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The influence of neurovegetative and psychological characteristics of infertile patients with long-term COVID-19 on the effectiveness of assisted reproductive technologies

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The connection of the long-COVID-19 symptom with violations of various systemic factors, in particular with the female reproductive system, is considered, but the number of such studies is not large.

The purpose of the study is the influence of neurovegetative and psychological characteristics of infertile patients with long-term COVID-19 on the effectiveness of assisted reproductive technologies (ART).

Materials and methods. The main group consisted of 80 women with infertility and «long-COVID», the comparison group — 40 patients without a history of COVID-19. In the main group, 2 subgroups were distinguished: 1 — 64 women with unsuccessful ART and 2 — 16 patients in whom ART was successful (a live birth was obtained). Socio-economic status and stress factors (questionnaire), fear of stress-19 (FCV-19S scale), autonomic dysfunction were assessed using the O.M. questionnaire. Wayne (1998), Anxiety and Depression Levels on the Hospital Anxiety and Depression Scale (HADS). The used methods of variational statistics using the Student's t-test and Fisher's angular transformation with a critical significance level of $p<0.05$ were used to calculate the odds ratio (OR) and its confidence interval (CI).

Results. Women with infertility and «long-COVID-19» are characterized by a relatively low level of socio-economic status: a lower level of income, a smaller share of entrepreneurs and housewives, not comfortable enough living conditions. These patients have a higher level of stressogenic load: comorbidity with chronic somatic pathology (58.8%), conflict situations in the family (31.3%), dissatisfaction with their sexual relationships (58.7%), a significantly higher level of fear of COVID —19 (29.73±1.31 points). Vegetative dysfunction is diagnosed in 82.5% of patients. Symptoms that are typical for «long-COVID-19» are most often noted: reduced work capacity/fatigue (82.5%), attack-like headaches (72.5%), difficulty breathing (47.5%), sleep disturbances (47 .5%). Unfavorable medico-social and psychological risk factors for the failure of ART programs in patients with «long-COVID-19» can be a point assessment of the autonomic dysfunction syndrome above 25 (OR=5.80, CI 1.22–27.64), anxiety (OR=5.80, CI 1.56–21.62), presence of depression (OR=4.20, CI 1.27–13.89), chronic somatic disease (OR=4.20, CI 1.30–13.62), conflict situations (OR=3.86, CI 1.24–12.04).

Conclusions. Women with infertility and «long-COVID-19» need additional examinations to assess the medical and social status, vegetative function and psychological state, correction of detected violations.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The research protocol was approved by the Local Ethics Committee of the institution mentioned in the work. Informed consent of the women was obtained for the research.

No conflict of interests was declared by the authors.

Keywords: long-covid-19, infertility, socioeconomic status, fear of covid-19, autonomic dysfunction, anxiety, depression, assisted reproductive technologies.

Вплив на ефективність допоміжних репродуктивних технологій нейровегетативних та психологічних особливостей безплідних пацієнток із лонг-COVID-19

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Розглядається зв'язок симптому лонг-COVID-19 із порушеннями різних систем організму, зокрема, з репродуктивною системою жінки, проте кількість таких досліджень не значна.

Мета — визначити вплив на ефективність допоміжних репродуктивних технологій (ДРТ) нейровегетативних і психологічних особливостей безплідних пацієнток із лонг-COVID-19.

Матеріали та методи. Основну групу становили 80 жінок із безпліддям і лонг-COVID-19, групу порівняння — 40 пацієнток без COVID-19 в анамнезі. В основній групі виділено дві підгрупи: 1-ша — 64 жінки з неуспішним ДРТ; 2-га — 16 пацієнток, у яких ДРТ було успішним (отримано живонародження). Оцінено соціально-економічний статус і фактори стресогенного навантаження (анкета), страх перед COVID-19 (шкала FCV-19S), вегетативну дисфункцію за допомогою опитувальника О.М. Вейна (1998), рівень тривоги та депресії — за госпітальною шкалою тривоги і депресії (HADS). Використано методи варіаційної статистики з використанням t-критерію Стьюдента та кутового перетворення Фішера з критичним рівнем значущості $p<0,05$, розраховано відношення шансів (ВШ) та його 95% довірчий інтервал (ДІ).

