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The reproductive function of women with infertility after suffering COVID-19 infection

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The aim was to assess the status of reproductive function of infertile women after COVID-19 infection.

Materials and methods. The thorough examination included 120 patients who appealed to the reproductive clinic for infertility treatment. These women were divided into 2 groups: the main group — 80 women after COVID-19 infection (exclusion criteria — patients solely with the male factor of infertility), and the comparison group included 40 patients without COVID-19 infection in anamnesis.

Results. Patients with infertility and «long-COVID» have more pronounced disorders of the reproductive function compared to women without history of COVID-19 infection, namely: a decrease in the ovarian reserve (28.8% vs. 10.0%; p<0.05), various menstrual disorders (35.0% vs. 12.5%; p<0.05), including amenorrhea, irregular menstrual cycle and luteal phase insufficiency, high prevalence of genitourinary infections (37.5% vs. 17.5%; p<0.05). Against these disorders background, patients with «long-COVID» have significantly inferior results of in vitro fertilization programs: one in five has «poor ovarian response» (21.3% vs. 2.5%; p<0.05). Clinical pregnancy was diagnosed in 22.5% of patients versus 40.0% (p<0.05), and 2 women had a pregnancy loss in the 1st trimester, while all 16 women in the comparison group carried fetuses to live birth, i.e., the live birth rate was 20.0% versus 40.0% (p<0.05).

Conclusions. Determined changes in reproductive function may be directly or indirectly related to the «long-COVID» consequences, namely, a high level of stress, anxiety and depression, pernicious habits, general fatigability that leads to a sedentary lifestyle, sleep disturbances, the developing or exacerbation of somatic pathologies, among which stand out metabolic disorders and pathology of the liver and gastrointestinal tract.

This study was conducted in accordance with the principles of the Declaration of Helsinki. The research protocol was approved by the Local Ethics Committee of the abovementioned institution. Informed consents of the women were obtained for participation in this study.

The author declares no conflicts of interest.

Keywords: woman, reproductive function, COVID-19, long-COVID, infertility, assisted reproductive technologies.

Стан репродуктивної функції жінок із безпліддям після перенесеного захворювання на COVID-19

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Мета — оцінити стан репродуктивної функції жінок із безпліддям після перенесеного захворювання на COVID-19.

Матеріали та методи. До комплексного обстеження залучено 120 пацієнток, які звернулися до клініки репродуктивних технологій з приводу лікування безпліддя, яких поділено на дві групи: основна група — 80 жінок після COVID-19 (критерій вилучення — пацієнтки з тільки чоловічим фактором безпліддя), група порівняння — 40 пацієнток без COVID-19 в анамнезі.

Результати. У пацієнток із безпліддям і «лонг-COVID» відмічаються більш виражені порівняно з жінками без перенесеного захворювання COVID-19 порушення репродуктивної сфери: зниження овариального резерву (28,8% проти 10,0%; p<0,05), різноманітні порушення менструального циклу (35,0% проти 12,5%; p<0,05), зокрема, аменорея, нерегулярний цикл та недостатність лютеїнової фази, високий рівень поширеності сечостатевих інфекцій (37,5% проти 17,5%; p<0,05). На тлі цих порушень у пацієнток із «лонг-COVID» значно гірші результати програм екстракорпорального запліднення: у кожної п'ятої «бідна відповідь яєчників» (21,3% проти 2,5%; p<0,05). Клінічна вагітність діагностована у 22,5% пацієнток проти 40,0% (p<0,05), причому 2 жінки втратили вагітність у I триместрі, тоді як усі 16 жінок групи порівняння доносили вагітність до народження дитини, тобто частота живонародження становила 20,0% проти 40,0% (p<0,05).

Висновки. Встановлені зміни репродуктивної функції можуть бути прямо або опосередковано пов'язані з наслідками «лонг-COVID», зокрема, високим рівнем стресу, тривожності і депресії, шкідливими звичками, загальною втомою, яка призводить до малорухливого способу життя, порушення сну, виникнення або загострення соматичної патології, серед якої виділяються метаболічні порушення та патологія печінки і шлунково-кишкового тракту.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначеної в роботі установи. На проведення досліджень отримано інформовану згоду жінок.

Автор заявляє про відсутність конфлікту інтересів.

Ключові слова: жінка, репродуктивна функція, COVID-19, лонг-COVID, безпліддя, допоміжні репродуктивні технології.

