

# COVID-19 as a multidisciplinary problem: impact on reproductive health (Literature review)

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COVID-19 is an infectious disease which is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). According to the WHO, on March 11, 2020, COVID-19 was declared a global pandemic. Undoubtedly, no one will deny that infectious pathology occupied and is occupying a significant place among all diseases of different age groups. The ongoing pandemic of coronavirus infection is a vivid proof of this.

There is probably no such person in the world who would never “has his own little war” with infectious pathogens. Therefore, the disease is constantly looking for means that would give it an advantage in the fight against pathogens. Research in recent years indicates that COVID-19 affects not only the respiratory, circulatory and nervous systems, but also the reproductive system, in particular the female one.

The article is devoted to a review of scientific publications that describe the impact of COVID-19 on women's reproductive health. The COVID-19 pandemic has sparked debate in the scientific community focusing on the risk of menstrual changes in women with COVID-19, such as disorders in the duration, frequency, regularity, and volume of menstruation (including increased bleeding and clotting), increased severity of dysmenorrhea, and premenstrual syndrome. However, there is not enough data or information about the impact of COVID-19 on reproductive health.

The problem of remote potential negative impact of the COVID-19 pandemic on women's reproductive health is becoming more and more relevant in the practice of gynecologists. It is important to emphasize the need for high-quality work of gynecologists, which includes early diagnosis of reproductive disorders, adequate diagnosis and treatment in order to prevent complications in case of ovarian-menstrual cycle disorders, infertility and miscarriage.

Unfortunately, to date there are no unambiguous data on the impact of SARS-CoV-2 on the reproductive system. Therefore, further research into the long-term consequences of the transferred coronavirus infection in women of reproductive age is critically important.

**Keywords:** coronavirus infection, COVID-19, pandemic, reproductive health.

## COVID-19 як мультидисциплінарна проблема: вплив на репродуктивне здоров'я (Огляд літератури)

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COVID-19 – це інфекційна хвороба, що спричинена тяжким гострим респіраторним синдромом коронавірусу-2 (SARS-CoV-2). Згідно з даними ВООЗ, 11 березня 2020 р. COVID-19 було оголошено глобальною пандемією. Однозначно, ніхто не заперечить, що інфекційна патологія посідала та посідає значне місце серед усіх захворювань різних вікових груп. Триваюча пандемія коронавірусної інфекції є яскравим доказом цього.

Напевно немає у світі такої людини, яка б жодного разу не «вела власну маленьку війну» з інфекційними збудниками. Тому людство постійно шукає засоби, які б надали йому перевагу у боротьбі зі збудниками. Дослідження останніх років свідчать про те, що COVID-19 впливає не тільки на дихальну, кровоносну та нервову системи, але й на репродуктивну, зокрема жіночу.

Стаття присвячена огляду наукових публікацій, які описують вплив COVID-19 на репродуктивне здоров'я жінок. Пандемія COVID-19 викликала дискусії у науковому співтоваристві, у яких звертається увага на ризик менструальних змін у жінок із COVID-19, таких, як порушення тривалості, частоти, регулярності та обсягу менструацій (включаючи посилення кровотечі та згортання крові), збільшення вираженості дисменореї та передменструального синдрому. Проте даних чи інформації про вплив COVID-19 на репродуктивне здоров'я недостатньо.

Дедалі все більшої актуальності у практиці гінекологів набуває проблема віддаленого потенційного негативного впливу пандемії COVID-19 на репродуктивне здоров'я жінок. Важливо акцентувати увагу на необхідності якісної роботи гінекологів, що включає раннє виявлення репродуктивних порушень, адекватну діагностику та лікування з метою попередження ускладнень у випадку порушення оваріально-менструального циклу, безпліддя та невиношування вагітності.

На жаль, до сьогодні немає однозначних даних щодо впливу SARS-CoV-2 на репродуктивну систему. Тому подальше дослідження віддалених наслідків перенесеної коронавірусної інфекції у жінок репродуктивного віку є критично важливим.

**Ключові слова:** коронавірусна інфекція, COVID-19, пандемія, репродуктивне здоров'я.

The coronavirus infection is not completely new to us. Back in 1965, M. Binoy and D. Tyrell isolated a virus of a previously unknown form from a volunteer who was infected with nasal secretions from a patient with acute rhinitis. In 1968, a new family was recognized - Coronaviridae. In 1975, the corona virus was also detected in the stools of children suffering from gastroenteritis. This family of viruses did not have unique pathogenicity factors, did not cause serious diseases, therefore did not arouse significant interest among scientists. And only in 2002–2003, the corona virus infection reminded itself again. Over the past 50 years, we have made significant progress in the fight against infectious diseases.