Результати. Жінки з безпліддям та лонг-COVID-19 характеризуються відносно зниженим рівнем соціально-економічного статусу: нижчий рівень доходу, менша частка підприємців і домогосподарок, недостатньо комфортні умови проживання. У цих пацієнток вищий рівень стресогенного навантаження: коморбідність із хронічною соматичною патологією (58,8%), конфліктні ситуації в сім'ї (31,3%), невдоволеність сексуальними стосунками (58,7%), достовірно вищий рівень страху перед COVID-19 (29,73±1,31 бала). Вегетативна дисфункція діагностується у 82,5% пацієнток. Найчастіше відмічаються симптоми, характерні і для лонг-COVID-19: зниження працездатності/втомлюваність (82,5%), нападоподібний головний біль (72,5%), затруднення дихання (47,5%), порушення сну (47,5%). Несприятливими медико-соціальними і психологічними факторами ризику неуспішності програм ДРТ у пацієнток із лонг-COVID-19 можуть бути бальна оцінка синдрому вегетативної дисфункції понад 25 (ВШ=5,80% 95% ДІ: 1,22–27,64), тривожний стан (ВШ=5,80; 95%

ДІ: 1,56–21,62), наявність депресії (ВШ=4,20; 95% ДІ: 1,27–13,89), хронічного соматичного захворювання (ВШ=4,20; 95% ДІ: 1,30–13,62), конфліктних ситуацій (ВШ=3,86; 95% ДІ: 1,24–12,04).

Висновки. Жінки з безпліддям і лонг-COVID-19 потребують додаткових обстежень з оцінювання медико-соціального статусу, вегетативної функції та психологічного стану, проведення корекції виявлених порушень.

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

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: лонг-COVID-19, безпліддя, соціально-економічний статус, страх перед COVID-19, вегетативна дисфункція, тривога, депресія, допоміжні репродуктивні технології.

Introduction

In the wake of the COVID-19 pandemic, the so-called long-COVID, a complication that includes a range of symptoms such as fatigue, cognitive dysfunction, headaches, sleep disorders, and muscle aches that remain after the illness and persist, is attracting much attention from researchers. up to six months or longer [7]. The connection of this symptom with disorders of various body systems [3,4], in particular with the female reproductive system [16], is also considered, but the number of such studies is small.

Socio-economic status (SES) is considered one of the most important determinants of preventable health disparities in the burden of disease or opportunities to achieve optimal health commonly experienced by disadvantaged groups [15]. Lower SES is associated with various adverse health outcomes, such as cardiovascular disease, diabetes and cancer, pregnancy complications, and poorer outcomes [12].

Studies have been conducted that found that women with higher incomes were less likely to develop pregnancy complications, including gestational hypertension, preeclampsia, eclampsia, gestational diabetes, preterm premature rupture of membranes, and placental abruption, and they were less likely to die in utero [12] .

There is growing recognition that public health measures taken to control the spread of the COVID-19 pandemic have had unintended consequences for socioeconomic security and health inequalities, with the greatest impact on the most vulnerable populations. The authors [17] showed that the risk of financial insecurity increased dramatically during the pandemic. In addition, this study demonstrated that there is a strong relationship between financial insecurity and measures of maternal health and well-being: mothers who experience financial insecurity are more likely to report poorer general health and clinically significant symptoms of depression and anxiety, which associated with «long-COVID-19». The results of this study highlight that the effects of financial insecurity faced by mothers and their families throughout the pandemic were severe, wide-ranging and affected the most vulnerable populations.

The relationship between SES and fertility is a topic that receives a lot of attention. However, little is known about whether SES affects the outcome of infertility treatment. Although there is evidence that SES can affect reproduction [13] and influence fertility treatment-seeking behavior [19], there is a paucity of data on socioeconomic factors of infertility treatment and assisted reproductive technology (ART) outcomes [10].

Psychosocial aspects can also include fears of diseases, especially infectious ones, which have greatly increased during the COVID-19 pandemic due to extremely high infection rates and relatively high mortality. Such fear can worsen the consequences of the disease, lead to other psychosocial problems, including stigma, discrimination, anxiety and stress related to the virus. An effective tool was proposed for quantitative assessment — the scale of fear of coronavirus-19 (FCV-19S) [1]. According to the authors, FCV-19S was significantly correlated with depression, anxiety (according to the HADS).

The syndrome of autonomic dysfunction (SAD), which was previously called vegetative-vascular dystonia, is again attracting the attention of researchers, in particular in association with «long-COVID-19», an increase in stressogenic loads. At present, the term somatoform autonomic dysfunction (AD) is used in world medicine, which most often refers to symptoms that are a consequence of another disease.

