

## Hormonal Change in Virus Corona in Iraq

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### Abstract:

In this research, the changes that may occur to the sex hormones when infected with Covid-19 and their effect on estrogen and progesterone and on the immune response were discussed, and whether the infection has an effect on the menstrual cycle, and how the effect can be reduced, if any, and What is the duration of the effect. It is not surprising that some women suffer from menstrual irregularities to longer cycles or a change in bleeding patterns. So far, the most changes have been due to the pressure of the epidemic, especially (the protracted epidemic), stress and changing behavior, Menstrual disorders can be reduced by reducing stress and tension. Estrogen plays an important role in the female immune response against the viral infection on the immune system, because there is not yet enough research on its effect on covid (estrogen can control infection).

Progesterone is an important factor in promoting faster recovery, as it contributes to the antiviral activity of SARS-COV-2, its association with ACE2 and immune regulation.

In the end, the Corona virus led to several psychological and physiological changes, but most of the changes are temporary and do not cause concern.

## 1. Introduction

Hormones Is any member of the class of signaling molecules, which is produced by Multicellularity, which is transferred glands in organisms by rotating device nature of the hormone. [5] [7] A hormone is a chemical that is secreted into body fluids. A single cell or a group of cells has a controlling effect Physiological to other cells in the body through hormone receptor - specific responses to each hormone; Some of them are local hormones, and others general hormones. The different types of hormones secreted in the body, with a difference in Biological roles and functions. Peptide hormones contain the releasing hormone Thyroid stimulant, antidiuretic hormone urine. Peptides consist of twenties or Hundreds of amino acids, which go back to proteins. It includes hormones and proteins Growth hormone and insulin. Carriers hormones Proteins are the most complex carbohydrates on the side chain, called hormones glycoproteins. yellow body stimulating hormone and follicle stimulating hormone , Thyroid stimulating hormone are examples of glycoprotein hormones. Progesterone is a female hormone secreted by the corpus luteum in the progestogenic phase, i.e. in the last two weeks of a ovary during the female's menstrual cycle after ovulation. It is also secreted in large quantities in the placenta during pregnancy and its quantities increase with the progression of pregnancy and decline a few days before birth. Progesterone works by thickening the mucous lining of the uterus so that a fertilized egg can implant.[13\_15]. Estrogen refers to a steroid hormone that is important in the reproductive development in females Produced by the growing Grafian follicle Secreted by ovaries prior to ovulation; also produced by the placenta during pregnancy Secretion is regulated by FSH Involved in the formation and maintenance of secondary sex characteristics; also important in bone resorption

Hormones heavily control the human reproductive system, and body's hormone is one of those hormones. With different roles in luteinizing the bodies of men and women, this important hormone is crucial to ensuring a healthy reproductive system. Taking control of your reproductive health requires understanding this essential hormone. Luteinizing hormone (LH) is produced and released in the anterior pituitary gland. This hormone is considered a gonadotrophic hormone because of its role in controlling the function of ovaries in females and testes in males, which are known as the gonads. For men, luteinizing hormone stimulates the production of testosterone from Leydig cells in the testes. Testosterone, in turn, stimulates sperm production and helps accentuate male characteristics\_ like a deep voice or growth of facial hair. [16] Hormonal change in virus corona The three major sex hormones are estrogen, progesterone, and testosterone. Estrogen is a hormone with a wide range of regulatory effects that are closely related to the development of the immune system as well as the occurrence of infectious diseases, autoimmune diseases, and tumors; therefore, it has attracted much attention. A large number of studies have shown that the body's susceptibility and immune response to viruses can be modified by estrogen. Estrogen can directly inhibit SARSCOV replication by regulating cell metabolism, which can protect mice from viral infection. Furthermore, gonadectomy or antiandrogen therapy in male mice infected with SARS-CoV did not affect morbidity or mortality, suggesting that a lack of androgen does not affect the immune response[18]. Influenza A virus (IAV) mouse experiments have shown that estrogen treatment can reduce morbidity and mortality caused by the infection [19,20]. Female mice receiving high levels of estrogen have been reported to have increased survival and lower cytokine production in the lungs after influenza infection [20,21]. Adult female mice exhibit a stronger innate immune response and a more sensitive influenzaspecific antibody response than male mice during influenza virus infection. This is because there exist more virus-specific memory T cells in their lungs, and thus they are better protected from secondary immune attacks [22,23]. In addition, estrogen can inhibit the replication of influenza virus in nasal epithelial cells and upregulate the estrogen receptor signaling pathway at the same time. Estrogen can also help maintain cell integrity through genetic modification and improve metabolic function [24] It has long been recognized that estrogen plays a role in the immune response to infection and that it regulates the innate immune system (monocytes/macrophages, granulocytes, natural killer cells, dendritic cells) and the adaptive

