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Symptoms and Duration of the Menstrual Cycle and Vaccination against Coronavirus Disease (COVID-19)

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The purpose of the study was to determine the association of COVID-19 vaccination with changes in cycle or duration of menstruation during menstrual cycles while receiving vaccine doses.

Materials and methods. The study included 200 women aged from 20 to 38 who had at least three cycles after pregnancy or after using hormonal contraception. The women were vaccinated with Pfizer-BioNTech (Pfizer) and CoronaVac (Sinovac) (Sinovac Biotech) vaccines. The distribution of women by age is as follows: 20–24, 25–29, 30–34, 35–38 years. Additional characteristics included parity (nulliparous versus parous), body mass index, which was classified as underweight or normal weight, overweight or obese; education and relationship status (sustainable relationship or not).

Results and discussion. Of 200 women included in the study, 110 (55.0%) patients were vaccinated, 90 (45.0%) were unvaccinated. Average age of vaccinated was 31.6 ± 2.88 years, unvaccinated -29.3 ± 3.05 years (t = 0.55, p = 0.584). Among 110 vaccinated women, 73.6% had regular menstrual cycles before the introduction of the vaccine during the last year, among 90 unvaccinated women, 74.4% of women had regular menstrual cycles. Menstrual irregularities among those who were vaccinated and those who did not undergo COVID-19 were 11.8% and 14.5%, respectively. Symptoms appeared within a week in 27.6%. In 62.1% of cases, symptoms appeared after the first dose, in 37.9% of cases – after the second dose. There was a significant difference between menstrual irregularities during the COVID-19 pandemic and menstrual irregularities after vaccination (p < 0.001).

The study showed that 26.4% of our sample complained of menstrual irregularities after vaccination against COVID-19, especially after the first dose (16.4%). The type of vaccine did not affect the frequency of menstrual disorders in these women. After vaccination, women reported significantly longer average duration of menstruation and duration of the menstrual cycle compared to their condition before vaccination. These symptoms decreased a month after vaccination. Although 27.6% had a clinically noticeable change in cycle duration by 7-8 days, this change rapidly weakened during two post-vaccination cycles. We found no significant changes in the duration of menstruation between vaccination doses. *Conclusion.* Among women who received vaccines against COVID-19, 26.4% of cases had menstrual irregularities. When counseling women who have received a COVID-19 vaccine, it is advisable to inform them of the possible occurrence of temporary and self-limiting menstrual irregularities in the following months.

Keywords: reproductive age, menstrual cycle, symptoms, COVID-19, vaccination.

Introduction. Menstrual cycles are a clear sign of health and reproduction. Menstrual characteristics are not static, and they change from month to month throughout life. The International Federation of Gynecology and Obstetrics classifies a change in cycle length as normal if it is less than 8 days. Women who regularly menstruate may also experience sporadic or stress-induced ovulation disorders, which can lead to skipping a cycle or a temporary change in the duration of the cycle. This normal variability can be perceived as alarming, especially in connection with new exposure, such as vaccination against COVID-19. By mid-2021, three billion doses were administered worldwide [1]. This rapid use of vaccines worldwide has prompted the Centers for Disease Control and Prevention to use a real-time vaccine side effect reporting system called V-Safe to track potential vaccine side effects [2]. A number of studies have reported various vaccine-related side effects, ranging from mild symptoms such as fever, chills, headache, fatigue, and arm pain, to severe side effects such as thrombosis and anaphylaxis [3-6]. In addition, a recent study reported several menstrual irregularities after vaccination against COVID-19, including increased cycle duration, pain and bleeding [7].

Concerns about a possible link between vaccination against coronavirus disease 2019 (COVID-19) and abnormal menstrual cycles may lead to distrust of vaccination. However, clinical trials of modern vaccines against COVID-19 did not collect information about the outcomes of the menstrual cycle after vaccination [8-10]. The Vaccine Side Effect Reporting System (VAERS) does not actively collect information about menstrual cycles, and by May 2021, only a small number of people (less than 200) reported menstrual cycle-related problems to VAERS [11]. Social media posts suggest that menstrual irregularities are much more common, but these irregularities seem temporary. The lack of promising data on the relationship between vaccination against COVID-19 and menstrual cycles at the population level limits our ability to adequately address these problems and advise people who have menstruation about what to expect from vaccination.

