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O.G. Boichuk, I.S. Golovchak
**Risk factors for the ineffectiveness
of assisted reproductive technology programs after
a woman's illness with COVID-19**

Ivano-Frankivsk National Medical University, Ukraine

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No conflict of interests was declared by the authors.

Keywords: woman, COVID-19, long-COVID, infertility, assisted reproductive technologies, risk factors.**Фактори ризику неефективності програм допоміжних репродуктивних технологій після перенесеного жінкою захворювання на COVID-19****О.Г. Бойчук, І.С. Головчак**

Івано-Франківський національний медичний університет, Україна

Мета — визначити фактори ризику неефективності програм допоміжних репродуктивних технологій (ДРТ) після перенесеного жінкою захворювання на COVID-19.**Матеріали та методи.** У групі з 80 обстежених пацієнток з ознаками «лонг-COVID», які звернулися до клініки репродуктивних технологій з приводу лікування безпліддя, виділено дві підгрупи: підгрупа 1 — 64 пацієнтки, у яких застосування ДРТ було неуспішним (відміна переносу, ненастання вагітності або її втрата); підгрупа 2 — 16 жінок з успішним ДРТ (отримано живонародження).**Результати.** Спостерігаються суттєві відмінності пацієнток із неуспішним застосуванням ДРТ за частотою основних симптомів «лонг-COVID», виділяються такі симптоми: «депресія, тривожність» (54,7% проти 18,8%; $p < 0,05$) і «порушення сну» (59,4% проти 31,3%; $p < 0,05$). Значуща різниця виявлена за соціально-побутовими факторами: наявність стресів (35,9% проти 12,5%; $p < 0,05$), особливо в побуті (31,3% проти 6,3%; $p < 0,05$), наявність шкідливих звичок (21,9% проти 6,3%; $p < 0,05$).Відмічається вірогідно вища частота зниження оваріального резерву (32,8% проти 12,5%; $p < 0,05$) і відповідних гормональних порушень: підвищення фолікулостимулюючого гормону та його зниження (21,9% проти 6,3%; $p < 0,05$) і зниження антимюллерового гормону (25,0% проти 6,3%; $p < 0,05$).Серед соматичної патології особливо виділяється ендокринна патологія (45,3% проти 12,5%; $p < 0,05$), зокрема, метаболічні порушення (34,4% проти 12,5%; $p < 0,05$). Вірогідна різниця встановлена також за частотою захворювань печінки (21,9% проти 6,3%; $p < 0,05$) і шлунково-кишкового тракту (23,4% проти 12,5%; $p < 0,05$).Спостерігається вища частота порушень менструальної функції, зокрема, скорочення тривалості менструацій (20,3% проти 6,3%) або, навпаки, тривалі менструації (17,2% проти 6,3%), нерегулярний цикл (25,0% проти 6,3%; $p < 0,05$) і недостатність лютеїнової фази (21,9% проти 6,3%; $p < 0,05$). Урогенітальні інфекції відмічаються у 43,8% пацієнток (проти 12,5%; $p < 0,05$).**Висновки.** Встановлено фактори ризику неефективності програм ДРТ, серед цих факторів особливо виділяються стреси, депресія і тривожність, шкідливі звички, ендокринна патологія, метаболічні порушення, печінкова патологія, порушення менструального циклу та урогенітальні інфекції.

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: жінка, COVID-19, лонг-COVID, непліддя, допоміжні репродуктивні технології, фактори ризику.

One of the most important demographic indicators, the birth rate, is closely related to the stability of the social and economic system, confidence in the future. The most vivid reflection of negative changes in the country can be the depopulation trends, which are deepening as a result of the mass resettlement of refugees, departure of a large part of the population abroad as a result of hostilities on the territory of the country. The reproductive potential of Ukraine is steadily decreasing both quantitatively and qualitatively [12].