Introduction

One of the basic medical and social problems is the protection of the reproductive health of childbearing women, because the female population is the main demographic resource of any country. Reproductive health is a fundamental human right that is crucial for the health, well-being and quality of life of individuals, families and communities, society, and the state as a whole.

Today, the complex concept of sexual and reproductive health is often used. Aware of the importance of sexual and reproductive health,

in 2015 the UN included its protection in the objects of global 17 sustainable development goals (SDGs) 2030 [13].

The socio-political changes that have taken place in Ukraine in recent decades have been accompanied by an important transformation of the quality and style of life, the level of health, in particular reproductive health [6]. Negative medico-demographic trends have aggravated even more as a result of the coronavirus disease 2019 (COVID-19) pandemic and against the background of the armed conflict with the Russian Federation on 2014 and the full-scale intervention of the aggressor on February 24, 2022 [10].

The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread around the world and led to unprecedented medico-social consequences due to specific features of the virus, such as the ability to avoid the immunological response; tissue tropism; the ability to damage various organs and systems [2].

As 3-years studies have shown, most patients after «recovery» have a burden of delayed complications [3]. A large cohort study that included patient data 6 months after recovery showed a significant number of patients with persistent complaints of fatigue, muscle weakness, sleep problems, anxiety, and depression [7], which are manifestations of a new term called «post-COVID-19 syndrome» [11]. Obesity, comorbid chronic respiratory disease, decreased lung function, and female gender have been reported as potential risk factors for long-term outcomes [5].

To date, the role of SARS-CoV-2 infection in organs and systems other than the lungs and respiratory tract remains less clear. In particular, how SARS-CoV-2 can directly or indirectly affect the reproductive system in the long term remains to be studied [4]. Direct side effects are associated with the cytopathic actions of viral colonization, while indirect effects – with exacerbations caused by cytokine storm, inflammatory reactions, psychological disorders, and obesity [12]. Ukrainian researchers studied the specifics of the course and clinical consequences of the COVID-19 infection during pregnancy [8, 9].

The ***aim*** was to assess the state of reproductive function of infertile women after COVID-19 infection.

Materials and methods

To determine the possible impact of COVID-19 on women's reproductive health, a thorough examination included 120 patients who appealed to the clinic of reproductive technologies for the treatment of infertility. These women were divided into 2 groups: the main group — 80 patients who had COVID-19 in past and showed signs of «long-term COVID-19», the comparison group — 40 patients without a history of COVID-19 infection.

The study was conducted in accordance with the basic principles of the GCP ICH/Declaration of Helsinki and agreed with the ethics committee of the Ivano-Frankivsk National Medical University. All researches were conducted after obtaining informed consent from the patients for diagnosis and treatment.

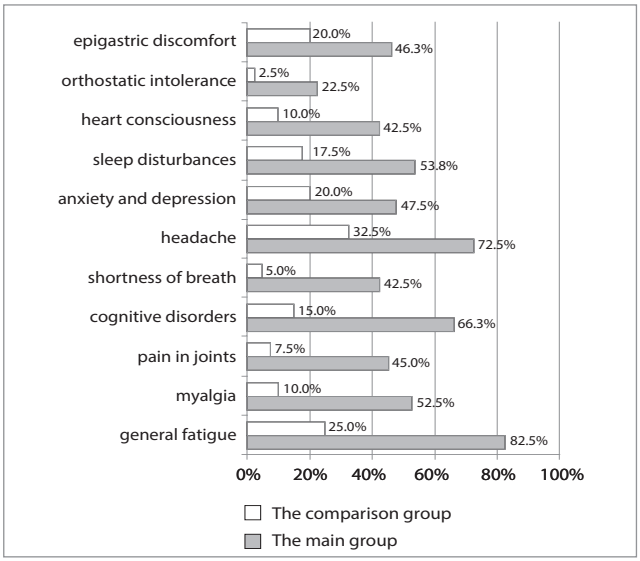
The obtained data were handling by the methods of variation statistics accepted in medicine, using Fisher's angular transformation (to compare groups of patients according to indices represented by incidences in percentages in the group) with a critical value for significance level of $p<0.05$. The Microsoft Excel statistical analysis package was used.

Results and discussion

The frequency of main symptoms of «long-COVID» in the main group (Fig. 1) ranged from 22.2% to 82.2%. However, these symptoms are non-specific and can accompany chronic fatigue, stress, be a sign of vegetative-vascular and other disorders; therefore they are also noted in patients from the comparison group, although with a significantly lower incidence. The common symptoms were general fatigue (82.5%) and headache (73.5%).

