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Menstrual Disorders after Covid-19 Disease

Usmanova N. Yu.
Republican Research Center for Emergency Medical Care Bukhara branch, Bukhara, Uzbekistan

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ABSTRACT

In 2020, the World Health Organization announced the development of the COVID-19 pandemic, and the International Committee on the Taxonomy of Viruses recorded the name of the infectious agent - severe acute respiratory syndrome coronavirus - 2 (SARS-CoV-2). The main target of SARS-CoV-2 is type II alveolar cells, which determines the development of pneumonia. Many aspects of the pathogenesis of COVID-19 require further study.

Relevance. Although women tolerate COVID-19 more easily than men, the likely consequences of the disease on reproductive health cannot be ignored [6,8,10]. Currently, the issue of the impact of COVID-19 on women's reproductive health has not been sufficiently studied. It is assumed that the pathogen can have a direct effect on the menstrual and reproductive functions of women by affecting the receptors of angiotensin converting enzyme 2, which is widely expressed in the ovaries and uterus. Specific interactions between the reproductive system and SARS-CoV-2 infection are believed to occur at the ovarian/endometrial level. Pronounced vasoconstriction of the spiral arterioles of the endometrium and activation of the coagulation system form pathological menstrual blood loss. COVID-19 induces endothelial cell dysfunction with changes in the blood coagulation system, which are critical components of endometrial function during menstruation, suggesting a potential endometrial mechanism for menstrual irregularity [1,3,7].

SARS-CoV-2 infection can affect the hypothalamus-pituitary-ovary-endometrium axis, leading to changes in the menstrual cycle [2,5]. There is a reciprocal connection between the hypothalamic-pituitary-adrenal axis, which provides the formation of a response to stress, and the hypothalamic-pituitary-ovarian axis, in which activation of one axis leads to suppression of the other [4,9]. Chronic stress suppresses estrogen production, which contributes to menstrual irregularities and anovulatory cycles. Stress-related menstrual disorders represent a spectrum of disorders including secondary amenorrhea (absence of menstruation for 3 months or more in the presence of a previous regular menstrual cycle) and a more rare form - primary stress-induced amenorrhea, therefore, it is necessary to evaluate the potential impact of COVID-19 on organs reproductive system.

The purpose of the study: to study the impact of coronavirus infection COVID-19 on the menstrual function of women of reproductive age.

Material and research methods. This study presents the results of a survey of 60 women of reproductive age. The patients were divided into 2 groups. The main group included 50 women who had COVID-19 and had menstrual irregularities that arose after the illness. The main group consisted of 2 subgroups: a subgroup of those with mild COVID-19 (n=30) and a subgroup of those with severe COVID-19 (n=20). The control group included 10 women who did not have COVID-19 and did not have menstrual irregularities.The severity of COVID-19 was assessed according to the classification presented in the clinical guidelines of the Ministry of Health of Uzbekistan for the prevention, diagnosis and treatment of COVID-19.

Inclusion criteria: age of women from 21 to 35 years; previous SARS-CoV-2 infection; irregular menstrual cycle for 3-6 months. after an illness; regular ovulatory menstrual cycle prior to a history of COVID-19; lack of hormonal disorders; absence of extragenital pathology before COVID-19 disease; signed informed consent.

Exclusion criteria: menstrual dysfunction prior to COVID-19 disease, a history of chronic somatic pathology.

A comprehensive examination of all patients included an assessment of the level of hormones in the blood, ultrasound and Doppler examination of the pelvic organs with an assessment of the hemodynamics of the endometrium and ovaries, and the determination of indicators of the hemostasis system.

In patients from the control group, blood samples were taken to determine hormone levels from the 3rd to the 7th day of the menstrual cycle; in patients from the main group, blood samples were taken without taking into account the phase of the menstrual cycle, since the menstrual cycle was disrupted from delay to amenorrhea .

The studies were performed on a Doppler ultrasonic device Toshiba Aplio using a multifrequency (3.5–5 MHz) transabdominal probe. Ultrasound examination was carried out in a horizontal position. Hemodynamic parameters were determined in the spiral and basal vessels of the endometrium, as well as in the ovarian artery on both sides. Hemodynamics was assessed by the level of systolic blood flow (Vmax), diastolic blood flow (Vmin), systolic-diastolic ratio (S/D), as well as by indicators of peripheral circulation: resistance index (RI) and pulsation index (PI).

Statistical analysis of the results of the study was carried out using the Statistica software package. To assess the differences between two independent samples, parametric methods were used with a normal distribution of indicators and non-parametric methods (Mann-Whitney test) with a distribution other than normal. Differences were considered significant at $p<0.05$.

Results and discussion. The average age of patients in both groups was 28.5±1.28 years. Women did not have bad habits that would have a negative impact on ovarian function. In the control group, 7 (70%) women had a history of childbirth, in the main group - in 18 (40%). All patients from the main group noted menstrual irregularities after undergoing COVID-19: the cycle was irregular, with a tendency to delay the next menstruation from several days to several weeks. The duration of the menstrual cycle in the control group was 28.3±1.21 days, and in the main group it was 53.1±0.84 days, i.e. 1.9 times longer ($p<0.05$). There was a trend towards a longer menstrual cycle in patients with severe COVID-19. If after mild COVID-19 the duration of the menstrual cycle reached 43.4±0.51 days, then after severe COVID-19 it was 57.3±1.25 days. In patients of the control group, the number of ovulatory cycles reached 100%. In patients with mild COVID-19, the proportion of anovulatory cycles was 25.8%, and in patients with severe COVID-19, it was 77.8%. Menstrual discharge had pathological signs - there was a tendency to oligomenorrhea, in 92% of cases there were spotting spotting.