Overcoming infertility as the main indicator of impaired reproductive health continues to remain in the center of attention of obstetrician-gynecologists. Despite the indisputable achievements of assisted reproductive technology (ART) methods that have taken place over 40 years since the birth of the first child as a result of in vitro fertilization (IVF), their effectiveness still remains relatively low, which, according to the authors [11], requires implementation of personalized approaches (another term precision medicine) adapted to the individual condition of each infertile couple. A personalized approach to infertility treatment should include different sequential stages of decision-making processes, including personalized strategy, personalized preventive measures, personalized diagnosis and personalized treatment, as well as follow-up after treatment.

A woman's reproductive system can be directly or indirectly affected by SARS-CoV-2 in the long term [1]. Direct effects are associated with the cytopathic effect of the virus, and indirect effects are associated with inflammatory reactions, psychological disorders and obesity [5].

Post-COVID-19 syndrome or long-term COVID syndrome includes complaints that persist for more than 12 weeks and are not associated with any other disease [3,6,10]. It has been reported that obesity, concomitant chronic respiratory disease, abnormal X-ray findings, decreased lung function during spirometry, and female gender are potential risk factors for long-term outcomes [4].

The authors [5] highlight different etiological pathways of the pathogenesis of female fertility complications associated with COVID-19, which are based on inflammatory reactions and psychosocial stress, which can also lead to pregnancy complications. A recent study showed that the SARS-CoV-2 pandemic causes not only medical problems, but also initiates various

psychological complications. Rates of anxiety, stress, and depression were reported to be around 31.9%, 29.6%, and 33.7%, respectively, during this pandemic [9]. The relationship between stress and impaired reproductive function in infertile women is recognized [8]. Therefore, it is possible to expect a violation of female reproduction with an adverse effect on the quality of oocytes [7].

The *purpose* of the study – to determine the risk factors for the ineffectiveness of ART programs after a woman's illness with COVID-19.

Materials and methods

320 patients, who applied for infertility treatment, were examined. Among them, 262 patients had a history of having been infected with COVID-19. The diagnosis of «long-COVID» was made in the presence of symptoms that were observed more than 12 weeks after the illness and were not associated with another pathology. These criteria were met by 91 patients who suffered from a moderate and severe coronavirus disease that required inpatient treatment. The frequency of «long-COVID» was 28.4% among all patients with infertility and 34.7% among those who suffered the disease [2].

In order to identify factors that negatively affect the results of ART in «long-COVID» in the group of 80 patients with symptoms of «long-COVID» who applied to the clinic of reproductive technologies for infertility treatment (10 patients with only male factor infertility were excluded, one patient refused to participate in the study), 2 subgroups were selected: the Subgroup 1: 64 patients in whom ART was unsuccessful (cancellation of transfer, non-occurrence of pregnancy or its loss) and the Subgroup 2: 16 women with successful ART (live birth).

The obtained data were processed by the methods of variational statistics accepted in medicine, using Fisher's angular transformation (to compare groups of patients according to indicators represented by frequencies in percentages in the group) with a critical significance level of $p < 0.05$, the odds ratio (OR) with a confidence interval was calculated (CI). The Microsoft Excel statistical analysis package was used.

The study was carried out in accordance with the main provisions of the ICH GCP and the Declaration of Helsinki, agreed with the ethics committee of the Ivano-Frankivsk National Medical University. All studies were carried out after receiving the patient's informed consent for diagnosis and treatment.

The frequency of the main symptoms of «long-COVID» depending on the success of ART programs, % Table 1

Symptom	Subgroup 1, n=64		Subgroup 2, n=16		OR	LL CI	UV CI
	abs.n.	%	abs.n.	%			
General fatigue	55	85.9	11	68.8	2.78	0.78	9.90
Myalgia	37	57.8*	5	31.3	3.01	0.94	9.69
Pain in the joints	31	48.4	5	31.3	2.07	0.64	6.63
Cognitive disorders	45	70.3	8	50.0	2.37	0.77	7.24
Dyspnea	30	46.9*	4	25.0	2.65	0.77	9.09
Headache	49	76.6	9	56.3	2.54	0.81	7.98
Depression, anxiety	35	54.7*	3	18.8	5.23#	1.36	20.14
Sleep disturbance	38	59.4*	5	31.3	3.22#	1.00	10.35
Heart palpitations	29	45.3	5	31.3	1.82	0.57	5.85
Orthostatic intolerance	16	25.0	2	12.5	2.33	0.48	11.40
Discomfort in the epigastrium	33	51.6*	4	25.0	3.19	0.93	10.96

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.