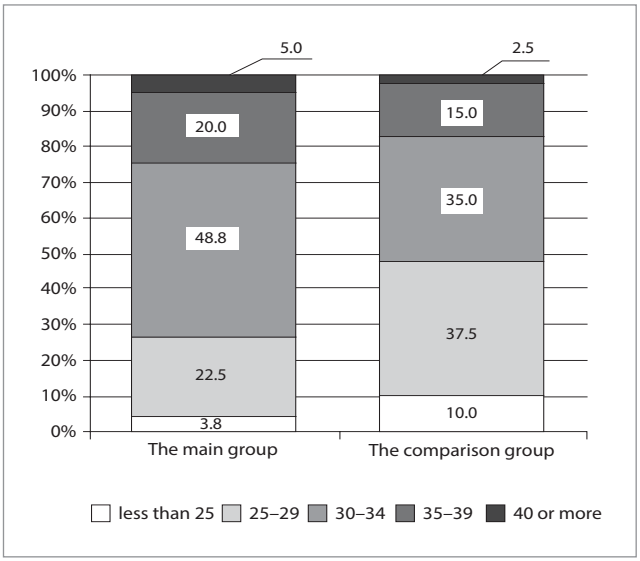
In the main group, the majority (66.3%) of women mentioned cognitive disorders (forgetfulness, decreased attention, concentration difficulty, lack of mental clarity – the so-called «brain fog»), which was accompanied in half of the patients by sleep disturbances (53.8%), anxiety and depression (47.5%). A significant number of women also complained of pain in joints (45.0%) and muscles (52.5%), epigastric discomfort (46.3%), heart consciousness (42.5%) and shortness of breath (42.5%). Orthostatic intolerance (dizziness or other symptoms provoked by standing upright, sometimes can also occur in a sedentary position) was noted in every fourth (22.5%) woman.

A distribution analysis of the studied groups by age (Fig. 2) showed that the largest proportion of patients with «long-COVID» was from 30 to 34 years old (48.8%), while in the comparison group the majority of women ranged from 25 to 29 years (37.5% vs. 22.5% in the main group, $p<0.05$). Among patients with «long-COVID»,



Note: a significant difference relative to pregnant women of the comparison group was established for all indicators (p<0.05).

Fig. 1 The frequency of main symptoms of «long-COVID» in women with infertility



Note: * — a significant difference relative to pregnant women of the comparison group (p<0.05).

Fig. 2 The distribution by age of patients with infertility depending on the transferred COVID-19

there were a slightly larger number of patients over 35 years of age, but the difference with the comparison group was not statistically significant (25.0% vs. 17.5%, p>0.05). Such differences may be related to the greater susceptibility of older age groups to infection and more severe consequences of COVID-19.

An analysis of the main social and living factors (Table 1) that, according to modern concepts, can cause health disorders, revealed their higher incidence in patients with «long COVID-19». Most often, insufficient physical activity was noted (37.5% vs. 20.0% in the group without COVID-19, p<0.05). The frequency of pernicious habits was more than twice as high (18.8% vs. 7.5%, p<0.05), and the incidence of alcohol abuse was more than 4 times higher (11.3% vs. 2.5%, p<0.05). One third of the patients from the main group mentioned stress (31.3% versus 20.0%, p<0.05), and in contrast to the comparison group, stress in everyday life prevailed (26.3% versus 10.0%, p<0.05).

As for the features of infertility (Table 2), in the main group, the proportion of women with primary infertility was 40% lower. In the main group, the proportion of women with more than 5 years infertility was significantly higher (21.3% versus 7.5% in the comparison group, p<0.05). Women in the main group had twice the incidence of unsuccessful previous one (16.3%) or two (6.3%) in vitro fertilization cycles (22.6% vs. 10.0%, p<0.05). In the main group, there was also a significantly higher incidence of decreased ovarian reserve (28.8% vs. 10.0%, p<0.05); according to this diagnosis, the incidence of discrepancy with age norms of follicle-stimulating hormone (FSH) (18.8% vs. 5.0%, p < 0.05) and anti-Müllerian (AMH) hormone (21.3% vs. 7.5%, p < 0.05) was higher.