immune system (T and B cells) [25]. ACE2 has been identified as a receptor for SARS-CoV-2, which is the key to the virus entering the body. SARS-CoV-2 infects human airways and enters cells by binding its S protein envelope to ACE2 after S protein priming by host serine protease TMPRSS2 (53). The distribution and expression of ACE2 is crucial for the target organs infected by SARS-CoV-2 because SARS-CoV-2 must be bound to ACE2 before entering human host cells (54). This study aimed to investigate the association of COVID-19 positivity and severity with estrogen exposure in women, in a population based matched cohort study of female users of the COVID Symptom Study application in the UK. Analyses included 152,637 women for menopausal status, 295,689 women for exogenous estrogen intake in the form of the combined oral contraceptive pill (COCP), and 151,193 menopausal women for hormone replacement therapy (HRT). Data were collected using the COVID Symptom Study in May-June 2020. Analyses investigated associations between predicted or tested COVID-19 status and menopausal status, COCP use, and HRT use, adjusting for age, smoking and BMI, with follow-up age sensitivity analysis, and validation in a subset of participants from the TwinsUK cohort. Menopausal women had higher rates of predicted COVID-19 ( $P = 0.003$ ). COCP-users had lower rates of predicted COVID-19 ( $P = 8.03E-05$ ), with reduction in hospital attendance ( $P = 0.023$ ). Menopausal women using HRT or hormonal therapies did not exhibit consistent associations, including increased rates of predicted COVID-19 ( $P = 2.22E-05$ ) for HRT users alone. The findings support a protective effect of estrogen exposure on COVID-19, based on positive association between predicted COVID-19 with menopausal status, and negative association with COCP use. HRT use was positively associated with COVID-19, but the results should be considered with caution due to lack of data on HRT type, route of administration, duration of treatment, and potential unaccounted for confounders and comorbidities [26]. In the series of 81 young men (median age 38 years) hospitalized with COVID-19 reported by Ma, et al. [27], estradiol levels (the main estrogen) were similar to those of healthy men (median 32 pg/ml). Shroeder, et al. [28] found that 47% of men (median age 62 years) had elevated estradiol levels between 52-185 pg/ml (normal male range 27.1-52.2 pg/ml). They also found a positive correlation between estradiol levels and the pro-inflammatory cytokine IL-6 [28]. In 78 premenopausal women hospitalized for COVID-19, Ding, et al. [29] found that estradiol levels greater than 70 pg/ml were associated with decreased risk of having severe COVID-19, hazard ratio 0.30 (95% CI 0.09-1.001;  $P=0.05$ ) after adjustment for age, phase of menstrual cycle and co-morbidities. In addition, there was inverse correlation between estradiol levels and the cytokines IL-6, IL-8 and TNF- $\alpha$  [29]. Hence, these results are consistent with estrogen protective effect in COVID-19. In a study from UK called The COVID Symptom Study Smartphone Application "app", Costeira, et al. [30] reported that postmenopausal women had a higher rate of predicted COVID-19 compared with premenopausal women (OR 1.22, 95% CI 1.07-1.39;  $P = 0.03$ ) [30]. Likewise, women using combined oral contraceptives (COCP) had a lower rate of predicted COVID-19 (OR 0.87, 95% CI 0.64-0.97;  $P=0.023$ ) compared with age-matched women not taking COCP [30]. Conversely, women aged 50-65 years using postmenopausal hormone replacement therapy had higher predicted COVID-19 than age-matched women not taking such therapy (OR 1.32, 95% CI 1.16-1.49) [30]. The authors mentioned that co-morbidities, duration and use of postmenopausal hormone therapy might explain the unexpected increase in predicted COVID-19 in this group of postmenopausal women [30].

