childbearing age infected with COVID-19 [40]. This study revealed that seriously unwell patients had more comorbidities and problems and a greater death rate than moderately ill patients [2]. Higher PCT and cytokine concentrations in severe patients imply more severe infection states and a cytokine storm [41].

Analysing the menstrual alterations of patients revealed that they had varying degrees of temporary menstrual abnormalities, which mainly manifested as longer cycles and reduced volume [6]. Infrequently found in the control group were shorter or disrupted menstrual periods and increased volume in a few individuals [42]. Consequently, it was discovered that systemic problems are closely connected with menstrual alterations. The ovary regulates menstruation, which external causes like infections, pharmacological treatments, and other organ dysfunctions are readily disrupted [29]. To explain the menstrual changes, these potential components were subjected to univariate logistic regression [30]. This indicated that individuals with multisystem dysfunction were more prone to exhibit menstrual abnormalities, which doctors frequently overlooked [43]. Furthermore, follow-up revealed that 84% of patients returned to a standard monthly volume, and 99% returned to their normal cycle within 1-2 months of discharge, indicating that COVID-19-induced menstrual alterations were most likely transient and resolved quickly [3]. In the follow-up, a 44-year-old patient reported that she had not menstruated for four months after the onset of COVID-19 and had ruled out pregnancy as the cause [13]. However, given that she was within the perimenopausal period, we believe the observation period for menstruation should be extended in her case [42].



The variations in sex hormone levels in 91 individuals during the disease were further analysed. There were no statistically significant differences between COVID-19 patients and controls for any sex hormone concentrations [6, 44]. A subgroup analysis based on menstrual variations also revealed no significant changes in sex hormone concentrations during changes in menstrual volume, simple cycle, or both volume and cycle [45]. This data suggests that the ovarian endocrine system of the majority of female COVID-19 patients was not significantly compromised [39]. Some individuals, however, exhibited aberrant changes in their sex hormone concentrations, such as excessively high levels of FSH and LH during the early follicular phase, which may indicate ovarian suppression in these patients [46]. Ovarian function is often inhibited in response to acute stress to ensure the proper operation of vital organs, and anovulation has been recorded in several acute illnesses [47]. Although this study did not re-examine the concentrations of sex hormones in the early follicular phase in the recovered patients, it is reasonable to assume that the changes in hormone concentrations were temporary and transient, given that menstruation returned to normal in the majority of patients after discharge [2, 18]. Nonetheless, the direct influence of the virus cannot be ruled out entirely [30, 41].

AMH testing was performed on patients further to investigate the impact of SARS-CoV-2 infection on ovarian reserve [32, 35]. AMH is released by tiny antral follicles and is a crucial measure of ovarian reserve [24]. It is unaffected by menstruation, exogenous sex hormones, and pregnancy [21]. The average AMH concentration of COVID-19 patients was comparable to that of the control group [19]. Given the temporary and reversible menstrual alterations and the fact that the amounts of oestradiol and progesterone did not decrease in female COVID-19 patients, it is believed that SARS-CoV-2 infection may have minimal effect on ovarian reserve [2, 28]. Further clinical evidence and test data are needed to corroborate this supposition [36]. There are some drawbacks to this study [48]. Due to the retrospective and descriptive nature of the study, the menstrual histories of certain patients were not documented in the electronic medical record system; thus, these patients were excluded from the menstrual and sex hormone analyses [48]. Second, only menstrual data was tracked after patients were discharged [48]. Sexual hormone and AMH tests were not conducted upon recovery [31]. Because no autopsy or biopsy specimens of the ovary were available, it was unable to determine if SARS-CoV-2 is present in ovarian tissue and whether it may cause long-term harm [45].

### ***C. Long COVID risk - a warning to address sex hormones and the health of women***

Sex-specific risks and consequences are multifactorial - a product of the intricate interplay between biology, behaviour, and broader health factors [49]. During the COVID-19 pandemic [50]. These variables lay the setting for Long COVID's disproportionate impact on women [51]. Female gender and age less than 50 are now recognised as risk factors for Long COVID symptoms [52]. However, recognised markers of acute COVID mortality risk (growing age, chronic illness, and male sex) do not accurately predict bad outcomes in Long COVID [6]. Long COVID risk appears to be largely unaffected by preexisting comorbidities or handicaps, making identifying at-risk women more challenging — an issue for both women and physicians [6]. Despite women's existing precarious socioeconomic circumstances during the epidemic, the persistence of Long COVID symptoms hinders their capacity to return to work [6]. This scenario is likely far more difficult for perimenopausal and menopausal women who already face considerable and extra employment discrimination [52].

From a biological standpoint, we believe that the asymmetry in risk and outcomes between sexes and the overlap of Long COVID symptoms with those of perimenopause and menopause indicates that sex hormone differences should be investigated further [53]. In addition, the increased incidence of Long COVID in women under 50 is a crucial and supportive indicator, given that the average age of natural menopause in the United Kingdom is 51 years [50]. Oestrogen and androgen receptors are ubiquitous, present in virtually all tissues of the body, indicating that sex hormones have responsibilities that extend far beyond their obvious reproductive functions [4, 52]. In HIV and Hepatitis B and C infections, sex hormone disruption resulting in premature menopause, menstrual irregularities, and miscarriage have been described [54]. In the setting of viral infections, dysfunctional sex hormones may be caused by multisystem disruption or organ-specific effects. Beginning to emerge now is the function of sex hormones in COVID-19 infection [23]. A recent study emphasises significant clinical and immunological gender differences in acute COVID-19 infection; women exhibited reduced mortality, lower levels of inflammation, more significant lymphocyte counts, and quicker antibody responses than males [35]. Specifically, oestradiol may be involved here due to its immunomodulatory, antiplatelet, and vasodilatory properties. Observational research identifies temporary menstruation anomalies following acute COVID-19, which the production of ACE2 receptor proteins may cause in the ovaries [34]. These data support the concept that a transient disturbance in the physiological synthesis of ovarian steroid hormones might increase the symptoms of perimenopause and menopause [27, 32].