Table 1

The social and living factors in patients with infertility depending on the transferred COVID-19

Factor	Group			
	main, n=80		comparison, n=40	
	abs.n.	%	abs.n.	%
Pernicious habits in particular:	15	18.8*	3	7.5
– alcohol consumption	9	11.3*	1	2.5
– tobacco smoking	13	16.3	3	7.5
Disturbed day and work regime	27	33.8	8	20.0
Sedentary lifestyle	30	37.5*	9	22.5
Stress, in particular:	25	31.3	8	20.0
– in everyday life	21	26.3*	4	10.0
– at work	17	21.3	7	17.5

Note: * — a significant difference relative to pregnant women of the comparison group (p<0,05).

Table 2

The features of infertility in patients depending on the transferred COVID-19

Indicator	Group			
	main, n=80		comparison, n=40	
	abs.n.	%	abs.n.	%
Primary infertility	13	16.3	11	27.5
More than 5 years infertility	17	21.3*	3	7.5
One in vitro fertilization cycles	13	16.3	3	7.5
Two and in vitro fertilization cycles	5	6.3	1	2.5
Decreased ovarian reserve	23	28.8	4	10.0
FSH is above age norms	15	18.8	2	5.0
AMH is below age norms	17	21.3	3	7.5

Notes: * — a significant difference relative to pregnant women of the comparison group (p<0.05); FSH – follicle-stimulating hormone; AMH – anti-Müllerian hormone.

Table 3

The features of menstrual function in patients with infertility depending on the transferred COVID-19

Indicator	Group			
	main, n=80		comparison, n=40	
	abs.n.	%	abs.n.	%
Amenorrhea	7	8.8	1	2.5
Duration of menstruation:				
– up to 3 days	14	17.5	3	7.5
– more than 6 days	12	15.0*	2	5.0
Blood loss:				
– decrease	13	16.3	3	7.5
– increase	15	18.8*	3	7.5
Duration of cycle:				
– more than 30 days	10	12.5	2	5.0
– up to 24 days	13	16.3	3	7.5
Irregular cycle	17	21.3*	3	7.5
Insufficiency of the luteal phase	15	18.8*	2	5.0

Note: * — a significant difference relative to pregnant women of the comparison group (p<0.05).

Patients of the main group significantly more often suffered from various somatic pathologies than women of the comparison group. Endocrinological pathology stands out especially (38.8% versus 17.5%, respectively, p<0.05), mainly due to metabolic disorders in a third of patients (30.0% versus 12.5%, p<0.05), which are clinically manifested by overweight and obesity. A significant difference between the groups was also found in hepatobiliary pathology (18.8% versus 7.5%, p<0.05). The revealed difference between the groups had a multifactorial nature in terms of somatic morbidity: on the one hand, this is the older age of women, on the other hand, these diseases are risk factors for COVID-19, and can also exacerbated or even developed against the «long-COVID» background.

Today, menstrual function is considered as a sensitive marker of a woman's physical, emotional, and mental health [1], and disturbance of all these aspects of health is inherent in «long-COVID». According to our data, there was a significantly higher incidence of menstrual dysfunction after suffering from COVID-19 infection (Table 3). Secondary amenorrhea due to a number of reasons (among which stress stands out as the cause of functional hypogonadal amenorrhea) was observed 3 times more often (8.8%) in women of the main group. Changes in the duration of menstruation and in the level of blood loss were observed, significantly more patients in the group after COVID-19 mentioned the duration of menstruation for more than 6 days (15.0% vs. 5.0% of patients in the comparison group, p<0.05) with an increase in blood loss (18.8% against 7.5%, p<0.05). Almost 3 times higher incidence of irregular cycle (21.3% vs. 7.5%, p<0.05) and more than 3 times – insufficiency of the luteal phase (18.8% vs. 5.0%, respectively, p<0.05). In general, more than a third of patients with «long-COVID» marked one or another menstrual cycle disorder (35.0% vs. 12.5% of women without a history of COVID-19, p<0.05), and almost half (15.8%) of them noted the onset of these symptoms immediately after COVID-19 infection.

Infertility in the examined patients was often associated with various gynecological mor-

Table 4

The associated gynecological pathology in patients with infertility depending on the transferred COVID-19

Indicator	Group			
	main, n=80		comparison, n=40	
	abs.n.	%	abs.n.	%
Genitourinary infections	30	37.5*	7	17.5
Pathology of the endometrium:				
- endometritis	15	18.8	4	10.0
- endometriosis	10	12.5	3	7.5
- endometrial hyperplasia	16	20.0	4	10.0
Diseases of the cervix	13	16.3	4	10.0
Myoma of the uterus	19	23.8*	3	7.5
Ovarian cysts	16	20.0	5	12.5
Polycystic ovary syndrome	12	15.0	4	10.0

Note: * — a significant difference relative to pregnant women of the comparison group (p<0.05).