Coronavirus disease (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2). According to the World Health Organization (WHO), on March 11, 2020, COVID-19 was declared a global pandemic [1–4]. As of 16 December 2020, there were 7,2196,732 confirmed cases and 1,630,521 deaths worldwide. In December 2022, more than 5 million cases of the disease caused by SARS-CoV-2 became known in Ukraine [4, 5]. The emergence of the disease COVID-19 has radically changed economic activity and social relations around the world [4].

Research in recent years indicates that COVID-19 has an impact not only on the respiratory, circulatory and nervous systems, but also on the reproductive, in particular female, systems. In the initial stage of infection with COVID-19, most patients have a low or normal white blood cell count, a low lymphocyte count, an elevated C-reactive protein level, a normal procalcitonin level, and positive imaging findings. Also, patients who were seriously ill from COVID-19 had an increase in pro-inflammatory cytokines such as Tumor necrosis factor-alpha (TNF- $\alpha$ ), Interferon-gamma (IFN- $\gamma$ /IFNG) and Interleukin-6 (IL-6). Some patients also had signs of a cytokine storm [6].

Autopsy of the first patient who died of COVID-19 showed diffuse alveolar damage and pleural effusion [6, 7] consistent with acute respiratory distress syndrome and similar pathological features to SARS and Middle East Respiratory Syndrome. More and more data and information about histopathological changes in various organs, especially in the lungs, have been found [6].

The COVID-19 pandemic has sparked discussions in the scientific community that indicate the possibility of menstrual changes in women with COVID-19, such as changes in the duration, frequency, regularity, and volume of menstruation (including increased bleeding and clotting), worsening of dysmenorrhea, and premenstrual syndrome (PMS) [2, 3, 8]. However, there is not enough data or information about the impact of COVID-19 on reproductive health.

The purpose of this analysis is to investigate the potential impact of the COVID-19 pandemic on women's reproductive health.

Google databases were used for the retrospective analysis of the literature Scholar, PubMed and Scopus, Web of Science, CrossRef, Medline. When searching for information on the prevalence and prevention of reproductive dysfunction in women with coronavirus infection, various combinations of the following keywords were used: «CO-

VID-19», «pandemic», «reproductive health», «menstrual cycle», «hormones». Based on the search results, the most recent publications (for the last 5 years) or the latest publications on this issue (regardless of the date of publication) were processed. After reviewing the abstracts and reading the full text of the articles, 50 sources were selected. The article provides a review and analysis of articles on the researched problem.

Some scientific studies document the effects of COVID-19 on human health and quality of life, including sexual and reproductive health. Reproduction is not only an innate biological function to create new individuals, but also has social and physical aspects. To achieve adequate physical, mental and social health, a high-quality sex life with frequent and safe sex is necessary [4, 9].

Administrative measures that were necessary to slow the spread of the disease, such as self-isolation and restrictions on exercise and travel, post-covid syndrome, negatively affected psychological health, but the long-term consequences are unknown [3, 9].

Couples who intend to use assisted reproductive technologies (ART) also face their own unique challenges. They are in a difficult situation because they already suffer from infertility and often have concerns about their fate [4, 10]. The COVID-19 pandemic has led to the temporary closure of many fertilities' treatment centers, putting great pressure on couples for whom age was a critical factor [4, 11].

COVID-19 has been shown to spread from person to person via the airborne route, especially when people are within two meters of each other. Infection can also occur if you touch an infected surface and then touch your mouth, nose, or eyes [12, 13].

Also, clinical studies have proven the possibility of other ways of infection, such as contact with blood, feces or semen of infected persons.

Sexual transmission is a major concern for couples planning to become pregnant, as well as for pregnant women. Interestingly, several studies confirm a high rate of infection among sexual partners of women who have COVID-19, suggesting the possibility of sexual transmission [12, 14]. To confirm this, we cite the fact that the COVID-19 virus was detected in saliva, feces, and semen samples of infected individuals. The highest amount of virus was found in saliva, and this may indicate the possibility of transmission of the virus through saliva during physical contact between couples [12, 15]. Reproductive risks associated with COVID-19 require careful identification of biological and behavioral factors. Previous studies with other viral diseases, such as the Zika virus, Ebola fever, hepatitis B and C, as well as human immunodeficiency virus, have shown the possibility of sexual transmission of the disease through the sperm of infected individuals during sexual intercourse [4, 17]. Studies of semen samples from infected men have tested positive for SARS-CoV-2. However, there is currently insufficient evidence that the virus can be transmitted through semen during vaginal or anal intercourse [12, 18].