In «long-COVID-19», neurological and/or neuropsychological disorders such as memory loss, «brain fog», fatigue, dizziness, headaches or general pain [11] are frequent complaints, which puts the nervous system in the center of interest when studying this state. Recently, more and more researchers have emphasized the potential importance of psychosomatic factors in the emergence and maintenance of the post-COVID-19 syndrome [2]. This idea is further

supported by similarities between post-COVID-19 syndrome and the manifestations of post-traumatic distress syndrome, depression, anxiety disorder, or ill-defined illnesses such as chronic fatigue syndrome [20], so supportive psychotherapy is effective in alleviating post-COVID-19 symptoms. [8].

A study by M. Fleischer and co-authors [9] showed that patients with post-COVID-19 syndrome suffer from a large number of neuropsychiatric syndromes. However, damage to the central or peripheral nervous system could only rarely be objectified and was associated with a specific neurological disease rather than a post-COVID-19 syndrome. The authors found evidence of significant psychiatric comorbidity and high levels of somatization, suggesting the possibility that psychosomatic mechanisms, such as somatosensory amplification, may play a significant role in the pathogenesis of the post-COVID-19 syndrome. The majority of patients were women and complained of numerous complaints, the most common of which were fatigue, difficulty concentrating, and headache. This observation highlights that neurological and neuropsychiatric symptoms are key features of post-COVID-19 syndrome and is consistent with several previous reports of symptomatology and female predominance in post-COVID-19 syndrome [18].

Authors from Greece [13,14] provide evidence that AD may contribute to the appearance of «long-COVID-19» symptoms that persist for several months after the acute form of COVID-19 has ended. Patients have been shown to have both parasympathetic and sympathetic changes. Other authors [6] described a group of individuals with symptoms of «prolonged COVID-19» and suggested that this condition may be associated with a viral or immune-mediated impairment of the autonomic nervous system.

The ***purpose*** of the study is to determine the effect of neurovegetative and psychological characteristics of infertile patients with long-term COVID-19 on the effectiveness of ART.

Materials and methods of the study

120 patients who applied to the clinic of reproductive technologies for infertility treatment were included in the comprehensive examination, who were divided into 2 groups: the main group — 80 women who showed signs of «long-COVID», the comparison group consisted of 40 patients without COVID-19 in anamnesis

A 10-item questionnaire was developed to determine SES and factors of stressogenic load. The scale of fear of COVID-19 FCV-19S [1] was used. The presence of SAD was established using the A.M. Wayne questionnaire. (1998) with a score. If the total number of points is 15 or more, the presence of SAD is confirmed. The Hospital Anxiety and Depression Scale (HADS) was used to determine and assess the severity of depression and anxiety symptoms, the advantages of which are its ease of use, which allows it to be used for primary screening of anxiety and depression in general medical practice.

In order to determine the medico-social and psychological factors that negatively affect the results of ART in case of «long-COVID-19», relevant indicators were analyzed in 2 subgroups of the main group: subgroup 1 — 64 women with unsuccessful ART (cancellation of transfer, non-occurrence of pregnancy or its loss) and subgroup 2 — 16 patients in whom ART was successful (a live birth was obtained).

The obtained data were processed by methods of variational statistics accepted in medicine, using the Student's t-test for numerical indicators with a normal distribution and Fisher's angular transformation for indicators represented by frequencies, the odds ratio (OR) and its confidence interval (CI), the critical level of significance were calculated accepted $p<0.05$. The Microsoft Excel statistical analysis package was used.

The study was carried out in accordance with the main provisions of GCP ICH and the Declaration of Helsinki, agreed with the ethics committee of the Ivano-Frankivsk National Medical University and the ethics and academic integrity commission of the [2]Shupyk National University of Health Care of Ukraine. All studies were carried out after receiving the patient's informed consent for diagnosis and treatment. The work is a fragment of the SRW «Improving tactics of preconception counseling and management of early pregnancy of women with reproductive health disorders».

