

Review Article

Changes in the Menstrual Cycle Secondary to SARS-COV-2 Infection

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Abstract

Introduction: Women's health can be affected by stress, infections and psychological well-being. In 2019, all aspects of human life were affected by the COVID-19 pandemic, virus infection can affect the hypothalamus-pituitary-ovary-endometrium axis with resulting changes in the menstrual cycle, which are associated with a series of impacts arising from the systemic inflammation caused and associated endometrial and vascular disorders, bringing fear, insecurity and anxiety to their lives.

Objective: Understanding the impacts that occurred in the context of women's health is the objective of this research, demonstrating menstrual changes resulting from SARS-CoV-2 infection, hormonal changes and how these are associated with vascular changes. Since hormonal changes, resulting from the infection seem to be related to irregularities in the menstrual cycle.

Methods: A bibliographical research was carried out with an integrative literature review based on academic and scientific journals, national and international, using the databases Medscape, Revista Interdisciplinary Science Doctors, PubMed/MEDLINE, Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature in Health Sciences (LILACS), Google Scholar, Virtual Health Library (VHL). Studies demonstrate the systemic biological effects resulting from COVID-19 infection, which were due to the involvement of ACE 2 expression and its influences on hormonal, endometrial and vascular changes.

Conclusion: The integrative review demonstrated, through several studies, the occurrence of changes in the cycle, such as menstrual irregularities, increased flow, intermenstrual leaks and subsequent changes, but further research is needed to establish a correct association.

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Citation: Alves NAR (2024) Changes in the Menstrual Cycle Secondary to SARS-COV-2 Infection. J Clin Stud Med Case Rep 11: 232.

Received: April 01, 2024; **Accepted:** April 11, 2024; **Published:** April 18, 2024

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Keywords: COVID-19; Menstrual cycle changes; Menstrual Cycle; Women's Health

Introduction

At the end of 2019, the world experienced the record of the first case of a disease that then became a huge health crisis. The first case of severe acute respiratory infection (SARS-CoV-2), caused by coronavirus (COVID-19), was reported on December 31, 2019, in Wuhan, China. Since then, the disease has spread rapidly around the world, leading the World Health Organization (WHO) to declare a pandemic on March 11, 2020. According to WHO data (2022), by November 2022 more than 630 million Cases have been detected worldwide and 6,584,104 people have lost their lives to the disease. In Brazil, there are more than 34 million confirmed cases and more than 688 thousand deaths [1].

Most cases of COVID-19 are mild and do not require medical care. However, 15% to 20% of infected people require hospitalization and 5% require mechanical ventilation. [2] The main symptoms of SARS-CoV-2 infection include fever, cough, myalgia, dyspnea, headache, diarrhea and anosmia. Severe cases lead to severe pneumonia and death. Risk factors for serious illness include age and comorbidities such as cardiovascular disease, cancer, and chronic respiratory disease [3].

Since the beginning of the pandemic, new research and further development in the area has been necessary for all health professionals, as it is a recent disease with limited specific knowledge about it. There were countless doubts that arose regarding diagnosis, clinical management, forms of treatment, prevention and especially the impacts it would have on health.

After the peak of the pandemic period, there are many doubts regarding the presence of complications after infection with the new coronavirus. Hormonal changes resulting from infection with the SARS-CoV-2 virus appear to be related to irregularities in the menstrual cycle. Women have reported longer and more irregular cycles after becoming infected with the virus, which can affect women's quality of life and reproductive health. This work will be important for understanding how SARS-CoV-2 affects the female menstrual cycle. Correlating the involvement of ACE 2 during the period of SARS-COV-2 infection with subsequent hormonal changes [4].

SARS-CoV-2 infection can affect the hypothalamic-pituitary-ovarian-endometrial axis with resulting changes in the menstrual cycle. Hypothalamic hypogonadism can occur in the presence of any serious illness, including COVID-19, and result in temporary amenorrhea or infrequent menstruation [5].

In this context in which all aspects of human life have been affected, it is important, in the context of women's health, to understand the impacts of COVID-19 on the menstrual cycle, as it is an important part of women's lives [6].

Therefore, this approach is necessary, given that women were widely affected during this pandemic period, manifesting a series of metabolic changes, which, for the most part, had no recent studies on their correlation.

In view of the above, the present review work aims to seek and gather information from studies carried out around the world, presenting the varied changes in the menstrual cycle observed after COVID-19 infection, as well as the pathophysiology associated with these changes and the consequences for female health. The importance of knowing these abnormalities that have arisen and their possible future complications is highlighted.

