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## **LONG-COVID IMPACT ON THE REPRODUCTIVE HEALTH OF WOMEN WITH FERTILITY**

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Reproductive health is a fundamental human right crucial for the health, well-being, and quality of life of individuals, families, communities, society, and the state. To determine the possible impact of COVID-19 on women's reproductive health, we included 80 patients who came to the clinic of reproductive technologies for infertility treatment in a comprehensive examination and were divided into 2 groups. The main group consisted of 60 women after COVID-19 (10 patients with only a male infertility factor were excluded, and one patient refused to participate in the study); the comparison group consisted of 20 patients without a history of COVID-19. The study was carried out using the principles of the Declaration of Helsinki. The research protocol was approved by the institution's Local Ethics Committee, mentioned in the work. Informed consent was obtained from the women for the study. Among patients with infertility, a high frequency of long COVID has been established, the consequences of which are various disorders of somatic and reproductive health, which often arise precisely after suffering from the coronavirus disease. A significantly lower success rate of assisted reproductive technologies programs in these patients was established, which is due to the systemic impact of the coronavirus infection on the woman's body and reproductive function in particular.

**Key words:** reproductive function, COVID-19, long COVID, infertility, assisted reproductive technologies, pandemic.

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## **ВПЛИВ «ЛОНГ-COVID» НА РЕПРОДУКТИВНУ СФЕРУ ЖІНОК З НЕПЛІДДЯМ**

Репродуктивне здоров'я є основним правом людини, яке має вирішальне значення для здоров'я, благополуччя та якості життя окремих людей, сімей і спільнот, суспільства, держави в цілому. Для визначення можливого впливу COVID-19 на репродуктивне здоров'я жінок до комплексного обстеження ми включили 80 пацієнок, що звернулись у клініку репродуктивних технологій з приводу лікування безпліддя, яких розділили на 2 групи: основна група – 60 жінок після COVID-19 (виключили 10 пацієнок з тільки чоловічим фактором непліддя, одна пацієнтка відмовилась від участі в дослідженні), групу порівняння склали 20 пацієнок без COVID-19 в анамнезі. Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначеної в роботі установи. На проведення досліджень отримано інформовану згоду жінок. Серед пацієнок з непліддям встановлена висока частота «лонг-COVID», наслідками якого є різноманітні порушення соматичного та репродуктивного здоров'я, які часто виникали саме після перенесеного коронавірусного захворювання. Встановлена суттєво нижча частота успішності програм допоміжних репродуктивних технологій у цих пацієнок, яка обумовлена саме системним впливом коронавірусної інфекції на організм жінки та репродуктивну функцію зокрема.

**Ключові слова:** репродуктивна функція, COVID-19, лонг-COVID, непліддя, допоміжні репродуктивні технології, пандемія.

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One of the leading medical and social problems is protecting the reproductive health of childbearing age women because the female population is the country's primary demographic resource. One of the most critical demographic indices, the birth rate, is closely related to the stability of the socioeconomic system and confidence in the future [1].

Reproductive health refers to general well-being in all aspects of reproduction, including physical, emotional and social well-being, not just the absence of disease or bodily infirmity. The concept covers the full range of issues related to the reproductive system and its functions, including access to reproductive

and sexual health services, reproductive and sexual health education and information, family planning, and prevention, diagnosis and treatment of sexually transmitted infections. Reproductive health is a fundamental human right crucial for the health, well-being, and quality of individuals' life, families and communities, society, and the state [2, 3, 4].

The coronavirus disease 2019 (COVID-19) pandemic, caused by the acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has engulfed the entire world. COVID-19 is recognized as a pandemic caused by the rapid spread of the SARS-CoV-2 coronavirus, and it has become a serious challenge for the healthcare system worldwide. In particular, how the reproductive system can be directly or indirectly affected by SARS-CoV-2 in the long term remains to be studied [5, 6].

Understanding the specific mechanisms and consequences of direct and indirect effects of SARS-CoV-2 on reproductive health is highly relevant. One of the leading medical and social problems is the protection of the reproductive health of childbearing-age women because the female population is the primary demographic resource of the country [7, 8, 11].

Reproductive health is a fundamental human right crucial for the health, well-being, and quality of life of individuals, families, communities, society, and the state. The COVID-19 pandemic, caused by the acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has engulfed the entire world and led to unprecedented medico-social consequences due to specific features of the virus, such as its ability to evade the immunological response, tissue tropism, and the ability to affect various organs and systems [9, 10, 12].