Results of the study and discussion

The analysis of SES indicators in patients with infertility depending on the transferred COVID-19 (Table 1) made it possible to establish certain trends. Thus, in the main group, there are more patients with a low and sufficient level of income and, accordingly, fewer with an average and high one (53.8% vs. 72.5% in the comparison group, $p<0.05$). In the distribution by

Table 1

Indicators of SES in patients with infertility depending on the transferred COVID-19

Indicator	Main group, n=80		Comparison group, n=40	
	abs. n.	%	abs. n.	%
Monthly income per family member				
low – at the level of subsistence minimum	8	10.0	2	5.0
satisfactory – up to 10,000 UAH	29	36.3	9	22.5
average – 10,000 – 40,000 UAH	38	47.5	23	57.5
high – more than 40,000 UAH	5	6.3	6	15.0
Professional activity				
worker	9	11.3	2	5.0
employee	40	50.0	17	42.5
businesswoman	7	8.8	6	15.0
student	5	6.3	1	2.5
housewife	12	15.0*	12	30.0
unemployment	7	8.8	2	5.0
Education				
incomplete secondary	7	8.8	1	2.5
average	26	32.5	12	30.0
medium special	15	18.8	9	22.5
incomplete higher	16	20.0	13	32.5
higher	16	20.0	5	12.5
Comfort of accommodation				
yes	60	75.0*	35	87.5
no	20	25.0*	5	12.5
How many people live with the woman				
1	36	45.0	22	55.0
2–3	17	21.3	11	27.5
4–6	16	20.0	5	12.5
more than 6	11	13.8	2	5.0

Note: * — the difference in the indicator relative to the group of women without a history of COVID-19 is statistically significant ($p<0.05$).

Table 2

Additional medical and social stressogenic factors in patients with infertility depending on the transferred COVID-19

Indicator	Main group, n=80		Comparison group, n=40	
	abs. n.	%	abs. n.	%
The presence of a chronic somatic disease	47	58.8*	15	37.5
The presence of conflict situations in a woman's life:				
- in the family	25	31.3*	6	15.0
- at work	20	25.0	7	17.5
- in the family and at work	10	12.5	2	5.0
- no	25	31.3*	25	62.5
Work at night	7	8.8	1	2.5
Presence of seriously ill family members/disabled persons	10	12.5	2	5.0
Dissatisfaction with sex life	47	58.8*	17	42.5

Note: * — the difference in the indicator relative to the group of women without a history of COVID-19 is statistically significant ($p<0.05$).

professional activity, among female patients of the main group, the share of female workers and students is twice as large, and there are 75% more unemployed women. At the same time, there is a smaller share of entrepreneurs and a significantly smaller share of housewives (15.0% vs. 30.0%, $p<0.05$). No significant difference was found in the distribution by level of education, one can only note a larger share of women with incomplete secondary education in the main group, while there are also more patients with higher education. A quarter of women after COVID-19 consider the conditions of their accommodation to be uncomfortable (insufficient space, disorganization, inconvenience and insufficient communications) (25.0% vs. 12.5%, respectively, $p<0.05$). In this group, 33.8% of respondents have more than 4 people living together with a woman (against 17.5%, $p<0.05$).

Table 3

The level of fear of COVID-19 in patients with infertility depending on the experienced COVID-19 (according to the FCV-19S scale), points

Indicator	Main group, n=80	Comparison group, n=40
I am most afraid of COVID-19	4.12±0.49*	2.52±0.58
I hate to think about COVID-19	4.35±0.67	3.56±0.45
My hands get sticky when I think about COVID-19	4.08±0.54*	2.75±0.41
I fear losing my life to COVID-19	4.64±0.49*	3.22±0.5
I get nervous or worried when I see news and stories about COVID-19 on social media	3.83±0.89	3.12±0.92
I can't sleep because I'm afraid of contracting COVID-19	4.29±0.38*	3.09±0.42
My heart races or pounds when I think about COVID-19	4.42±0.41*	3.13±0.43
Total score	29.73±1.31*	21.39±2.16

*Note: ** — the difference in the indicator relative to the group of women without a history of COVID-19 is statistically significant (p<0.05).

Table 4

Vegetative disorders in patients with infertility depending on the transferred COVID-19

Indicator	Main group, n=80		Comparison group, n=40	
	abs. n.	%	abs. n.	%
Tendency to redness/paleness of the face	17	21.3	4	10.0
Feeling of numbness or coldness of the fingers/whole hands, feet	29	36.3*	7	17.5
Change in color (paleness, redness, bluishness) of fingers or entire hands, feet	7	8.8	1	2.5
Increased sweating	34	42.5*	5	12.5
Frequent feeling of heartbeat, «fading», «cardiac arrest»	34	42.5*	4	10.0
Difficulty breathing	38	47.5*	5	12.5
Violation of the function of the gastrointestinal tract	34	42.5*	9	22.5
Fainting, loss of consciousness or the feeling of the possibility of losing it	6	7.5	1	2.5
Attack-like headaches	58	72.5*	13	32.5
Reduced work capacity, rapid fatigue	66	82.5*	10	25.0
Sleep disturbance	38	47.5*	8	20.0
The sum of points exceeds 15 points	69	86.3*	15	37.5

*Note: ** — the difference in the indicator relative to the group of women without a history of COVID-19 is statistically significant (p<0.05).