Materials and Methods

This is a bibliographical research, of the integrative literature review type, which aims to obtain answers regarding the problem presented in relation to the changes in the menstrual cycle found and their causes in the face of SARS-CoV-2 infection.

The research was carried out between the months of February 2023 and April 2023, using online access in the databases Medscape, Revista Interdisciplinária de Ciências Médicas, PubMed/MEDLINE, Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature in Health Sciences (LILACS), Google Scholar, Virtual Health Library (VHL). To search for works, the following descriptors were used: COVID-19, Menstrual Cycle, and Changes in the menstrual cycle, Women's Health.

The following inclusion criteria were established for the studies in this research: 1) Studies referring to Changes in the Menstrual Cycle Secondary to SARS-CoV-2 Infection. 2) Studies in English, Portuguese and Spanish. 3) Studies with complete texts, in full. 4) Studies that were published between 2020 and 2023. 45 articles that met the inclusion criteria were considered. Articles that were not in English, Portuguese or Spanish, in different databases and that were not related to the proposed theme or period were excluded.

Results and Discussion

Normal Menstrual Cycle

The menstrual cycle consists of a conglomerate of endometrial and systemic changes, which have an average duration of 28 days. This is related to a cascade of important events that occur in the hypothalamic-pituitary-ovarian axis (HHO), being responsible for the female sexual and reproductive cycle [7].

Some physiological factors influence this process and are characterized by a cyclical pattern of hormonal changes, related to the interaction between the hypothalamus, thalamus, pituitary gland, ovaries and uterus. The cycle is divided into ovarian and endometrial, the first is represented by the follicular and luteinizing phases, while the second involves the proliferative, secretory and desquamation phases [8].

The normal menstrual cycle has an average duration of 28 days. It can be as short as 20 days or as long as 45 days, this variation being normal in some women, although an abnormally long cycle is often associated with lower fertility. The ovarian changes that occur during the female sexual cycle depend entirely on the gonadotropic hormones follicle-stimulating (FSH) and luteinizing (LH), which are secreted by the anterior pituitary gland. In the absence of these hormones, the ovaries remain inactive, as occurs throughout childhood, when almost no gonadotropic hormones are secreted.

The normal ovarian cycle begins with the follicular phase, which requires the pulsatile secretion of gonadotropin-releasing factor (GnRH), of hypothalamic origin and which acts as an inducer of the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the hypophysis. The increase in FSH at the beginning of the follicular phase stimulates the growth of primordial follicles, and induces increased estrogen production by granulosa cells in the ovary. This hormone stimulates the increase in LH, and the selection of the dominant follicle for maturation and release. At the same time, the proliferative phase occurs in the endometrium, where there is an increase in the size of the vessels, stroma and glands [9].

Ovulation will occur 34 to 36 hours after the peak of LH secretion, approximately on the 14th day, with consequent expulsion of the dominant follicle by the ovary. The formation of the corpus luteum begins, characterizing the luteal phase, with an increase in progesterone, estrogen and inhibin, which generate negative feedback on the pituitary gland, inhibiting the release of FSH and LH. At the same time, the secretory phase occurs in the endometrium, characterized by thickening of the endometrium, vascular and glandular proliferation and maturation of the stroma. If fertilization does not occur, the corpus luteum begins to atrophy between 10 and 14 days, associated with a drop in estrogen and progesterone, leading to menstruation and stimulating an increase in FSH and LH, starting the cycle again.

This cycle involves complex interactions between various tissues, hormones and systems of the human body, such as the immune, vascular and blood systems. Thus, the menstrual cycle is sensitive to endogenous and exogenous factors, including infections and lifestyle changes [10,11].

Changes in the Menstrual Cycle

Abnormal uterine bleeding is defined as any disorder in which one or more of the parameters of normal uterine bleeding is altered: quantity, duration or frequency. To characterize this change, it is important to know what is considered normal uterine bleeding, which constitutes a menstrual flow lasting three to eight days, with blood loss of 5 to 80 milliliters and a cycle that varies between 24 and 38 days (variability of three days). Any bleeding that does not have these characteristics is considered abnormal [12].

An abnormal cycle is also defined as excessive menstrual loss with physical, emotional, social and material repercussions on a woman's quality of life, which can occur alone or in combination with other symptoms [13].

Among the causes of menstrual cycle abnormalities, nine categories are described, according to the acronym PALM-COEIN, which is subdivided into structural causes: polyp, adenomyosis, leiomyoma, malignancy and endometrial hyperplasia (PALM), and the causes non-structural: coagulopathy, ovulatory dysfunction, endometrial, iatrogenic and unclassified causes (COEIN). Among these, primary disorders of the endometrium often manifest as changes in local endometrial hemostasis, resulting from an inflammatory response [14].