The purpose of the study was to determine the relationship of vaccination against COVID-19 with changes in the cycle or duration of menstruation during menstrual cycles when receiving doses of the vaccine.

Materials and methods. We analyzed the data on the menstrual cycle, which were collected prospectively. The cycle data varied from October 2020

Table 4

to October 2021, with initial doses of the COVID-19 vaccine administered between December 2020 and July 2021. The study was conducted in Clinical Hospital No. 3, which is the clinical base of the Department of Obstetrics and Gynecology of the A. Aliyev Azerbaijan State Institute of Advanced Medical Training. The study included 200 women aged from 20 to 38 years who had at least three cycles after pregnancy or after using hormonal contraception. The included women had a normal duration of the menstrual cycle before vaccination (on average 24-38 days). For those who received the COVID-19 vaccine, we included three cycles before vaccination and three cycles after the first vaccine, including the vaccination cycle. For the unvaccinated, six consecutive cycles were included. Sinovac women were vaccinated with the following types of vaccines: Pfizer-BioNTech (Pfizer, USA) and CoronaVac (Sinovac) (Sinovac Biotech. China). All study participants signed a written consent to participate in the study. When conducting the study, we were guided by the principles of the Helsinki Declaration.

The distribution of women by age was as follows: 20–24, 25–29, 30–34, 35–38 years. Additional characteristics included parity (unborn versus those who gave birth), body mass index (BMI), which was calculated using the formula: weight (kg) / height (m)² and classified as underweight or normal weight, overweight or obese; education and relationship status (stable relationship or not).

SPSS version 26.0 (Chicago, USA) was used for statistical analysis. The data were described using variability analysis in the form of averages (standard deviation). Socio-demographic factors were calculated and presented in the form of frequencies (percentages) using standard descriptive statistical parameters. The relationship between the variables was investigated using a chi-square criterion. The paired parametric t-test was used to compare the average change in the duration of menstruation and menstrual cycle between baseline and after vaccination. Statistical significance was determined as p<0.05.

Results. Of 200 women included in the study, 110 (55.0%) were vaccinated, 90 (45.0%) were unvaccinated. The average age of vaccinated and unvaccinated women was 31.6 ± 2.88 years and 29.3 ± 3.05 years (t = 0.55, p=0.584) respectively. The indicators of the study participants are presented in **Table 1**.

Table 1 – Characteristics of the study participants						
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Characteristics of the study norticipants

Indicators	Group of vaccinated women (n=110)	Group of unvaccinated women (n=90)	χ2	Ρ
20-24 years old	16 (14.5)	11 (12.2)	0.229	0.633
25-29	20 (18.2)	28 (31.1)	4.537	0.034*
30-34	33 (30.0)	27 (30.0)	0.000	1.000
35-38	41 (37.3)	24 (26.7)	2.538	0.112
Parity:				
Nulliparous	48 (43.6)	39 (43.3)	0.002	0.966
Giving birth	62 (56.4)	51 (56.7)		
BMI:				
underweight	12 (10.9)	8 (8.9)	0.224	0.636
normal weight	44 (40.0)	36 (40.0)	0.000	1.000
overweight	38 (34.5)	37 (41.1)	0.910	0.340
obesity	16 (14.5)	9 (10.0)	0.935	0.334
Education:				
secondary	62 (56.4)	51 (56.7)	0.002	0.966
higher	48 (43.6)	39 (43.3)		
Married	64 (58.2)	62 (68.9)	0 1 2 1	0 110
unmarried	46 (41.8)	28 (31.1)	2.434	0.119
Type of vaccine				
Pfizer	22 (20.0)	0	-	-
Sinovac	88 (80.0)	0		

Note: Percentages are shown in parentheses: * – statistical significance of differences (p<0.05).

From **Table 1** it follows that the vaccinated cohort was slightly older (37.3% aged 35–38 years versus 26.7% among the unvaccinated) and statistically significantly differed from the unvaccinated cohort in the 25–29 age group (18.2% versus 31.1% among the unvaccinated). There were no statistically significant differences in other indicators. More than half of the vaccinated (80.0%) received the Sinovac vaccine.