Social and household factors in patients with «long-COVID» depending on the success of ART programs, % Table 2

Factor	Subgroup 1, n=64		Subgroup 2, n=16		OR	LL CI	UV CI
	abs.n.	%	abs.n.	%			
Harmful habits, in particular:	14	21.9*	1	6.3	4.20	0.51	34.62
- alcohol consumption	9	14.1	1	6.3	2.45	0.29	20.93
- smoking	12	18.8	1	6.3	3.46	0.42	28.82
Disturbed day and work schedule	23	35.9	4	25.0	1.68	0.49	5.82
Sedentary lifestyle	22	34.4	8	50.0	0.52	0.17	1.59
Stress, in particular	23	35.9*	2	12.5	3.93	0.82	18.82
- in everyday life	20	31.3*	1	6.3	6.82	0.84	55.24
- at work	16	25.0*	1	6.3	5.00	0.61	40.91

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 ($p < 0.05$); the statistical significance of OR was not revealed.

Results and discussion

Significant differences in the frequency of the main symptoms of «long-COVID» were established (Table 1). Thus, significantly more often women with a negative ART result complained of muscle pain (57.8% versus 31.3% of women with a positive result, $p < 0.05$), shortness of breath (46.9% vs. 25.0%, $p < 0.05$) and discomfort in the epigastrium (51.6% vs. 25.0%, respectively, $p < 0.05$). Symptoms with a significant OR should be highlighted in particular: «depression, anxiety» (54.7% in the Subgroup 1 vs. 18.8% in the Subgroup 2, OR=5.23, CI 1.36–20.14, $p < 0.05$) and «sleep disturbance» (59.4% vs. 31.3%, OR=3.22, CI 1.00–10.354, $p < 0.05$).

A significant difference between the patients of the Subgroups 1 and 2 was also found in certain social and household factors (Table 2). The role of stress stands out the most (35.9% in the Subgroup 1 vs. 12.5% in the Subgroup 2, $p < 0.05$), especially in everyday life (31.3% vs. 6.3%, $p < 0.05$). The presence of bad habits also turned out to be a significant factor (21.9% vs. 6.3%, $p < 0.05$).

According to infertility indicators, women of the Subgroup 1 have a slightly higher proportion of patients with primary infertility, infertility lasting more than 5 years, and unsuccessful attempts at ART in the anamnesis. However, the difference is not statistically significant (Table 3). A significant difference was established by the decrease in the ovarian reserve (32.8% in the Subgroup 1 vs. 12.5% in the Subgroup 2, $p < 0.05$) and the corresponding hormonal disorders: increased follicle-stimulating hormone (FSH) (21.9% vs. 6.3%, $p < 0.05$) and a decrease in anti-Müllerian hormone (AMG) (25.0% vs. 6.3%, $p < 0.05$).

Among somatic pathology in relation to the influence on the success of ART (Table 4), endocrine pathology stands out in particular (45.3% in the Subgroup 1 vs. 12.5% in the Subgroup 2, OR=5.80, CI 1.22–27.64, $p < 0.05$), in particular metabolic disorders (34.4% in the Subgroup 1 vs. 12.5% in the Subgroup 2, $p < 0.05$). A significant difference was also established in the frequency of liver diseases (21.9% vs. 6.3%, $p < 0.05$) and gastrointestinal tract diseases (23.4% vs. 12.5%, $p < 0.05$).