Many symptoms of Long COVID (fatigue, muscular pains, palpitations, cognitive impairment, and sleep disruption) coincide significantly with perimenopause and menopause, which can affect women of any age [22]. Such overlap may generate diagnostic confusion and necessitates that physicians examine for this differential diagnosis since it allows one to treat perimenopause and menopausal symptoms with safe and effective hormone replacement treatment (HRT) [55]. Failure to recognise this overlap loses a chance to treat many distressing symptoms impacting both physical and mental health and to minimise the risk of cardiovascular disease, type 2 diabetes, osteoporosis, obesity, and perhaps dementia in certain postmenopausal women. In addition, women experiencing perimenopause and menopausal symptoms may be misdiagnosed with Long COVID [55]. Identifying patients at the highest risk for Long COVID is currently of utmost significance [55]. This enables the prioritising of resources for patients with the most significant clinical needs, as well as the identification of multispecialty teams [49]. Clinicians in Long COVID clinics should be trained in menopause care so that perimenopausal and menopausal women may be immediately evaluated and provided with appropriate treatment [54]. Screening and diagnosis of perimenopause and menopause are easy and rapid, often do not need blood sex hormone analysis, and should be conducted frequently in all women attending Long COVID clinics. Changes in menstruation are frequently the first indication of perimenopause; additional typical symptoms of perimenopause and menopause include hot flashes, memory issues, brain fog, decreased stamina, tiredness, anxiety, and poor mood, joint pains, and headaches [56]. Clinicians should inquire about each of these symptoms aggressively [18]. A trial of HRT is a safe and effective therapeutic option for women and physicians to explore when appropriate since an improvement in symptoms confirms the diagnosis of hormone insufficiency [30]. Failure to investigate sex-specific risks and results in COVID-19 is unethical and has several concerns [38]. First, it undermines the possibility of finding causes and therapy targets for diseases for which there are now no therapies [57]. The potential of misdiagnosing Long Covid as perimenopause and menopause, as well as failure to apply appropriate treatment options, poses a hazard to women worldwide, both now and in the future [38]. Thirdly, it affects global economic recovery and future preparation due to the highly gendered character of labour and the predominance of women in areas such as health and social care [30].

In the future, there is an urgent need for a rigorous study to help understand the epidemiological and molecular reasons behind sex variations in Long COVID [30]. The lack of gender- and sex-specific outcomes in clinical trials is acknowledged, and recommendations have been made for the systematic adoption of gender-specific techniques [38]. This introductory study is supported by sex-disaggregated data and power calculations that treat sex as an a priori analytical variable [22, 30].

#### ***D. Further research***

Although new research on COVID-19 is regularly published, the scarcity of high-quality research on COVID-19 and the menstrual cycle reflects the more considerable emphasis of medical research, which does not prioritise women's health outside of pregnancy [12]. The conclusion that the COVID-19 pandemic has impacted menstrual periods may have significant repercussions for society, gender-based inequities, and the economic recovery following the COVID outbreak [36]. Women are more prone than males to have many parenting duties and precarious jobs and income; hence, women are disproportionately impacted by the COVID-19 pandemic; 26% of the world's population are women of reproductive age, and the great majority menstruate. This population is also of working age or is enrolled in school [58]. In addition to hurting women's physical, mental, and quality of life, menstruation-related symptoms are a significant source of economic hardship due to lower productivity and increased job and school absences [59]. Pandemic-related concerns with living arrangements and privacy, access to and cost of menstruation products, and decreased availability and accessibility of sexual and reproductive health care services may exacerbate the aggravation of menstrual symptoms during the pandemic [25, 27]. As the globe continues to cope with and recover from the COVID-19 pandemic, more study is needed to understand better and mitigate the pandemic's effects on menstrual health, which might help reduce gender-based health disparities and socioeconomic inequalities [2, 45]. The epidemic has also emphasised the need for more study into how external environmental variables may affect the menstrual period and how the menstrual cycle might interact with other areas of health [53, 60].

#### ***F. Conclusion***

In conclusion, there was no evidence to suggest that SARS-CoV-2 significantly impairs female COVID-19 patients' fertility. Nonetheless, transitory abnormalities in menstruation and alterations in hormone concentration were detected in specific individuals. After ruling out pregnancy, it is advised that COVID-19 patients with monthly anomalies be observed at home to



prevent wasting medical resources and hospital infections, especially given the severity of the present pandemic. Before planning a pregnancy, it is also indicated that patients have a test of their sex hormone levels and ovarian function. However, further research is required to evaluate the possible influence on the live birth rate.

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Cite this Article: Anchisa Sikiwat (2022). Menstruation and Sex Hormones in Covid-19: Effects in Women of Child-Bearing Age. *International Journal of Current Science Research and Review*, 5(8), 2799-2805