Analysis of clinical characteristics showed that 148 (74.0%) out of 200 study participants had regular menstrual cycles. At the same time, among 110 vaccinated women, 81 (73.6%) had regular menstrual

cycles before the introduction of the vaccine during the last year, and among 90 unvaccinated women, 67 (74.4%) had regular menstrual cycles. The vast majority (n = 177, 88.5%) of the participants were healthy. Nevertheless, in vaccinated and unvaccinated, according to the anamnesis, polycystic ovarian syndrome was present in 9 (8.2%) and 8 (8.9%), respectively, uterine fibroids – in 3 (2.7%) and 3 (3.3%), respectively. Over the past year, 38 (19.0%) study participants have started using contraceptives, mainly combined oral contraceptives (10.5%). At the same time, 19 (9.5%) women stopped using contraceptives during the last calendar year.

Among 110 patients, 85 (77.3%) women had not previously had COVID-19, 25 (22.7%) women had the disease. Menstrual cycle disorders among vaccinated, who had not undergone and who had undergone COVID-19, were in 13 (11.8%) and 16 (14.5%), respectively. In general, after vaccination, menstrual cycle disorders were noted by 29 (26.4%) women. Symptoms appeared a week later in 8 (27.6%) and within a month in 25 (86.2%) out of 29 women (**Figure**).



Figure – Frequency of post-vaccination symptoms

The majority (n = 18, 62.1%) had symptoms after the first dose, 11 (37.9%) – after the second dose. When comparing women vaccinated with the "Sinovac" (n = 17) and "Pfizer" (n = 12) vaccines, the difference in the frequency of menstrual cycle disorders was statistically insignificant (p = 0.190).

The study showed that out of 29 patients with menstrual disorders, 4 patients (13.8%) experienced violations during the COVID-19 pandemic before vaccination. There was a significant difference between menstrual cycle disorders during the COVID-19 pandemic and menstrual cycle disorders after vaccination (13.8% vs. 86.2%, χ 2 = 30.414, p < 0.001).

 Table 2 describes the symptoms that the participants experienced after vaccination after each dose and during the COVID-19 pandemic.

 Table 2 – Frequency of manifestations of menstrual cycle disorders

	After vaccination			
Symptoms	First dose	Second dose	X²	Р
Irregular cycles	5 (17.2)	3 (10.3)	0.580	0.447
Increasing the duration of menstruation	8 (27.6)	4 (13.8)	1.681	0.195
Menorrhagia	4 (13.8)	4 (13.8)	0.000	1.000
Intermenstrual bleeding	1 (3.4)	_	1.018	0.314

Note: Percentages are shown in parentheses

As can be seen from **Table 2**, after the first vaccination, an increase in the duration of menstruation was relatively often observed, after the second vaccination, an increase in the duration of menstruation and menorrhagia occurred with the same frequency. There was no significant difference in the frequency of

symptoms.

Thus, our results showed that there was no significant relationship between age, BMI, history of COVID-19 infection, duration of the menstrual cycle and duration of menstruation.

Discussion. Menstrual disorders are a serious problem for the health care system, especially given their impact on the quality of life of women. Our study showed that 26.4% of our sample complained of menstrual irregularities after vaccination against COVID-19, especially after the first dose (16.4%).

The type of vaccine did not affect the frequency of menstrual disorders in these women. After vaccination, women reported significantly longer average duration of menstruation and duration of the menstrual cycle compared to their condition before vaccination. These symptoms decreased a month after vaccination. Although 27.6% had a clinically noticeable change in cycle duration by 7-8 days, this change rapidly weakened during two post-vaccination cycles. We found no significant changes in the duration of menstruation between vaccination doses. According to M. A. Melikhova and Yu. V. Boklagov [12], women who underwent COVID-19 more often reported an increase in unpleasant sensations during menstruation than those who were not ill, however, a detailed survey did not reveal a significant association of these parameters. The authors report that there is no connection between vaccination and the severity of unpleasant sensations during menstruation [12].

