The biological and psychological impact of the Coronavirus disease-19 pandemic on the characteristics of the menstrual cycle

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Abstract

The Coronavirus disease-19 (COVID-19) pandemic was declared in March 2020 by the World Health Organization. The severe acute respiratory syndrome-coronavirus-2 virus enters host cells through angiotensin-converting enzyme 2 receptors and transmembrane serine protease type II that are expressed in pulmonary alveoli, as well as in hepatocytes, endothelium, ovaries, uterus, vagina, thyroid, and other tissues. In addition to viral injury, the COVID-19 pandemic, through protective measures such as social isolation and lockdown, has promoted a scenario of psychosocial stress, especially in women. In this context of isolation, anxiety, fear, and mental distress, there is dysregulation of the hypothalamic-pituitary-adrenal axis and subsequent gonadal side effects. Furthermore, studies report an association between COVID-19 and temporary menstrual cycle alterations such, as increased cycle duration, decreased cycle duration, increased menstrual flow, dysmenorrhea, and amenorrhea. Regarding COVID-19 vaccination, menstrual irregularities have been observed in about half of the women, predominantly with a decrease in cycle duration and increased menstrual flow, but without fertility sequelae. The aim of this study was to review the most up-to-date information on the relationship between the COVID-19 pandemic and menstrual irregularities. (J Turk Ger Gynecol Assoc. 2024; 25: 259-65)

Keywords: COVID-19, menstrual cycle, menstrual irregularity, SARS-CoV-2, women's health

Received: 24 November, 2023 **Accepted:** 05 June, 2024

Introduction

The novel severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) was first reported from China on December 2019, and in March 2020, the Coronavirus disease-2019 (COVID-19) pandemic was declared by the World Health Organization (WHO) (1,2). As the transmission of this disease occurs through droplets, preventive measures such as social distancing and lockdown were recommended during this pandemic scenario (2,3).

COVID-19 is preceded by the entry of SARS-CoV-2 into host cells, mainly through angiotensin-converting enzyme 2 (ACE2) receptors, but also through transmembrane serine protease type 2 (TMPRSS2) that are abundantly expressed in pulmonary alveoli, as well as in other tissues such as hepatocytes and endothelial cells (2,4,5). Regarding women's health specifically, there have been reports of viral entry into organs of the female reproductive system, including the uterus, vagina, and ovaries, as well as viral involvement of organs, such as the thyroid, that participate in the homeostasis of the female hormonal axis (4,5).

In addition to the direct damage caused by viral infection, the COVID-19 pandemic has indirectly affected mental health because of disease containment policies. Overall, the population has been subjected to anti-social restrictions, such as quarantine, physical and social isolation, together with financial complications that also arose (3). The female population is described as a vulnerable group in this context

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DOI: 10.4274/jtgga.galenos.2024.2023-6-9

because, as a result of quarantine measures, they were potentially exposed to financial dependence, increased responsibility for children, or domestic violence, which caused significant psychological and emotional distress (6-8).

The biological relationship between menstrual irregularities and psychosocial distress is mainly based on cortisol levels, a hormone that increases during psychological stress, which disrupts the hypothalamic-pituitary-adrenal axis and, consequently alters the hormonal regulation of follicle stimulating hormone (FSH) and luteinizing hormone (LH) in the menstrual cycle (9-11). Moreover, it has been reported that, in the presence of severe illness or infection, an energy diversion mechanism can occur in the female reproductive system which impacts the immune system or could give rise to compensatory reactions, resulting in menstrual cycle alterations in these patients (9,12,13). In the case of COVID-19, there are reports of ovarian suppression with altered levels of FSH and LH, directly affecting hormonal feedback regulation of menstruation (11,14).

The aim of the present study was to provide an up-to-date review on the biological or psychological impact of the COVID-19 pandemic on women's health, specifically in terms of menstrual cycle alterations.

Physiology of the menstrual cycle

The menstrual cycle is a natural process of the female reproductive system that occurs between menarche and menopause, and it extends from the first day of cyclic uterine bleeding, through endometrial shedding, until the next menstruation. An average menstrual cycle lasts for 28 days but can vary from 21 to 37 days (15,16). Briefly, the regulation of this cycle occurs through the stimulation of gonadotropin releasing hormone (GnRH), a hypothalamic hormone which stimulates the release of pituitary gonadotropin hormones, FSH and LH, which in turn stimulate production and ovarian hormones, estrogen, and progesterone (16,17).