Regarding the transmission of the virus through breast milk, some studies [12, 19, 20] claim that one in three samples of it obtained from infected pregnant women in the third trimester of pregnancy tested positive for COVID-19.

This indicates the possibility of transmission of the virus through breast milk. However, even if there is no virus in the milk, transmission can occur through close contact between mother and newborn during breastfeeding, so this must be taken into account. It should also be noted that transplacental transmission of SARS-CoV-2 infection is possible during the last weeks of pregnancy, which can cause inflammation of the placenta, neonatal viremia and neurological symptoms due to cerebral vasculitis [4, 21].

The WHO has proposed tactics to limit the spread of COVID-19, including personal preventive measures (environmental cleaning/disinfection, hand/respiratory hygiene, face covering, and cough etiquette) and social preventive measures such as physical/social isolation and staying at home. In this regard, sexual contact, especially between those who do not live together, is discouraged as it may contribute to the spread of COVID-19 [4, 22].

Sexual behavior is a term that encompasses a wide range of biological functions and psychological actions due to multiple causes related to physical and social factors. In fact, a successful sex life and good reproductive health depend on the integration of many events, including physical, mental, emotional and social. A major public health crisis such as the COVID-19 pandemic was expected to significantly affect sexual behavior at both biological and psychological levels. To a large extent, this concerned the impact of stress on women's sexual desire and the frequency of sexual acts.

The survey showed that during the COVID-19 pandemic, there was a significant decrease in the quality of sex life, the desire to get pregnant and give birth to a child, women's access to contraception, as well as an increase in menstrual disorders. As a result of quarantine and social distancing, people may experience depression, irritability, low mood, fear, guilt and nervousness. These factors can lead to decreased sexual desire, as depression and anxiety are often associated with decreased interest in intimate relationships [4, 23].

Fear of infection through physical contact between partners also negatively affects the quality of sexual life and sexual desire. All these factors threaten the duration and quality of normal intimate relationships in couples, which can have an impact on one of the most important aspects of social life - the family [4, 24, 25].

It is important to consider that the average age of couples trying to conceive is increasing every year, and older women who come to fertility clinics have smaller egg reserves. With such a prolonged COVID-19 pandemic and recommendations to suspend assisted reproduction procedures, many patients were concerned about the possible further decrease in their chances of pregnancy [4, 26].

An aspect that should be considered when prioritizing the use of any ART is the health status of the married couple, as couples with health problems, including hypertension and cardiovascular disease, are at high risk of contracting COVID-19. The available clinical data showed that patients with COVID-19 on the background of hypertensive and ischemic heart disease had an increased risk of developing cardiovascular complications, including arrhythmias, myocarditis, unstable coronary syndrome, venous and arterial thrombosis [4, 27].

The COVID-19 pandemic has different consequences for men and women, not only in the disease but also in the long-term health consequences. The coronavirus disease can be especially dangerous for women who have not yet completed their reproductive function [3, 28, 29].

The severe stress caused by the new infection and the unknown long-term consequences accompanying the pandemic can significantly affect a woman's reproductive function. Violation of the menstrual cycle can lead to anemia, ectopic pregnancy, infertility, benign neoplasms, endometriosis, hair loss, acne, headaches, and also affect the neurological and psychoemotional state [3, 6]. All this has a significant negative impact on the quality of life and is a huge socio-economic burden for women, their families and health.

The main consequences of the direct impact of COVID-19 on the female reproductive system include [3, 30]:

- changes in the frequency of the menstrual cycle, arising due to the impact on the hypothalamic-pituitary system, ovaries;
- change in the volume and severity of bleeding during menstruation, which may be the result of an effect on the thickness of the endometrium.

The expression of angiotensin-converting enzyme 2 (ACE2) receptors in various endocrine glands, such as the testes, ovaries, and pituitary gland, as well as in the pancreas, thyroid gland, and adrenal glands, regulates reproductive functions and affects the higher reproductive centers of the brain. This fact highlights the potential impact of COVID-19 on women's reproductive health [12, 31].