The menstrual cycle time is regulated by the hypothalamic-pituitary-ovarian axis, which can be influenced by life factors, the environment and stressors for health [13, 14]. Our results cannot be explained by generalized pandemic stress, because no changes were observed in the unvaccinated group over a similar period of time. The results obtained are consistent with the analysis of 18,076 users of the Natural Cycles application before and during the pandemic, which also did not show significant violations of cycle synchronization at the population level due to pandemic stress [15]. mRNA vaccines create a strong immune response or stressor, which can temporarily affect the hypothalamic-pituitary-ovarian axis if the time is calculated correctly [16, 17]. Our results for women who received two doses in one cycle confirm this hypothesis. The variability of the cycle duration is the result of events leading to recruitment and maturation of the dominant follicle during the follicular phase, processes that are known to be affected by stress [18]. The nature of menstrual bleeding is an important indicator of reproductive health. However, menstrual symptoms such as perimenstrual mood disorders, menstrual cramps and copious menstrual bleeding are considered common gynecological problems [19]. Stressors can activate the hypothalamic-pituitary-gonadal axis, which leads to a violation of the regularity of hormone release. These menstrual changes can affect women's quality of life, leading to restrictions in work and study, hindering achievements and affecting social and professional activities, which can further cause stress [2].

One of the sources of stress that shocked the world was the COVID-19 pandemic, so several studies have shown an increase in menstrual disorders during the pandemic compared to the previous period [2, 8, 20]. In our study, 13.8% of participants experienced menstrual changes during the COVID-19 pandemic before vaccination. However, 26.4% of women had abnormal menstruation after vaccination. Even taking into account changes in menstrual bleeding during the COVID-19 pandemic, there is a significant difference between changes in the menstrual cycle during the COVID-19 pandemic and menstrual cycle disorders after vaccination. Our results are consistent with a recent preliminary study of 39,129 participants in the United States, where 42% reported more severe bleeding after vaccination [2]. The frequency of irregular menstruation in the literature ranges from

5% to 35.6%, depending on the profession, age and area of residence [20].

After the first vaccine, menstrual cycle disorders were noted by 62.1%. Most of these women menstruated 1-5 days earlier than expected, and this change occurred mainly when the first dose of the vaccine was administered during the first 14 days of the menstrual cycle. However, we did not find significant differences in the occurrence of this menstrual cycle disorder depending on when the first dose of the vaccine was administered (follicular phase versus luteal phase). A frequent change was more abundant than usual menstruation, which occurred mainly when the vaccine was administered during the first 14 days of the menstrual cycle. In general, menstrual disorders after the first dose of the vaccine were spontaneously resolved in about half of the cases within two months. As in the case of the first dose, a frequent change in frequency was menstruation, which occurred 1-5 days earlier than expected. The occurrence of menstrual cycle disorders, according to our results, is slightly higher after the first dose.

Currently, by September 2, 2021, more than 30,000 reports of menstrual irregularities have been registered for all COVID-19 vaccines [21]. According to the latest data comparing women who received vaccination and an unvaccinated control group [18], vaccination against COVID-19 was associated with a change in cycle duration of less than 1 day for both cycles of vaccine administration compared to cycles before vaccination (an increase in the first dose by 0.71 days, confidence interval (CI) - 98.75%, 0.47-0.94; the second dose - 0.91, 98.75% CI 0.63-1.19). Menstrual changes after vaccination are really not that unusual, given that such modifications have been observed after vaccination against other microbes, such as human papillomavirus [22], or human hormones, such as human chorionic gonadotropin [18]. Such disorders may probably be associated with an inflammatory/immunological reaction resulting from adjuvants contained in vaccines, at least in some cases [19]. Nevertheless, we cannot rule out that the spike protein associated with COVID-19 may play a causal and pathogenic role, since similar changes in the menstrual cycle were recorded during COVID-19 infection [23]. Moreover, spike protein diffusion in women's tissues – either associated with COVID-19 infection or released after mRNA-based vaccination may also disrupt endocrine homeostasis of the menstrual cycle, given that the use of combined oral contraceptives was associated with lower chances of reporting any menstrual changes [15]. We believe that what we observed may be related, at least in part, to phase-specific hormonal changes caused by potential pro-inflammatory and pro-coagulation changes. Some data suggest crosstalk between inflammatory homeostasis and menstrual cycle regulation [24], which may be slightly disrupted by temporary hormonal changes and secondary to the inflammatory response caused by the vaccine. According to K. Li et al. [24] mean concentrations of sex hormones and ovarian reserve did not change significantly in women of childbearing age with COVID-19. In almost one fifth of the patients, the authors observed a decrease in menstrual volume or an elongation of the cycle. According to the authors, menstrual changes in these patients may be the result of transient changes in sex hormones caused by suppression of ovarian function, which quickly resume after recovery [24].