**The purpose** of the study was to establish the mechanisms and consequences of direct and indirect effects of SARS-CoV-2 on a woman's reproductive health, in particular on the efficacy of using assisted reproductive technologies

**Materials and methods.** To determine the possible impact of COVID-19 on women's reproductive health, we included 80 patients who came to the clinic of reproductive technologies for infertility treatment in a comprehensive examination and were divided into 2 groups. The main group consisted of 60 women after COVID-19 (10 patients with only a male infertility factor were excluded, and one patient refused to participate in the study); the comparison group consisted of 20 patients without a history of COVID-19.

The "long COVID" diagnosis was made when symptoms were observed more than 12 weeks after the disease and were not associated with another pathology.

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

**Results of the study and their discussion.** The analysis of the distribution of the studied groups' patients by age showed that the largest proportion of patients with long COVID were aged between 30 and 34 years (48.8 %), while in the comparison group, there were most women aged 25–29 years (37.5 % versus 22.5 % in the main group,  $p < 0.05$ ). Among patients with long COVID, there are slightly more patients older than 35, but the difference with the comparison group is statistically unreliable (25.0 % vs. 17.5 %,  $p > 0.05$ ). Such differences may be due to the greater susceptibility of older age groups to infection and the severe consequences of COVID-19.

As for the specifics of infertility, the proportion of women with primary infertility is by 40 % lower among patients with long COVID. In the main group, the proportion of women with infertility lasting more than five years was significantly higher (21.3 % compared to 7.5 % among patients in the comparison group,  $p < 0.05$ ). Women in the main group were by two times more likely to have already had one (16.3 %) or two (6.3 %) unsuccessful IVF attempts (22.6 % vs. 10.0 %,  $p < 0.05$ ). The main group also has a significantly higher frequency of decreased ovarian reserve (28.8 % vs 10.0 %,  $p < 0.05$ ). By this diagnosis, there was a higher frequency of non-compliance with the age norms of follicle-stimulating drugs (18.8 % vs 5.0 %,  $p < 0.05$ ) and Anti-Mullerian hormones (21.3 % vs 7.5 %,  $p < 0.05$ ).

Patients with infertility and long COVID suffered from various somatic pathologies significantly more often than women in the comparison group (Table 1). Endocrine pathology stands out (35.0 % vs. 15.0 %, respectively,  $p < 0.05$ ), mainly due to metabolic disorders in a third of patients (31.6 % vs. 15.0 %,  $p < 0.05$ ), which are clinically manifested by overweight and obesity. A significant difference between groups was also found for hepatobiliary pathology (18.8 % vs. 7.5 %,  $p < 0.05$ ). The incidence of thyroid diseases, diabetes mellitus, and pathologies of the gastrointestinal tract and urinary system is also increased, but the difference is not statistically significant. The revealed difference between groups in terms of somatic morbidity is multifactorial. On the one hand, it is the older age of women. On the other hand, these diseases are risk factors for COVID-19 and can also deepen or even develop against the background of long COVID.

Table 1

**Somatic pathology of patients with infertility, %**

	After COVID-19, n=60		Without a history of COVID-19, n=20	
	abs.n.	%	abs.n.	%
Endocrine pathology, in particular	21	35.0*	3	15.0
Thyroid diseases	11	18.3	2	10.0
Diabetes mellitus	4	6.0	1	2.5
Metabolic disorders	19	31.6*	3	15.0
Gastrointestinal tract pathology	12	20.0	2	10.0
Liver pathology	9	15.0*	1	2.5
Urinary system pathology	8	13.3	1	2.5
Cardiovascular pathology	9	15.0	2	10.0

Notes: \* – the difference is significant in the group of patients without COVID-19 ( $p < 0.05$ )