Damage to the hypothalamic-pituitary regulation of the ovarian cycle can be caused both by a severe course of a coronavirus infection (including hypoxia, microangiopathy, hemorrhagic infarction and ischemia), and by the effect of a pandemic (for example, psychological stress and changes in weight) [3, 32]. It is known that periods of psychological stress can affect the menstrual cycle of women. Stressors can activate the hypothalamic-pituitary-gonadal axis and can alter the neuromodulatory cascade that regulates the production of gonadotropin-releasing hormone. This can lead to functional hypothalamic amenorrhea, which is accompanied by chronic anovulation, which has no underlying organic cause [3, 33, 34].

The authors of the study [28] studied menstrual cycle disorders in women and established that the frequency of menstrual cycle disorders was more often observed 2–4 months after the experienced COVID-19 disease, which necessitates a more detailed study of the effect of the virus on the reproductive potential of women of reproductive age. Many researchers studied the state of the menstrual cycle in women during the COVID-19 pandemic and found that almost half of women of various age groups reported a general change in their menstrual cycle: worsening of premenstrual symptoms and lengthening or shortening of the average length of the cycle [3, 9, 33].

There is currently insufficient information on the effects of the COVID-19 virus on ovarian function in women. Many studies on this topic have looked at the relationship between common ovarian dysfunction in women polycystic ovary syndrome (PCOS) and the incidence of severe infections and/or symptoms of COVID-19. Re-

search suggests that PCOS may be responsible for approximately 10–15% of endocrine disorders in women, and about 75% of women with PCOS also face obesity and other health problems such as type 2 diabetes and hypertension, etc [12, 35, 36].

Women with comorbidities associated with ovarian dysfunction should be informed of the increased possible risk of infection with COVID-19. To prevent possible pathological complications, they should be subject to regular medical supervision by specialists. The use of therapy that includes vitamin D may be an effective approach to reduce the severity of COVID-19 symptoms and the risk of infection in women with PCOS. It is known that women with PCOS often have low levels of vitamin D, and prescribing this vitamin may be helpful in regulating the menstrual cycle and follicular development in patients with this syndrome.

In addition, there is some association between vitamin D deficiency and the severity of PCOS symptoms such as infertility, hyperandrogenism, insulin resistance, and cardiometabolic disease. Vitamin D may help strengthen the immune response by regulating IL-6 levels during inflammation, and this may be useful in fighting viral infections, including COVID-19. Although studies on the effect of vitamin D on the course of COVID-19 are not yet conclusive, its use as a preventive measure against COVID-19 in women planning to become pregnant naturally or using ART may be considered [12, 36, 37].

There are also concerns about vertical transmission of COVID-19 from a pregnant mother to her fetus. Questions about the potential risks of this type of transmission, in particular the method/time of transmission (during pregnancy, childbirth and breastfeeding), the impact on the health of pregnant and postpartum women, the fetus and newborn children, remain the subject of research [4, 25, 38].

Therefore, couples who are planning to conceive a child, as well as women who are already pregnant, should exercise caution and avoid potential risks to the health of both the mother and the baby [12, 19].

It has been suggested that COVID-19 may alter the expression of ACE2 in the placenta, leading to a risk of pregnancy-related complications such as placental abruption. These hypotheses require confirmation by the results of published studies in this area.

According to the literature, women infected with COVID-19 are at risk of preterm birth, fetal distress, premature rupture of the amniotic sac, and cesarean delivery [12]. Immunohistochemical analysis of placental tissue confirms the presence of ACE2 in various types of placental cells, such as syncytiotrophoblasts, cytotrophoblasts, endothelium, and vascular smooth muscle. Pathways mediated by ACE2 can influence trophoblast migration, vascular remodeling and maternal vasodilation. Disruption of ACE2-mediated pathways can cause miscarriage, ectopic pregnancy, and preeclampsia [12, 39].

The literature also suggests that the placenta may be susceptible to the effects of COVID-19 through other mechanisms of infection, not just the inflammatory response. Therefore, infection with the COVID-19 virus has a negative effect on the functions of the placenta and intrauterine growth of the fetus [12, 40]. COVID-19 could

change the placental permeability and increase the titer of anti-D antibodies. But it did not contribute to fetal and newborn hemolytic disease [41].