The menstrual cycle is divided into three phases: the follicular phase, ovulation, and the luteal phase. The follicular phase begins with menstruation and lasts until ovulation. It is characterized by the maturation of the ovarian follicle under the influence of FSH and, at the end of this phase, by an estrogen peak that precedes ovulation (15,16). During ovulation, estrogen, in turn, exerts negative feedback on FSH while exerting positive feedback on LH (18,19). Ovulation occurs approximately on the 14th day of the cycle and is characterized by the expulsion of the oocyte from the dominant follicle, which happens after the LH surge. From there, the luteal phase begins, lasting until menstruation, and it is the period during which the remnants of the dominant follicle transform into the corpus luteum, leading to elevated progesterone levels. If there is no ongoing pregnancy, at the end of the luteal phase, endometrial shedding occurs, and a new cycle begins (16,20). Simultaneously with the ovarian cycle, there is also a uterine cycle within the menstrual cycle, as the endometrium prepares for implantation and the continuation of pregnancy. During the follicular phase, the proliferative phase of the endometrium occurs, characterized by an increase in stromal thickness and glandular growth. The secretory phase of the endometrium begins with ovulation and involves endometrial thickening and vascular proliferation (20).

Menstrual cycle alterations are named according to which characteristic of the cycle is affected. In terms of cycle duration, if it is less than 21 days, it is called polymenorrhea, and if it is longer than 37 days, it is called oligomenorrhea (16). Regarding menstrual flow, if it exceeds 150 mL, it is called hypermenorrhea. Uterine bleeding that occurs outside the menstrual cycle is referred to as metrorrhagia. In addition, the absence of the menstrual cycle is called amenorrhea, and the presence of pain during the menstrual cycle is called dysmenorrhea, both of which can be classified as primary or secondary conditions (20,21).

Other hormones can indirectly influence the hypothalamic-pituitary-ovarian axis. For example, in hypothyroidism, there is an increase in the hypothalamic hormone thyrotropin releasing hormone, which elevates levels of pituitary hormones thyroid stimulating hormone and prolactin. Prolactin, in turn, exerts negative feedback on gonadotropin hormones, which can result in menstrual irregularities, such as amenorrhea (18,22).

The relationship between SARS-CoV-2 and the hypothalamic-pituitary-ovarian axis

ACE2 receptors, besides being present in the uterus, vagina, and ovaries, directly participate in the follicular phase of the ovarian cycle, follicular development, ovulation, and luteal angiogenesis. They also participate in the uterine cycle during the secretory phase.

These receptors are used by the SARS-CoV-2 virus to enter cells, and this process itself produces tissue damage that can lead to functional impairment (4,23). Furthermore, ACE2 receptors are also present in the thyroid, which could facilitate the entry of this virus into the organ and cause hypothyroidism, among other conditions. Altered prolactin secretion due to hypothyroidism can subsequently affect ovarian hormone production (4,24).

Hypothalamic-pituitary-adrenal axis

In a context of stress, whether physical or psychological, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the pituitary to synthesize and secrete adrenocorticotropin hormone (ACTH), which acts on

the adrenal cortex to increase cortisol levels. The increase in cortisol exerts negative neuroendocrine feedback (9,25). Hypercortisolism affects the reproductive system both through direct action on the ovaries, by reducing gonadotropins, and through reduced LH levels resulting from hypothalamic and pituitary feedback, providing the environment for menstrual irregularities or even amenorrhea to occur (26,27).

There is also literature describing the influence of gonadotropins on the psychological and emotional state of women. Estrogen appears to regulate dopamine levels and has antipsychotic action while progesterone has been reported to have anxiolytic effects (28). Therefore, ovarian suppression due to increased cortisol levels could further promote the psychological stress brought on by the elevation of this hormone, as gonadotropins would not be exerting these actions (29).