Once installed, the inflammatory process is disseminated hematogenously throughout the body, generating a series of systemic manifestations.

More than two years after the start of the COVID-19 pandemic, there is growing interest in understanding the consequences that arise after infection, including in the menstrual cycle of people with a uterus.

SARS-COV-2 infection

In December 2019, the first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were recorded in Wuhan, China, later being officialized by the World Health Organization (WHO) as Coronavirus Disease-2019 (COVID-19). This syndrome quickly acquired a pandemic character, reaffirming its high potential for dissemination and mobilizing the scientific community to understand its viral mechanisms, clinical manifestations and possible treatments. [15,16] As of February 19, 2023, more than 757 million confirmed cases and more than 6.8 million deaths have been reported globally [17].

SARS-CoV-2 belongs to the coronaviridae family, a family of RNA viruses single-stranded, non-segmented and enveloped, which has four subdivisions, this virus being classified as beta-coronavirus (B-CoV). This presents fundamental structural proteins for its infection potential, the main one being the spike protein that facilitates the infection of the virus in human cells, as it is capable of binding to the angiotensin-2 converting enzyme (ACE2) receptor, allowing passage of viral material to the host cell with consequent entry of viral RNA into the nucleus for replication and synthesis of viral proteins.

Transmission of the virus occurs mainly through contact with the infected person and inhalation of respiratory droplets generated when the person coughs, sneezes, or through droplets of saliva or nasal secretion, aerosol, fomites or personal objects with subsequent contact with mucous membranes [18,19].

The infection begins in the respiratory system due to the highest concentration of ACE2 receptors, and then is transmitted hematogenously to other systems. SARS-CoV-2 entry is highly dependent on the expression of ACE2 and the transmembrane receptor serine protease subtype-2 (TMPRSS2) on the cell surface. [20] Therefore, both ACE2 and TMPRSS2 are necessary for viral infection [21].

Despite being a predominantly respiratory disease, COVID-19 causes damage to several organs, including vascular complications, normally associated with a poor prognosis. [22,23] These vascular lesions are due to extensive endothelial dysfunction. [24] Intermediated by inflammatory cytokines and thrombogenic factors, causing disseminated microvascular lesions. [25] In this context, these vascular lesions have been strongly associated with systemic changes present in patients after SARS-COV-2 infection, since after infection the individual can suffer a series of hematological changes regardless of the stage of the disease.

Some authors mention that the pathophysiological mechanism involved in injuries caused by SARS-CoV-2 is due to direct cellular injury, due to viral toxicity. Cellular endothelial damage and thromboinflammation occurs due to excessive production of thrombin, inhibition of fibrinolysis and activation of the complement system, which initiates thromboinflammation, leads to the deposition of microthrombi and microvascular dysfunction. Dysregulation of the immune response, commonly associated with severe conditions when linked to cytokine release syndrome, and dysregulation of the renin-angiotensin-aldosterone system (RAAS), caused by the involvement of the ACE2 receptor in the cellular infection process, affects the hydroelectrolyte balance, regulation of blood pressure, vascular permeability and tissue growth [26].

SARS-CoV-2 infection is very variable and can be asymptomatic or present with different symptoms ranging from mild, moderate and

severe, with a high risk of sepsis and death. [27] Having an incubation period that varies from 1 to 14 days [28].

The infection begins in the respiratory system after contagion through contact with contaminated droplets, and is subsequently disseminated to other systems by hematogenously route, generating extra pulmonary manifestations: neurological (headache, anosmia and ageusia), renal (acute renal failure, proteinuria and hematuria), hepatic (increase in aminotransferases and bilirubin), gastrointestinal (diarrhea, nausea, vomiting, abdominal pain and anorexia), vascular (deep vein thrombosis and pulmonary thromboembolism), cardiac (arrhythmias and myocardial ischemia), dermatological (urticaria, petechiae and rash erythematous) and endocrine, which are associated with an increase in cytokines that harm pancreatic beta cells, generating apoptosis, which decreases insulin production and generates ketosis, predisposing to insulin deficiency and hyperglycemia [29,30].

The increase in the inflammatory response, resulting from cellular damage caused by SARS-CoV-2, triggers an oxidative process and the release of cytokines (cytokine storm), stimulating a pro-coagulant process. [31] In this way, the tissue factor is expressed, producing thrombin, and together with fibrinogen, the fibrin clot is formed [32].