Table 5

The results of ART programs depending on the transferred COVID-19

Indicator	Group			
	main, n=80		comparison, n=40	
	abs.n.	%	abs.n.	%
The number of received oocytes:				
– 4 or less (poor ovarian response)	17	21.3*	1	2.5
– 5–8	29	36.3*	5	12.5
Had oocytes with pathology	26	32.5*	7	17.5
Transfer cancellation	12	15.0	3	7.5
Biochemical pregnancy	20	25.0*	17	42.5
Clinical pregnancy	18	22.5*	16	40.0
Pregnancy loss in the 1st trimester	2	2.5	0	0.0
Live birth	16	20.0*	16	40.0

Note: * — a significant difference relative to pregnant women of the comparison group (p<0,05).

bidities (Table 4). Noteworthy is the high prevalence of genitourinary infections in patients after COVID-19 (37.5% vs. 17.5% in women with infertility without COVID-19 in history, p<0.05), which may be due to changes in the immune system, dysbacteriosis and other damages caused by «long-COVID». The incidence of such pathology as endometritis (18.8%) and endometrial hyperplasia (20.0%) was increased, but without significance. The incidence of uterine fibroids was significantly increased (23.8% vs. 7.5%, p<0.05).

All women of the main group and the comparison group, after appropriate preparation, were included in assisted reproductive technologies (ART) programs and after appropriate pretreatment, they underwent in vitro fertilization. Significantly inferior results were obtained in the main group (Table 5). Thus, in every fifth patient, the number of received oocytes was 4 or less (the so-called «poor ovarian response»), while in the comparison group, only one woman had such result, which was 2.5% compared with 21.3% in the main group (p<0.05). Ovarian response (5–8 mature oocytes) was inadequate in more than a third of women in the main group (36.3% vs. 12.5% in the comparison group, p<0.05). A third of the patients had oocytes with cytoplasmic and extracytoplasmic pathology (32.5% vs. 17.5%, respectively, p<0.05). A biochemical pregnancy had only quarter of patients with «long-COVID», which is significantly less than in women without COVID-19 in anamnesis (25.0% vs. 42.5%, p<0.05). Accordingly, clinical pregnancy was diagnosed in 22.5% of women in the main group and 40.0% in the comparison group (p<0.05); 2 women had a pregnancy loss in the 1st trimester, while all 16 women in the comparison group carried fetuses to live birth, i.e., the live birth rate was 20.0% in women of the main group versus 40.0% in the comparison group (p<0.05).

Such unsatisfactory results of ART programs in women of the main group are to some extent due to reproductive health disorders as a result of the negative impact of COVID-19 with the development of a symptom complex called «long-COVID».

Conclusions

Patients with infertility and «long-COVID» have more pronounced disorders of the reproductive function compared to women without a history of COVID-19 infection, namely: a decrease in the ovarian reserve (28.8% vs. 10.0%, p<0.05), vari-

ous menstrual disorders (35.0% vs. 12.5%, p<0.05), including amenorrhea, irregular menstrual cycle and luteal phase insufficiency, high prevalence of genitourinary infections (37.5% vs. 17.5%, p<0.05).

Against these disorders background, patients with «long-COVID» had significantly inferior results of in vitro fertilization programs: one in five had «poor ovarian response» (21.3% vs. 2.5%, p<0.05). Clinical pregnancy was diagnosed in 22.5% of patients versus 40.0% (p<0.05), and 2 women had a pregnancy loss in the 1st trimester, while all 16 women in the comparison group carried fetuses to live birth, i.e., the live birth rate was 20.0% versus 40.0% (p<0.05).

Determined changes in reproductive function may be directly or indirectly related to the consequences of «long-COVID», particularly, a high level of stress, anxiety and depression, pernicious habits, general fatigability that leads to a sedentary lifestyle, sleep disturbances, the developing or exacerbation of somatic pathologies, among which stand out metabolic disorders and pathology of the liver and gastrointestinal tract.

Prospects for further research. Further research will focus on in-depth study of the mechanisms of reproductive disorders in women with «long-term COVID» and on the identification of risk factors.

The author declares no conflict of interest.

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