Due to hormonal feedback in the hypothalamus and pituitary, there are other axes and hormones that can trigger ACTH stimulation and consequent cortisol elevation, similar to how hypercortisolism can disrupt the levels of these hormones (30-32). It is known that basal cortisol release is controlled by the circadian cycle. Therefore, alterations in the sleep-wake cycle, such as sleep deprivation, prolong cortisol release throughout the day. In a mentally healthy individual, the hypothalamic-pituitary-adrenal axis is inhibited by GnRH during sleep. However, in an individual experiencing psychological distress, there is a predominance of CRH action, promoting wakefulness and compromising pulsatile GnRH secretion, affecting the entire hormonal cascade (29). In addition, both cortisol elevation and sleep deprivation can alter the synthesis of the hormones leptin, which inhibits appetite, and ghrelin, which stimulates appetite, both of which have effects on the hypothalamus (32). Leptin and ghrelin secretion is regulated by the circadian cycle. Therefore, an alteration in the hypothalamic-pituitary-adrenal axis due to elevation of cortisol not only disrupts the circadian cycle but also disrupts the balance between appetite stimulation and inhibition, as cortisol itself also stimulates appetite (31,32). Another component modulated by cortisol is the immune system. The interaction between cortisol and pro-inflammatory cytokines initially plays a role in the mechanism of homeostasis in response to stress, whether it be of immunological, psychological, or emotional origin. However, exposure to excessive or chronic stress, with constantly elevated cortisol levels, disrupts the synthesis of these cytokines, resulting in immunosuppression (34,35). In COVID-19, the use of exogenous corticosteroids in patient management in an attempt to suppress hyper-immune dysregulation was notable (36,37).

Thus, in addition to the viral injury itself and the pandemic scenario, which led to biological and mental stress, the treatment of the disease that may have resulted in elevation of serum cortisol levels, which can result in menstrual irregularities should also be considered (9,38).

Psychological and emotional changes in COVID-19

The experience of the COVID-19 pandemic caused a series of problems that are not limited to SARS-CoV-2 infection. Significant damage and sequelae to mental health have been observed, even in those who did not suffer from viral infection (39,40). The measures proposed by the WHO (41), such as social isolation and lockdown, implemented to curb viral transmission, have resulted in various behavioral, emotional, and cognitive changes, whether directly or indirectly (42,43).

Among the psychosocial consequences, an increase in stress was observed in individuals who were subjected to physical and social distancing. This stress was directly related to isolation, but also to secondary conditions, such as sleep deprivation, sedentary lifestyle, and changes in eating habits (39,44,45). It is important to note that a vicious cycle of stress may be created, in which social isolation promotes stress, which in turn causes sleep disturbances that further increase stress and disrupt appetite. This disruption of eating habits also contributes to hormonal dysfunction in the neuroendocrine axes, leading to increased stimulation of cortisol and thus a rise in its secondary effects, such as ovarian suppression (17,45,46).

Fear and anxiety related to the risk of contracting COVID-19 or, if already infected, developing a severe condition or even dying, as well as fear of seeing friends and relatives under the same risk, are reported as significant causes of psychosocial disorders during the pandemic (47). In the literature, in addition to fear and anxiety, an exacerbation of emotions such as anger, sadness, boredom, and loneliness is described, all of which contribute to mental distress (48). Another source of psychological and emotional distress experienced during the pandemic was the grief over the loss of loved ones, which has caused intense psychological stress for many people (49).

Unfortunately, due to pre-existing gender inequality, women have been more affected by the economic crisis caused by the pandemic, experiencing termination of employment and consequent loss of income, which has led many women to become financially dependent on their partners (6,50). As a result, there has been an increase in cases of domestic violence during the pandemic, including psychological, physical, and sexual violence, subjecting these women to extreme psychosocial and biological stress (6,51). Furthermore, due to the patriarchal nature of some societies, women may have been more exposed to increased domestic demands during the isolation period, as they were assigned responsibilities such as housekeeping and childcare (47,52).

All of these psychological, behavioral, and emotional experiences have served as triggers for the emergence of psychiatric disorders in some individuals. During or after the pandemic, there have been reports of mental health condition diagnoses, with depression and anxiety being the most predominant (53).