Today, a woman's menstrual function is considered a sensitive marker of a woman's physical, emotional and mental health. Violations of all these health aspects are characteristic of long COVID. According to our data, a significantly higher frequency of menstrual dysfunction was noted after suffering from COVID-19. Secondary amenorrhea is due to several reasons, among which stress stands out as a cause of functional hypothalamic amenorrhea, which is noted by three times more often in women of the main group (8.8 %). Changes in the duration of menstruation and the level of blood loss were observed. Patients in the group after COVID-19 significantly more often indicated that the duration of menstruation was 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 % relative to 7.5 %,  $p < 0.05$ ). The frequency of irregular cycles was almost by 3 times higher (21.3 % vs. 7.5 %,  $p < 0.05$ ), and luteal phase insufficiency was more than by 3 times higher (18.8 % vs. 5.0 %, respectively,  $p < 0.05$ ). In general, more than a third of patients with long COVID indicated one or another violation of the menstrual cycle (35.0 % vs. 12.5 % in women without a history of COVID-19,  $p < 0.05$ ), and almost half (15.8 %) of them indicated the occurrence of these symptoms precisely after suffering from COVID-19.

The high prevalence of genitourinary infections in patients after suffering from COVID-19 is noteworthy (33.3 % vs 15.0 % in women with infertility without a history of COVID-19,  $p < 0.05$ ), which may be due to changes in the immune system, dysbacteriosis and other disorders caused by long COVID. The frequency of such pathologies as endometritis (23.3 %) and endometrial hyperplasia (20.0 %) is increased, but not reliably. Significantly increased frequency of uterine fibroids (31.6 % vs. 15.0 %,  $p < 0.05$ ).

Table 2

**Concomitant gynecological pathology in infertility, %**

	After COVID-19, n=60		Without a history of COVID-19, n=20	
	abs.n.	%	abs.n.	%
Urinary-genital infections	20	33,3*	3	15.0
Endometrial pathology				
– endometritis	14	23.3	4	20.0
– endometriosis	8	13.3	2	10.0
– endometrial hyperplasia	16	26.6	4	20.0
Diseases of the cervix	13	21.6	2	10.0
Uterine fibroids	19	31,6*	3	15.0
Ovarian cysts	16	26.6	4	10.0
Polycystic ovary syndrome	11	18.3	4	10.0

Notes: \* – the difference is significant in the group of patients without COVID-19 ( $p < 0.05$ )

Infertility in the examined patients was often associated with various gynecological diseases. The first places in the structure of gynecological morbidity are occupied by inflammatory diseases of the genital organs in women (endometritis, salpingitis, oophoritis), which remain the leading causes of impaired fertility. Yes, chronic endometritis can be asymptomatic, but it occurs in approximately 40 % of infertile patients and is responsible for repeated implantation failure and repeated miscarriages [2, 4, 13].

Although the link between endometriosis and infertility as a matter of ultimate cause and effect is still debatable, it is clinically recognized and well supported by scientific studies [9, 12].

After appropriate preparation, all women of the main group and the comparison group were included in IVF programs. Patients with long COVID had significantly worse results. Thus, in every fifth patient, the number of received oocytes was four or less (the so-called poor ovarian response), while in the comparison group, only one woman had such a result, which was 5.0 % (vs 38.3 % in the main group,

$p < 0.05$ ). Ovarian response (5–8 mature oocytes) was insufficient in more than a third of women in the main group (41.6 % vs. 15.0 % in the comparison group,  $p < 0.05$ ). Oocytes with cytoplasmic and extracytoplasmic pathology were found in a third of patients (36.6 % vs. 15.0 %, respectively,  $p < 0.05$ ).

Biochemical pregnancy was recorded in a quarter of patients with long COVID, which is significantly less than in women without a history of COVID-19 (41.6 %,  $p < 0.05$ ). Accordingly, clinical pregnancy was diagnosed in 11 (18.3 %) women of the main group and 9 (45.0 %) in the comparison group ( $p < 0.05$ ), and 2 women in the main group lost the pregnancy in the 1st trimester. At the same time, all 16 women in the comparison group carried the pregnancy to term before the child's birth. Live birth was recorded in 11 (18.3 %) women of the main group against 11 (55.0 %) of the comparison group ( $p < 0.05$ ).

### Conclusion

Patients with infertility and long COVID have more pronounced disorders of the reproductive sphere than women without a history of COVID-19. Namely: a decrease in the ovarian reserve, various disorders of the menstrual cycle, in particular, amenorrhea, an irregular cycle and luteal phase insufficiency, a high prevalence of urogenital infections.

Such low results of assisted reproductive technology programs among women of the main group are, to some extent, due to reproductive health disorders as a result of the COVID-19 negative impact with the development of a symptom complex called long COVID.

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