Furthermore, COVID-19 causes abnormal activation of the RAAS, which explains vasoconstriction and decreased blood flow, increasing the expression of von Willebrand Factor and which, together with pro-inflammatory cytokines, triggers clot formation. Decreasing fibrinolytic activity and the endogenous anticoagulant pathway.

ACE 2 has a fundamental role in the ovary, promoting the secretion of steroids. [33] Helps with follicular development and oocyte growth, influences ovulation, and maintains the function of the corpus luteum [34,35].

In view of this, the importance of ACE 2 in the female hormonal cycle is clear, as its action is extremely important for the secretion and maturation of steroids, especially estrogen.

Due to the involvement of ACE2 in SARS-CoV-2 infection, due to a high expression of its surface receptors, it is necessary to correlate the effects of this involvement with the changes caused in the female hormonal cycle.

Menstrual changes after SARS-COV-2 Infections

The menstrual cycle involves complex interactions between various tissues, hormones and systems of the human body, such as the immune, vascular and blood systems, and these interactions can influence both menstrual bleeding and the severity of symptoms associated with menstruation. The menstrual cycle is highly sensitive to systemic changes; however, it can be easily modified in the presence of viral infections.

Viral infections can affect the female reproductive system and cause menstrual disorders, as has already been demonstrated in the case of hepatitis B, hepatitis C and HIV viruses. [36] Anovulation has been recorded in serious illnesses, probably related to the transient suppression of ovarian function to ensure the function of vital organs.

SARS-CoV-2 infection can affect the hypothalamic-pituitary-ovarian-endometrial axis with resulting changes in the menstrual cycle. Hypothalamic hypogonadism can occur in the presence of any serious illness, including COVID-19, and result in temporary amenorrhea or infrequent menstruation [37].

When exposed to stress, ovarian function is often suppressed to ensure the normal functioning of other organ systems that are essential for life, and amenorrhea has also been previously reported in acute illnesses. This finding corroborates the presence of menstrual changes in patients with involvement of multiple organ systems, which has been clinically observed in several studies [38].

In the presence of systemic stress, the adrenal glands secrete glucocorticoids, such as cortisol, which reduce the release of LH in the production of pituitary and sexual hormones in the gonads. [39] Some studies have linked this change to the absence of menstruation, swollen and painful breasts, increased appetite, irritability, sadness and anxiety. [40] Furthermore, the COVID-19 pandemic has increased the prevalence of sleep disorders, caused changes in habits related to physical exercise, and mental health has been negatively affected. [41] Contributing factors to menstrual dysregulation.

With the emergence of these abnormalities in the menstrual cycle, a new problem is raised with regard to female fertility, as a change in the duration of the menstrual period, frequency, regularity and volume (more intense bleeding and with clots), an increase in dysmenorrhea, and worsening of premenstrual tension. In the study by Herme-negildo it states that there was a change in the volume and duration of bleeding during the menstrual period.

Li *et al.* analyzed sex hormone levels and menstrual patterns in a cross-sectional study that included women of reproductive age hospitalized due to COVID-19. Patients who had menstrual changes during COVID-19 infection were more likely to have decreased menstrual volume and longer cycles (8 to 14 days) [42].

In this context, abnormal uterine bleeding is correlated with endothelial changes triggered by the inflammatory process and the formation of fibrinogenic factors, which can manifest with involuntary bleeding or the formation of thrombi. Furthermore, some studies have associated SARS-COV-2 infection with hematological changes in the blood count, such as thrombocytopenia, however, it is associated with the severity of the disease and a more considerable drop in the platelet count was observed [43,44].

Furthermore, female health has been widely affected directly or indirectly, since the pathophysiology of SARS-COV-2 infection causes systemic stress affecting the hypothalamic-pituitary-gonad and hypothalamic-pituitary-adrenal axes, being responsible for changes in the menstrual cycle, which will consequently affect psychosocial factors and premenstrual tension.

This premenstrual tension negatively affects women’s daily lives, as it is associated with a series of mood disorders, which increase the intensity of the cycle, associating it with pain, anxiety and depression. Furthermore, changes in the cycle favor greater patient insecurity regarding health conditions, since the increase in these cycles can arouse patients’ curiosity regarding the presence of diseases of greater magnitude, which can manifest themselves in the same way as the infection. Associated with this, menstrual delay can be associated by women as a possible ongoing pregnancy, which can further exacerbate psychological symptoms, and lead to unnecessary expenses, such as the use of emergency pills or rapid pregnancy tests.

Another important point is the increased use of daily pads, due to the increased intensity and flow of menstrual bleeding, leading to greater financial expenses as a result. [45] Therefore, the range of impacts to which women are exposed after infection with SARS-COV-2 is visible.