Table 3

Indicators of infertility in patients with «long-COVID» depending on the success of ART programs, %

Indicator	Subgroup 1, n=64		Subgroup 2, n=16		OR	LL CI	UV CI
	abs.n.	%	abs.n.	%			
Primary infertility	11	17.2	2	12.5	1.45	0.29	7.32
The duration of infertility is more than 5 years	10	15.6	2	12.5	1.30	0.25	6.60
One IVF attempt in history	11	17.2	2	12.5	1.45	0.29	7.32
2 or more IVF attempts in history	5	7.8	–	–	–	–	–
Decreased ovarian reserve	21	32.8*	2	12.5	3.42	0.71	16.45
FSH is above age norms	14	21.9*	1	6.3	4.20	0.51	34.62
AMH is below age norms	16	25.0*	1	6.3	5.00	0.61	40.91

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 ($p < 0.05$); the statistical significance of OR was not revealed.

Table 4

Somatic pathology of patients with «long-COVID» depending on the success of ART programs, %

Somatic pathology	Subgroup 1, n=64		Subgroup 2, n=16		OR	LL CI	UV CI
	abs.n.	%	abs.n.	%			
Endocrine pathology, in particular	29	45.3*	2	12.5	5.80#	1.22	27.64
- thyroid disease	17	26.6*	1	6.3	5.43	0.67	44.26
- diabetes	7	10.9	–	–	–	–	–
- metabolic disorders	22	34.4*	2	12.5	3.67	0.76	17.60
Pathology of the gastrointestinal tract	15	23.4*	2	12.5	2.14	0.44	10.51
Liver pathology	14	21.9*	1	6.3	4.20	0.51	34.62
Pathology of the urinary system	12	18.8	2	12.5	1.62	0.32	8.07
Cardiovascular pathology	12	18.8	1	6.3	3.46	0.42	28.82

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 ($p < 0.05$); the statistical significance of OR was not revealed.

Table 5

Peculiarities of the menstrual function of patients with «long-COVID» depending on the success of ART programs, %

Peculiarities of the menstrual function	Subgroup 1, n=64		Subgroup 2, n=16		OR	LL CI	UV CI
	abs.n.	%	abs.n.	%			
Amenorrhea	6	9.4	1	6.3	1.55	0.17	13.89
Duration of menstruation:							
- up to 3 days	13	20.3	1	6.3	3.82	0.46	31.66
- more than 6 days	11	17.2	1	6.3	3.11	0.37	26.09
Blood loss:							
- reduced	11	17.2	2	12.5	1.45	0.29	7.32
- reinforced	12	18.8	3	18.8	1.00	0.25	4.07
Cycle duration:							
- more than 30 days	8	12.5	2	12.5	1.00	0.19	5.24
- less than 24 days	11	17.2	2	12.5	1.45	0.29	7.32
Irregular cycle	16	25.0*	1	6.3	5.00	0.61	40.91
Insufficiency of the luteal phase	14	21.9*	1	6.3	4.20	0.51	34.62

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 ($p < 0.05$); the statistical significance of OR was not revealed.

In women with «long-COVID» and an unsuccessful ART attempt, a higher frequency of menstrual dysfunction was found (Table 5), namely a decrease in the duration of menstruation (20.3% vs. 6.3%) or, conversely, prolonged menstruation (17.2% vs. 6.3%). A significant difference was established for the frequency of an irregular cycle (25.0% vs. 6.3%, $p < 0.05$) and luteal phase insufficiency (21.9% vs. 6.3%, $p < 0.05$), which is often attributed to stress-induced disorders.

Accompanying gynecological pathology is also more often noted in patients with «long-COVID» in case of failure of ART programs (Table 6), especially this applies to urogenital infections, which were noted by 43.8% of patients in the Subgroup 1 (against 12.5% in the Subgroup 2, OR=5.44, CI 1.14–25.95, $p < 0.05$). Endometritis (21.9% vs. 6.3%, $p < 0.05$) and endometrial hyperplasia (23.4% vs. 6.3%, $p < 0.05$) were observed significantly more often, however, with an insignificant OR.