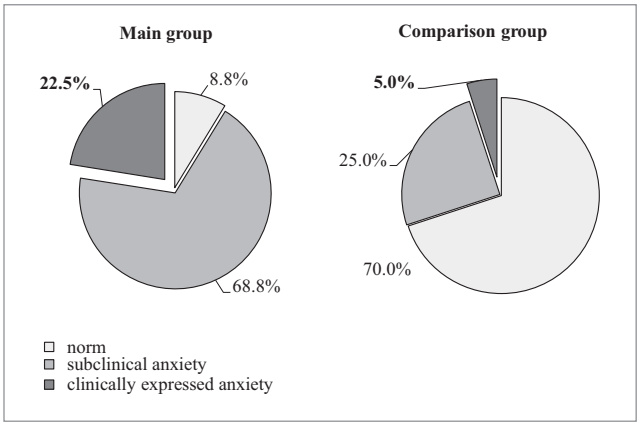
The analysis showed a significantly higher frequency of stressogenic load factors in «long-COVID-19» (Table 2). Thus, more than half of the women in the main group have a chronic somatic disease (58.8% vs. 37.5%, p<0.05). The frequency of conflict situations is significantly higher, especially in the family (31.3% vs. 15.0%, p<0.05). They work somewhat more often at night and have seriously ill family members. The significantly lower percentage of respondents of the main group who are satisfied with their sexual relations (41.3% versus 57.5%, p<0.05) is noteworthy.

According to the FCV-19S survey (Table 3), patients with long-term COVID-19 have a significantly higher level of fear of COVID-19 as the sum of the scores of all indicators of the scale (29.73±1.31 vs. 21.39±2.16 score, p<0.05), as well as by individual indicators.

According to Table 4, SAD (the sum of Wayne's points is more than 15) can be diagnosed in the vast majority of women with «long-COVID-19» (82.5% of patients in the main group versus 37.5% of patients in the comparison group, p<0.05). They also have a significantly higher frequency of certain autonomic symptoms, especially those that are characteristic of «long-COVID-19» itself, the most frequent of which were reduced work capacity/fatigue, attack-like headaches, and difficulty breathing. It should be especially noted that almost half of the patients had sleep disturbances (47.5% vs. 20.0%, p<0.05).

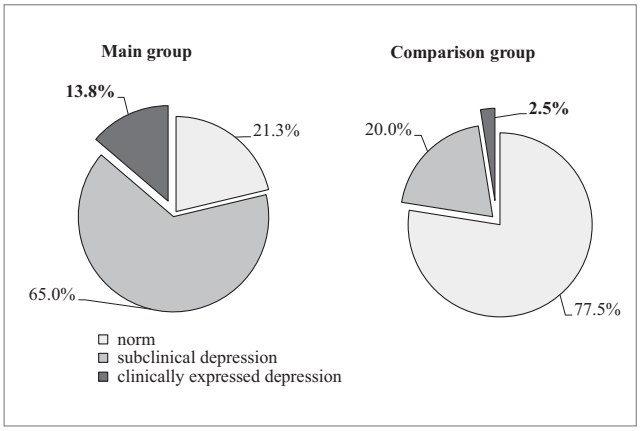
According to the calculations, the distribution of women in the groups according to the HADS scale both on the «anxiety» subscale (Fig. 1) and on the «depression» subscale differed significantly (Fig. 2). Thus, the vast majority of women with long-COVID-19 were in a state of anxiety (91.2% versus 30.0% of women in the comparison group, p<0.05), 22.5% had an anxiety level of 11 or higher and corresponded to clinically expressed, only 5.5 patients with clinically expressed anxiety were found in the group without COVID-19 (p<0.05).

As for the state of depression (see Fig. 2), according to the corresponding subscale, 78.8% of patients in the main group received a score of 8 or more, that is, their condition was assessed as depressed (compared to 22.5% of women in the comparison group, p<0, 05). Clinically expressed de-



Note: the difference between the corresponding indicators of women in the groups is significant (p<0.05).