### **-COVID-19 in pregnancy**

Since pregnancy is characterized by extremely high levels of circulating estrogen, evaluation of susceptibility and clinical severity of COVID-19 in pregnant women may be a useful tool to examine the possible protective effect of estrogen. In general, available data suggest that severity of COVID-19 in pregnant women may not be different from non-pregnant women [31, 32]. This notion is limited, however, by the lack of direct comparison with age-matched non-pregnant women with similar comorbidities. A possible protective effect of estrogen was suggested in the study of Chen, et al. [32] including 118 pregnant women hospitalized for COVID-19. In this study, 6 of the 9

pregnant women whose condition deteriorated did so following delivery when serum estrogen levels declined. Effect of progesterone in coronavirus disease 2019: SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) infection is a global medical challenge. Experience based medicines and therapies are being attempted and vaccines are being developed. SARS-CoV-2 exhibits varied patterns of infection and clinical presentations with varied disease outcomes. These attributes are strongly suggestive of some variables that differ among individuals and that affect the course of SARS-CoV-2 infection and symptoms of COVID-19 (Corona Virus Disease of 2019). Sex hormones vary with ageing, between the sexes, among individuals and populations. Sex hormones are known to play a role in immunity and infections.[33] Progesterone is a critical host factor to promote faster recovery following Influenza A virus infection. Anti-inflammatory effects of progesterone are noted. the regulatory role of progesterone for SARSCoV-2 infection and COVID-19 is analyzed. The role of progesterone at different stages of the SARS CoV-2 infection is investigated with respect to two types of immunity status: immune regulation and immune dysregulation. Progesterone could have various alleviating impacts from SARS-CoV-2 entry till recovery: reversing of hypoxia, stabilizing of blood pressure, controlling thrombosis, balancing electrolytes, reducing the viral load, regulation of immune responses, damage repair, and clearance of debris among others. The present research adds to the available evidence by providing a comprehensive and thorough evaluation of the regulatory role of progesterone in SARS COV-2 infection, COVID-19 pathogenesis, and immune dysregulation. The available evidence has implications for upcoming studies about pathophysiology of COVID-19, as well as the roles of progesterone and other hormones in other infectious diseases[33]. Progesterone could exhibit anti-viral activity at three stages of the SARSCOV-2 infection: upper respiratory tract, lower respiratory tract, and within the cells and neurons [34].

#### **Upper respiratory tract:**

The major entry of SARS-CoV-2 is via the upper respiratory tract. Whether the virus can successfully enter and establish itself in the host cell or fails depends on the proteases and protease-inhibitors, which are secreted from the respiratory epithelium. More protease and less protease inhibitors is associated with increased susceptibility to respiratory viral infections and severity of symptoms [35]. Serine protease inhibitors (serpins) are the major protease inhibitors in the lung that protect cells from protease-mediated injury. They assist the immune system by limiting tissue damage and unwarranted cell death caused by infection-associated proteases [36]. They are the key regulators of numerous biological pathways that initiate inflammation, coagulation, angiogenesis, apoptosis, and complement activation; and are associated with cell survival, development, repairs, and host defense at the sites of infection and inflammation [37,38]. Progesterone increases secretory leukocyte protease inhibitor (SLPI), a serpin secreted by the human nasal epithelial cells and saliva. This is an important respiratory tract host defense protein which confers local protection against microbial, fungal, and viral infections [39,40]. Increase of SLPI by progesterone also contributes to the confinement of inflammation and tissue damage, thereby facilitating wound healing. It promotes infection clearance at mucosal sites by maintaining sufficient monocytes for infection and inflammation resolution [41].

#### **Lower respiratory tract:**

Two main host factors are required for successful SARS-CoV-2 entry in the lung: angiotensin converting enzyme 2 (ACE2), and the transmembrane protease serine 2 (TMPRSS2). SARS-CoV-2 enters cells by binding its spike protein to ACE2. To accomplish this binding, the SARS-CoV-2 needs to prime its spike protein; which it does by using TMPRSS2 [42]. Androgens upregulate the TMPRSS2 and facilitate the SARS-CoV-2 to establish itself [43]. Progesterone is anti-androgenic and can block the upregulation of TMPRSS2 by androgens [44]. Notably, progesterone and the serpin alpha-1 antitrypsin which inhibits the SARSCoV-2 priming protease TMPRSS2 are higher in adult females than in adult males [45]. This is an important observation because SARS-CoV2

infection and mortality due to COVID-19 are significantly more severe in males than in females [46]. Receptor binding is a major determinant of tissue tropism for SARSCoV-2. Sigma receptors might play a role in the infectivity of SARS-CoV2 [47]. These receptors are highly expressed in intracellular locations: the olfactory bulb, lung, liver, intestine, kidney, spleen, adrenal gland, central nervous system (brain and the periphery), and placenta. Sigma receptors are predominantly localized intracellularly in the endoplasmic reticulum (ER) [48]. When an agonist binds to the sigma receptor, it acts as an upstream accelerator of ER stress through modulation of a voltage-gated ion channel [49]. Corona viruses exhibit identical effects on ER stress and may have a role in the agonist activation of the sigma receptors. Replication of the coronaviruses occurs in membranous compartments derived from the ER, which causes host cell stress and activates pathways to facilitate adaptation of the host cell machinery to viral needs. Progesterone is an antagonist of sigma receptors that blocks the receptor-mediated modulation of the voltage-gated ion channel [50]. This way it blocks action of the agonist [51] on the sigma receptors and controls the ER stress. This is a disadvantage for the virus. Gordon et al [47] have reported that progesterone could exert antiviral activity on SARS-CoV-2 through its sigma activity