Accompanying gynecological pathology of patients with «long-COVID» depending on the success of ART programs, %

Table 6

Pathology	Subgroup 1, n=64		Subgroup 2, n=16		OR	LL CI	UV CI
	abs.n.	%	abs.n.	%			
Infections of the genitourinary sphere	28	43.8*	2	12.5	5.44#	1.14	25.95
Pathology of the endometrium:							
- endometritis	14	21.9*	1	6.3	4.20	0.51	34.62
- endometriosis	10	15.6	—	—	—	—	—
- endometrial hyperplasia	15	23.4*	1	6.3	4.59	0.56	37.70
Diseases of the cervix	11	17.2	2	12.5	1.45	0.29	7.32
Myoma of the uterus	17	26.6	2	12.5	2.53	0.52	12.32
Ovarian cysts	15	23.4*	1	6.3	4.59	0.56	37.70
Polycystic ovary syndrome	11	17.2	1	6.3	3.11	0.37	26.09

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.

Conclusions

Significant differences in the frequency of the main symptoms of «long-COVID» among patients with unsuccessful use of ART have been established. The symptoms: «depression, anxiety» (54.7% vs. 18.8%, OR=5.23, CI 1.36–20.14, $p < 0.05$) and «sleep disturbances» (59.4% vs. 31.3%, SD=3.22, CI 1.00–10.35, $p < 0.05$).

A significant difference was also found in social and household factors: the presence of stress (35.9% vs. 12.5%, $p < 0.05$), especially in everyday life (31.3% vs. 6.3%, $p < 0.05$). The presence of bad habits also turned out to be a significant factor (21.9% vs. 6.3%, $p < 0.05$).

A significantly higher frequency of decreased ovarian reserve (32.8% vs. 12.5%, $p < 0.05$) and corresponding hormonal disorders: increased FSH (21.9% vs. 6.3%, $p < 0.05$) and decreased AMH (25.0% vs. 6.3%, $p < 0.05$).

Among somatic pathology, endocrine pathology stands out (45.3% vs. 12.5%, OR=5.80, CI 1.22–27.64, $p < 0.05$), in particular metabolic disorders (34.4% vs. 12.5%, $p < 0.05$). A significant difference

was also established in the frequency of liver diseases (21.9% vs. 6.3%, $p < 0.05$) and gastrointestinal tract (23.4% vs. 12.5%, $p < 0.05$).

There is a higher frequency of menstrual disorders, namely a decrease in the duration of menstruation (20.3% vs. 6.3%) or, conversely, prolonged menstruation (17.2% vs. 6.3%), an irregular cycle (25.0% vs. 6.3%, $p < 0.05$) and luteal phase insufficiency (21.9% vs. 6.3%, $p < 0.05$). Urogenital infections were noted in 43.8% of patients (against 12.5%, OR=5.44, CI 1.14–25.95, $p < 0.05$).

Therefore, a significantly lower rate of success of ART programs in patients with «long-COVID» was established, which is due to the systemic impact of the coronavirus infection on the woman's body and reproductive function in particular. Risk factors for the ineffectiveness of ART programs have been established, among which stress, depression and anxiety, bad habits, endocrine pathology, metabolic disorders, liver pathology, menstrual cycle disorders, and urogenital infections are especially highlighted.

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Відомості про авторів:

Бойчук Олександра Григорівна — д.мед.н., проф., проф. каф. акушерства і гінекології імені І.Д. Ланового Івано-Франківського НМУ. Адреса: м. Івано-Франківськ, вул. Чорновола, 49. <https://orcid.org/0000-0003-4439-3099>.

Головчак Ігор Степанович — к.мед.н., доц. каф. акушерства і гінекології імені І.Д. Ланового Івано-Франківського НМУ. Адреса: м. Івано-Франківськ, вул. Чорновола, 49, КНП «МКПЦ ІФМР». <https://orcid.org/0000-0002-8076-0506>.

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