Fig. 1. Distribution of examined women in groups according to the «anxiety» subscale of the HADS scale



Note: the difference between the corresponding indicators of women in the groups is significant (p<0.05).

Fig. 2. Distribution of examined women in groups according to the «depression» subscale of the HADS scale

Table 5

The frequency of medico-social and psychological risk factors in patients with «long-COVID» depending on the success of ART programs

Risk factor	Subgroup 1, n=64		Subgroup 2, n=16		OR	LL CI	UV CI
	abs. n.	%	abs. n.	%			
Monthly income per family member up to 10,000 UAH	33	51.6*	4	25.0	3.19	0.93	10.96
Uncomfortable accommodation	17	26.6*	5	18.8	1.57	0.40	6.18
The presence of a chronic somatic disease	42	65.6*	7	31.3	4.20#	1.30	13.62
The presence of conflict situations in a woman's life	48	75.0*	6	43.8	3.86#	1.24	12.04
Dissatisfaction with sex life	41	64.1*	6	37.5	2.97	0.96	9.23
The level of fear of COVID-19 is more than 25 points	39	60.9*	2	37.5	2.60	0.84	8.05
The sum of SAD points is above 25	29	45.3*	10	12.5	5.80#	1.22	27.64
Anxiety	58	90.6*	9	62.5	5.80#	1.56	21.62
Depression	54	84.4*	4	56.3	4.20#	1.27	13.89

Notes: OR — odds ratio, LL CI — lower limit of confidence interval, UL CI — upper limit of confidence interval; * — the difference is significant in relation to the subgroup 2 patients (p<0.05); # — OR is statistically significant.

pression in the main group was diagnosed 5 times more often than in the comparison group (13.8% vs. 2.5%, respectively, p<0.05).

According to the table 5, the frequency of adverse medical, social and psychological risk factors in patients with «long-COVID-19» is significantly higher when ART programs are unsuccessful. The highest reliably significant OR was obtained for two risk factors: the sum of SAD points above 25 (45.3% in subgroup 1 vs. 12.5% in subgroup 2, OR=5.80, CI 1.22–27.64, p<0 .05) and anxiety according to the HADS scale (90.6% in subgroup 1 vs. 62.5% in subgroup 2, OR=5.80, CI 1.56–21.62, p<0.05). The presence of depression also has a statistically significant effect on the results of ART in patients with long-term COVID-19 (84.4% in subgroup 1 vs. 56.3% in subgroup 2, OR=4.20, CI 1.27–13.89, p <0.05), chronic somatic disease (65.5% vs. 31.3%, respectively, OR=4.20, CI 1.30–13.62, p<0.05), conflict situations (75.0% against 43.8%, OR=3.86, CI 1.24–12.04, p<0.05).

Conclusions

The socio-economic status of female infertility patients with long-term COVID-19 is characterized by a reduced level of income (46.2%), a larger share of workers, students and unemployed women, and a smaller share of housewives. Unfavorable factors include uncomfortable living conditions (25.0%) and more than 4 people living with a woman (33.8%). The presence of a chronic somatic disease (58.5%), conflict situations in the family (31.3%) can be considered as additional factors of stressogenic load.

The level of fear of COVID-19 is significantly increased (29.73±1.31 points according to the FCV-19S questionnaire). Women with infertility and «long-COVID-19» suffer from various manifestations of autonomic disorders – autonomic dysfunction is diagnosed in 82.5% of patients. Symptoms that are typical for «long-COVID-19» are most often noted: reduced work capacity/

fatigue (82.5%), attack-like headaches (72.5%), difficulty breathing (47.5%), sleep disturbances (47 .5%).

The vast majority of women with long-term COVID-19 were in an anxious state (91.2%), in 22.5% the level of anxiety corresponded to the clinically expressed. The condition of 78.8% of patients is assessed as depressed, clinically expressed depression is diagnosed 5 times more often (13.8%).

Unfavorable medico-social and psychological risk factors for the failure of ART programs in patients with «long-COVID-19» can be the sum of SAD points above 25 (OR = 5.80, CI 1.22–27.64), anxiety according to the HADS scale (OR=5.80, CI 1.56–21.62), presence of depression (OR=4.20, CI 1.27–13.89), chronic somatic disease (OR=4.20, CI 1.30–13.62), conflict situations (OR=3.86, CI 1.24–12.04).

Therefore, women with infertility and «long-COVID-19» need additional examinations to assess the medical and social status, vegetative function and psychological state, and to carry out the correction of the detected violations.

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