Data from two cross-sectional studies of maternal health risk during pregnancy showed that symptoms associated with COVID-19 infection in early pregnancy were not more severe than in non-pregnant women. However, some infected patients in late pregnancy suffered from severe respiratory symptoms, many of them giving birth after developing these severe symptoms. Adverse health outcomes have also been reported in neonates, however, whether these outcomes are directly related to COVID-19 infection has not yet been investigated [42].

Around the world, various fertility societies such as the European Society of Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM), called for the postponement of most in vitro fertilization (IVF), gamete (egg and sperm) cryopreservation, and fresh/frozen embryo transfer operations in reproductive centers. For those already undergoing fertility treatment, WHO, ESHRE and ASRM have emphasized the importance of strict adherence to all hygiene measures and recommendations to reduce the risk of infection in such patients [43–45].

The global anxiety among scientific/medical associations regarding ART treatment is mainly related to the desire to avoid the spread of COVID-19 or possible complications during various fertility treatments and also during pregnancy. According to the researchers, outbreaks of COVID-19 can occur in fertility treatment centers or among medical personnel not only through human-to-human contact, but also through the handling of samples taken from patients, such as semen, because the virus can be stored in cryopreserved semen samples from patients who were infected with COVID-19 [12].

Elevated levels of reactive oxygen species are considered a possible cause of male infertility. These active molecules can negatively affect sperm motility and sperm deoxyribonucleic acid (DNA) integrity, which can affect their ability to fertilize an egg. Likewise, infection with COVID-19 may affect oocyte maturation through the same oxidative stress pathways. Given these effects, IVF results may be impaired by infection with COVID-19 [12, 46].

Researchers have developed preventive measures and recommendations for maintaining reproductive health in the conditions of the COVID-19 pandemic. The Tokyo Midwives Association conducted a survey of 62 district midwives who provided maternal and child health services in municipalities during the COVID-19 crisis. Some pregnant women have had to change their birth plans because hospitals have restricted visits from family members to avoid infection. The initiative created a smartphone-based cognitive behavioral therapy program for pregnant women and is conducting a randomized controlled trial to evaluate its effectiveness in preventing antenatal and postpartum depression [16].

Also, sexually active couples are encouraged to follow a number of precautions and tips to ensure safe sex during the COVID-19 pandemic, including [12, 47]:

- minimize the number of sexual partners and avoid sex with those who have symptoms of COVID-19;

- avoid sexual practices that involve the risk of faeces entering the mouth or other practices that may cause partners to come into contact with semen or urine;
- use condoms and oral rubber barriers during anal and oral sex;
- consider wearing a mask during sexual activity;
- wash hands and shower before and after sexual activity;
- wash sex toys before and after use and clean the area where sexual activity takes place.

For women in the postpartum period, it is recommended to carefully follow the rules of hygiene, in particular, wash your hands and wear a mask before and during feeding the newborn. Consider formula feeding or start breastfeeding after 14 days of quarantine after recovery and discharge. To avoid direct contact, use a disinfected breast pump for feeding newborns [12].

Patients without children and medical staff in medical centers are recommended in the conditions of the COVID-19 pandemic [12, 47]:

- expand telemedical and psychological support between patients and ART specialists;
- provide priority access to new ART treatments according to urgent need, particularly for women over 40 years of age or with reduced ovarian reserve, and avoid procedures that may be less important;
- avoid treatment of patients with significant susceptibility to infection with COVID-19 due to existing clinical diseases and weakened immunity;
- observe hygiene rules and disinfection recommendations;
- adopt ART protocols that can minimize the need for frequent monitoring;

- minimize social contact between different patients and different professional groups using online health support services.

### CONCLUSIONS

1. The problem of remote potential negative impact of the COVID-19 pandemic on women's reproductive health is becoming more and more relevant in the practice of gynecologists.

2. It is important to emphasize the need for high-quality work of gynecologists, which includes early detection of reproductive disorders, adequate diagnosis and treatment in order to prevent complications in case of ovarian-menstrual cycle disorders, infertility and miscarriage.

3. Unfortunately, until now there are no unambiguous data on the impact of SARS-CoV2 on the reproductive system. Therefore, further research on the long-term consequences of the transferred coronavirus infection in women of reproductive age is critically important.

### Prospects for further research:

1. Development of effective measures to reduce the spread of remote complications of COVID-19.

2. To optimize the follow-up of women with menstrual cycle disorders, identify early manifestations of lesions and improve the primary prevention of complications after COVID-19.

3. Conduct a comprehensive assessment tailored to the patient's fertility needs to provide informed advice and counseling for pregnancy planning after experiencing COVID-19.

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