Thus, despite the fact that reports of changes in the menstrual cycle after vaccination are temporary and self-limiting, and no case has led to clinically significant consequences, the relationship between vaccination against COVID-19 and menstrual disorders deserves to be studied in further specific studies. The study does not allow us to draw any clear conclusion about the potential causal relationship between the COVID–19 vaccine and menstrual cycle disorders or about any potential fertility disorder. This study provides preliminary evidence that women who have been vaccinated against COVID-19 may experience menstrual irregularities, including, but not limited to, a longer duration of menstruation and an increase in the duration of the menstrual cycle. Further prospective cohort studies are needed to identify the temporal relationship between menstrual cycle changes and different types of COVID-19 vaccines.

Conclusion. Based on the study, 26.4% of women of reproductive age who received the first and second doses of the COVID-19 vaccine had menstrual irregularities at least in the next menstrual cycle, regardless of the type of vaccine and the phase of the menstrual cycle during which the vaccine was administered. However, it was found that menstrual irregularities after administration of both the first and second doses of the vaccine pass independently for two months without clinically significant consequences.

Perspectives of further research. Further studies are needed to confirm or predict observational data when analyzing a large data set, and we suggest taking this element into account during counseling women who received the COVID-19 vaccine, informing them about the possible occurrence of temporary and self-limiting menstrual disorders in the following months.

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УДК 616.371:616.921.5]:618.17-008.8]=111 СИМПТОМИ ТА ТРИВАЛІСТЬ МЕНСТРУАЛЬНОГО ЦИКЛУ ТА ВАКЦИНАЦІЯ ПРОТИ КОРОНАВІРУСНОЇ ХВОРОБИ (COVID-19) Акпербекова С. А.

Резюме. *Мета* – визначення зв'язку вакцинації проти COVID-19 із змінами циклу або тривалості менструацій під час менструальних циклів при отриманні доз вакцини.

Матеріал та методи. До дослідження включено 200 жінок віком від 20 до 38 років, які мали не менше трьох циклів після вагітності або після використання гормональної контрацепції. Жінки були щеплені вакцинами Pfizer-BioNTech (Pfizer) та CoronaVac (Sinovac) (Sinovac Biotech). Розподіл жінок за віком наступний: 20-24, 25-29, 30-34, 35-38 років. Додаткові характеристики включали паритет (що народжували проти тих, хто народив), індекс маси тіла (IMT), який класифікувався як недостатня вага або нормальна вага, надмірна вага або ожиріння; освіту та статус відносин (стійкі відносини чи ні).

Результати. 110 (55,0%) пацієнток були щеплені, 90 (45,0%) – нещеплені. Середній вік щеплених 31,6±2,88 років, нещеплених – 29,3±3,05 років (t=0,55, p=0,584). Серед 110 щеплених регулярні менструальні цикли були у 73,6% до введення вакцини протягом останнього року, серед 90 нещеплених – у 74,4% жінок. Порушення менструального циклу серед щеплених, що не перенесли та перенесли COVID-19, були у 11,8% та 14,5% жінок відповідно. Після вакцинації порушення менструального циклу відзначали 6,4% жінок. Симптоми з'явилися за тиждень у 27,6%. У 62,1% випадків симптоми з'явилися після першої дози, у 37,9% випадків – після другої дози. Після першої та другої вакцинації збільшення тривалості менструацій відзначалося у 27,6% та 13,8% випадків відповідно. Між порушеннями менструального циклу під час пандемії COVID-19 та порушеннями менструального циклу після вакцинації спостерігалася значна різниця (p<0,001).

Висновки. Серед жінок, які отримали вакцини проти COVID-19, у 26,4% випадків спостерігалися порушення менструального циклу. Під час консультування жінок, які отримали вакцину проти COVID-19, доцільно повідомляти про можливе виникнення тимчасових і самообмежуючихся порушень менструального циклу в наступні місяці.

Ключові слова: репродуктивний вік, менструальний цикл, симптоми, COVID-19, вакцинація.

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A - Work concept and design, B - Data collection and analysis,

C - Responsibility for statistical analysis, D - Writing the article,

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