### **The relationship of covid and the menstrual cycle:**

The menstrual cycle is regulated by a complex interplay of hormones that interact with the immune, vascular and coagulation systems, and these interactions can influence menstrual bleeding and severity of (pre)menstrual symptoms.[62] SARS-CoV-2 infection and COVID-19 illness could affect the hypothalamic-pituitary-ovarian-endometrial axis with resulting changes to the menstrual cycle. Hypothalamic hypogonadism may occur in the presence of any severe illness, including COVID-19, and result in temporary amenorrhoea or infrequent menses. This protective mechanism enables diversion of energy resources from reproduction to the immune response.[55] COVID-19 mitigation and control strategies, like lockdowns and social distancing, have led to increases in psychological stress, depression and anxiety and reductions in general well-being, particularly in young adults and women.[56] Studies have also identified associations between the pandemic and weight gain and changes in health behaviours.[57] Psychological stress is a known risk factor for hypothalamic hypogonadism, resulting in infrequent or absent menstruation.[58] There is also a well-known link between changes in weight and the menstrual cycle, and some(inconclusive) evidence that the menstrual cycle can be altered by health behaviours such as changes in alcohol consumption, diet and physical activity. [59] It's possible that the infection itself could stress your body or disrupt hormone levels, leading to noticeable changes in your period.[60]. During times of stress, the HPA axis stimulates the release of the stress hormone cortisol to help the body prepare to fight or flee from a threat. With ongoing stress, "increased cortisol levels can affect a woman's menstrual cycles," Dr. Shirazian says. In addition, with prolonged periods of stress, the stress response system can burn out, and the HPA axis can be suppressed, which drives down the pituitary production of follicle stimulating and luteinizing hormones (FSH and LH), which then drive down ovarian production of estrogen and progesterone. With complete suppression of the HPA axis, a woman may experience amenorrhea, the absence of periods. With partial suppression, a woman could have spotty periods or periods of bleeding every few weeks. "There isn't one clear pattern we can expect — women respond differently to suppression of the HPA axis," Shirazian says.[61] As far as the stress of the pandemic goes, it's occurring on two fronts. Besides the fact that stress itself increases cortisol levels, which can affect menstruation, the disruptions that have occurred in people's lifestyles and routines during the pandemic can affect a woman's menstrual cycle. And if women have become more sedentary or gained weight during the pandemic, Shirazian notes, these changes can affect their periods, perhaps leading to missed menstrual periods, longer spans between periods, or longer bleeding time. what do we know about COVID-19 and menstruation? A 2021 study Trusted Source assessed data from 177 menstruating people with COVID-19. Let's take a closer look at the results. Changes in menstrual volume were found in 45 out of 177 people (25 percent). Out of these 45 individuals, 36 experienced a significantly lighter period while 9 had a

significantly heavier period. People with severe COVID-19 were more likely to have a menstrual cycle that was longer than 37 days. Researchers found that 34 percent of people with severe illness had long cycles, compared to 19 percent of people with mild illness. When researchers compared menstrual cycle length during COVID-19 to an individual's normal cycle length, they found that 50 out of 177 people (28 percent) had changes in their menstrual cycle. Most experienced a longer-than-normal cycle during their illness, although some had a shorter cycle. The levels of sex hormones, such as follicle-stimulating hormone, estrogen, and progesterone, from 91 people with COVID-19 were compared to 91 people without COVID-19. No difference was found between the two groups. Lastly, researchers observed that 84 percent and 99 percent of participants had returned to their normal menstrual volume and cycle length, respectively, 1 to 2 months after having COVID-19.[60]

## CONCLUSION

We conclude from this research that the effect of Covid on hormones and the menstrual cycle needs more study and investigation and more detailed information on several cases.

It is not surprising that some women suffer from menstrual irregularities to longer cycles or a change in bleeding patterns. So far, the most changes have been due to the pressure of the epidemic, especially (the protracted epidemic), stress and changing behavior,

Menstrual disorders can be reduced by reducing stress and tension. Estrogen plays an important role in the female immune response against the viral infection on the immune system, because there is not yet enough research on its effect on covid (estrogen can control infection).

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