The secretion of follicle-stimulating hormone (FSH) is known to actively increase at the

beginning of the follicular phase of the menstrual cycle, so that the values of the basal secretion of the hormone are several times higher than those in the luteal phase of the cycle. FSH stimulates the proliferation of granulosa cells and promotes the transformation of the stromal tissue surrounding the follicle into a layer of theca cells, thus regulating the differentiation and organization of the steroid-producing tissues of the follicle. Adequate development of the follicle and the implementation of its steroidogenic activity are necessary prerequisites for the implementation of ovulation. In the control group, the concentration of FSH at the level of increasing estradiol was 5 IU / l. The level of FSH in patients of the main group was higher against the background of a decrease in estradiol.

During a normal ovulatory cycle, the frequency and amplitude of luteinizing hormone (LH) impulses change according to the phase of the menstrual cycle. In terms close to ovulation, peak values of LH and FSH are recorded - synchronized in time, but with varying degrees of increase in concentration. In the main group, the LH indicator had a stable level, which did not change depending on the phase of the menstrual cycle, did not depend on the severity of the COVID-19. In the control group, the LH level was 6.75 IU/l.

As a result of the comparison of hormone levels between the subgroups of the main group, a greater severity of disorders was noted in patients from the subgroup of the severe course of the transferred COVID-19, however, there were no significant differences in the level of LH. Comparison of hormonal levels in patients is presented in Table 1.

Comparative levels of hormones			
References	Control group	Main group	
		Mild COVID-19	Severe COVID-19
FSH, IU/L	5,0	17,65	23,6
LG/ IU/L	6,75	12,8	12,8
FSG/LG	1,6	2,05	2,8
Estradiol, pg/ml	58,05	23,15	24,4
Progesteron, nmol/l	12,1	12,45	11,85

Dynamic monitoring of ovarian function was carried out: there was no direct dependence of the level of anti-Mullerian hormone on the severity of COVID-19, however, the absence of dynamic changes in the follicular apparatus during ultrasound monitoring, low progesterone levels in the expected second phase of the cycle indicated the formation of an anovulatory cycle. In the main group of patients with severe COVID-19, the maximum size of the dominant follicle in the ovary was 14.00 ± 0.38 mm, in the group with a mild course of the disease - 16.0 ± 0.16 mm. In patients from the control group, the dominant follicle reached 21.8 ± 0.34 mm, which is 1.3 times more than in patients of the main group with a mild course, and 1.5 times more than in patients with a severe course of COVID-19. 19 ($p<0.05$).

As noted above, one of the complications of COVID-19 is the development of coagulopathy with the occurrence of thrombosis in large and small vessels (not only in the lungs, but also in the heart, brain, kidneys, liver) and the risk of DIC. Thrombosis at various levels, including in the microvasculature, leads to damage to many organs and the development of multiple organ failure. In patients in the control group, there were no abnormalities, while in the main group, all patients had coagulopathy, the severity of which depended on the severity of the disease. Comparative analysis of hemostasis parameters in the main group (subgroup with a severe course versus a subgroup with a mild course of COVID-19) at the time of the study showed that patients with a severe course of COVID-19 were statistically significantly ($p<0.05$) higher than patients with mild COVID-19, the following indicators: the level of D-dimer (2.30±0.16 µg/ml versus 1.30±0.16 µg/l, respectively), the level of fibrinogen degradation products (7.30±0 .16

µg/l vs. 6.20±0.34 µg/l, respectively), prothrombin time (14.7±0.72 s vs. 13.6±0.32 s, respectively). An increase in the level of D-dimer, fibrinogen, prothrombin time indicated a severe course of COVID-19 and confirmed the high likelihood of developing systemic thrombosis, as well as circulatory disorders in the pelvic organs of women. Dopplerometry of the basal and spiral arteries of the endometrium revealed hemodynamic disturbances in patients from the main group. An analysis of the state of blood flow in the endometrium showed that in patients from the main group, hemodynamic parameters were significantly higher than in the control group, and in the main group, these indicators changed depending on the severity of COVID-19. Noteworthy is the rate of systolic blood flow, which significantly decreased depending on the severity of the course of the disease, and the indicators of peripheral blood flow were significantly higher.

With dynamic ultrasound monitoring, the thickness of the endometrium in patients from the control group was 10.64 mm. Patients from the main group showed a decrease in endometrial thickness to 3.20 mm in the subgroup of severe COVID-19 and to 6.31 mm in the subgroup of mild COVID-19 ($p<0.05$). A study of hemodynamics in the ovarian arteries was carried out both in the control group and in the main group with past COVID-19. The rate of systolic blood flow in the ovarian artery also significantly decreased with a more severe course of COVID-19, while diastolic blood flow tended to increase. The indicators of peripheral blood flow in patients who underwent severe COVID-19 increased.

All hemodynamic parameters in the ovarian artery in patients of the main group significantly differed from those in the control group, there was a dependence on the severity of the disease.

Conclusion. When analyzing the parameters of the hormonal background, the state of hemostasis, hemodynamic parameters in the pelvic organs of women in the reproductive period who underwent COVID-19, menstrual irregularities were revealed. The multifactorial impact of coronavirus infection on the organs of the reproductive system dictates the need for an in-depth study to better understand the impact of SARS-CoV-2 infection on women's menstrual function. Timely diagnosis of pathological conditions of women's reproductive health after suffering COVID-19 will make it possible to identify new preventive and therapeutic strategies to restore women's reproductive health.

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