Female findings resulting from SARS-COV-2 Infection

When analyzing studies carried out around the world, several changes in the menstrual cycle related to COVID-19 were observed, which may be linked to frequency, duration, regularity or volume, as illustrated in Figure 1, developed based on Sharp (2022).

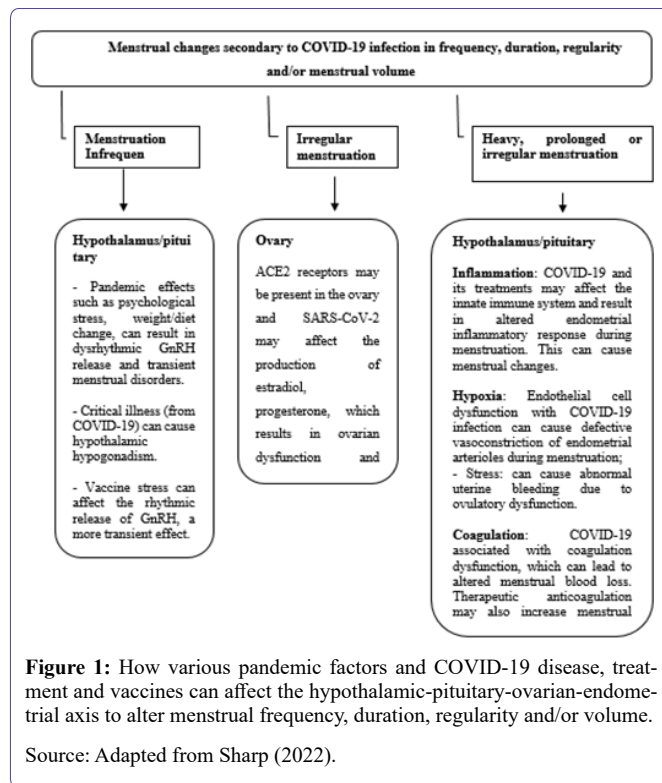


Figure 1: How various pandemic factors and COVID-19 disease, treatment and vaccines can affect the hypothalamic-pituitary-ovarian-endometrial axis to alter menstrual frequency, duration, regularity and/or volume.

Studies Takmaz *et al.*, which analyzed 127 women, aged 18-40 with regular periods for more than 1 year before the pandemic, menstrual cycle irregularities were observed in 28.7% of women, 10.7% had shorter menstrual cycles or long and 12.9% had the duration of menstruation altered by more than 9 days. In that same study, it was observed that women who suffered from menstrual irregularity had significantly higher levels of depression, anxiety and stress [46].

Malloy and Bradley analyzed 12,302 women regarding aspects associated with menstruation after the period of COVID-19 infection, where an imbalance in the hormonal cycle pattern was observed in 87% of women, 29% presented more symptoms during menstruation, mainly changes in volume and abdominal pain, 27% of the women analyzed showed increased uterine bleeding. A higher level of stress has been found in women with menstrual disorders [47].

Bruinvels *et al.* analyzed 749 women over 18 years of age, which resulted in an increase in cycle length in 25% of women, 20% of these showed a decrease in cycle length, more than 50% had menstrual symptoms related to issues psychosocial: mood changes, decreased focus and lack of motivation and 17% felt stressed about their menstrual cycle changes [48].

Conclusion

In summary, it is concluded that SARS-CoV-2 infection may have influenced the hormonal, vascular and menstrual changes found. Virus infection depends on the expression of ACE 2 in the lung, which

has an extremely important action for the secretion and maturation of steroids, especially estrogen.

COVID-19 infection triggers systemic stress affecting the hypothalamic-pituitary-gonad and hypothalamic-pituitary-adrenal axes, which are responsible for ovarian suppression and systemic inflammation with consequent endometrial vascular changes. This change results in a change in the average period of menstruation, the volume of the flow, the duration of the menstrual cycle and the appearance of menstrual discomforts, which have been analyzed in several studies.

There are several studies from different areas on the phenomena involved with COVID-19 infection and its subsequent changes in the menstrual cycle. The correct association between the impacts on the hormonal cycle and the effects resulting from the infection require studies designed specifically for the topic.

More research is needed to establish a correct association between these, as it is extremely important for health professionals to have assertive knowledge of these correlated changes. More than three years after the start of the pandemic, studies carried out and published to date provide several important findings, but which still do not provide a sufficiently robust basis for the medical and scientific communities to reach definitive conclusions on the topic.

In view of this, it is important to highlight the scarcity of studies that bring such comparisons in the literature, as this approach is still considered a recent topic. Therefore, new research that addresses this topic is important.

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