Changes in the menstrual cycle in COVID-19

There are reports of positive SARS-CoV-2 real time-polymerase chain reaction results in vaginal samples (54,55), although the possibility of COVID-19 transmission through sexual contact by women is believed to be very low (56). The virus has also been detected in ovarian tissue, which reinforces its potential interference in the female reproductive system (57). However, SARS-CoV-2 has not been detected in endometrial tissue (58,59), although it is known that the uterus expresses ACE2 and TMPRSS2 receptors, which would allow viral entry (4,5,58). In their study, Li et al. (60) reported that women in the menacme who were hospitalized for COVID-19 experienced menstrual irregularities, such as increased cycle duration, variation in cycle length, and decreased menstrual flow, with normalization of the cycle three months after disease. Alessa et al. (61) evaluated 663 menacme women, of whom 206 tested positive for COVID-19, and among these 206, there was a predominance of complaints of dysmenorrhea (73.8%), reduced menstrual flow (51.5%), and polymenorrhea (40.8%). In the study by Lasta et al. (20), out of the 112 women in the sample who previously had regular cycles, 12 experienced a decrease in cycle duration due to COVID-19, and there were also reports of increased menstrual flow. Meanwhile, in a study conducted by Khan et al. (62), in a sample of 127 menacme women who tested positive for SARS-CoV-2, dysmenorrhea (45%) and oligomenorrhea (35%) were predominant. Demir et al. (63) sampled of 263 menacme women, after excluding women with a history of menstrual irregularity or current use of contraceptives, and found a decrease in cycle duration and menstrual flow volume during COVID-19. Notably, this study showed that patients with menstrual changes also mentioned psychological stress as a complaint.

Takmaz et al. (11) conducted a study on menstrual cycle changes in female healthcare professionals who worked in the COVID-19 pandemic setting. Out of a sample of 952 women, 273 experienced menstrual irregularities during the COVID-19 pandemic, with a notable decrease in cycle duration and an increase in menstrual flow. What is noteworthy in this study is that among these 273 women, those with a diagnosis of depression, anxiety, or other mental disorders were prevalent.

Other authors who associate menstrual cycle changes with mental distress in COVID-19 are Ozimek et al. (64), who describe exclusively increased menstrual flow in patients who complained of psychosocial stress, as well as increased cycle duration and dysmenorrhea in women in the sample, regardless of mental distress. In general, these studies reported an increase in behavioral and emotional symptoms, known as premenstrual tension, preceding menstrual cycles during COVID-19.

In a study by Ding et al. (65), which included 78 women with COVID-19, with 17 of them having severe disease, dysmenorrhea, amenorrhea, and hypermenorrhea were reported as changes. In another study by Phelan et al. (66), which had a sample of 1,031 women, 9% reported experiencing their first episode of amenorrhea during COVID-19. Another important finding reported by Nguyen et al. (67) was that in their sample of 18,706 women, regardless of the type of alteration, any COVID-19-related menstrual irregularity ceased shortly after the resolution of the condition in all women, except for one. It is worth noting that several studies describe an association between SARS-CoV-2 infection and coagulation dysregulation, from laboratory abnormalities to hemorrhagic or thromboembolic events (2,68,69).

Vaccination for COVID-19 and menstrual irregularity

There is a description in the literature regarding the association between COVID-19 vaccination and menstrual cycle alterations (9,70). It is essential to remember that in several studies conducted, no negative impact of COVID-19 vaccination on female fertility was detected (5). Laganà et al. (71) reported that around 60% of women, regardless of the vaccine administered, experienced menstrual irregularities, mainly after the second dose, with a predominance of reduced cycle duration and increased menstrual flow. Other studies that found very similar results were those by Lee et al. (72) and Muhaidat et al. (73). In the study by Nazir et al. (74), 39,759 (52.05%) women experienced menstrual irregularities after COVID-19 vaccination, with a high prevalence of polymenorrhea, hypermenorrhea, and metrorrhagia. This latter study highlights the presence of women who had a prior SARS-CoV-2 infection or were under intense psychological stress before vaccination among the most symptomatic patients in terms of menstrual cycle alterations.

Regarding these menstrual cycle alterations after vaccination, it is observed that they cease within a period of up to two subsequent menstrual cycles (5).

Conclusion

It is evident, therefore, that a relationship can be established between the COVID-19 pandemic and apparently temporary menstrual cycle alterations. Both the biological component of SARS-CoV-2 infection or its vaccination and their interaction with organs of the female reproductive system, as well as the

psychosocial component of the social experiences resulting from the pandemic scenario, have descriptions in the literature that support the impact of COVID-19 on menstrual irregularity. However, it is still not possible to establish a predominance of menstrual irregularities present in COVID-19, as a variety of alterations have been reported in the studies published to date. Regarding COVID-19 vaccination, menstrual irregularity was observed in approximately half of the female population, with a predominance of polymenorrhea and/or hypermenorrhea, but without any impact on fertility.

Conflict of Interest: *No conflict of interest is declared by the authors.*

Financial Disclosure: *The authors declared that this study received no financial support.*

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