

Effectiveness of modified therapy for post-COVID ovarian-endometrial dysregulative cycle disorders

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Post-COVID syndrome has an impact on women of reproductive age, causing menstrual cycle disorders that are pathophysiologically associated with the multisystem consequences of COVID-19, including endothelial dysfunction, microthrombosis, and neuroendocrine disturbances affecting the function of the hypothalamic-pituitary-gonadal and hypothalamic-pituitary-adrenal axes. Existing treatment protocols are primarily focused on classical causes such as hormonal imbalance and structural abnormalities, but they often fail to take into account the vascular, immune, and neuroendocrine mechanisms induced by SARS-CoV-2. The aim of our study was to evaluate the clinical efficacy and tolerability of a pathogenetically based modified therapy for menstrual cycle disorders in women after COVID-19 compared with standard treatment protocols. The study included 158 women of reproductive age with menstrual disorders in the post-COVID period. Patients of group 2 (n = 78) received treatment according to the Unified Clinical Protocols of the Ministry of Health of Ukraine, clinical guidelines, and international recommendations. Patients of group 1 (n = 80) received a modified comprehensive pathogenetic regimen that included hormonal, vascular-metabolic, neuroendocrine, and micronutrient support. Treatment schemes were adapted depending on the type of disorder (polymenorrhea, hypomenorrhea, menometrorrhagia, opsoligomenorrhea, secondary amenorrhea). According to the results of the study, the relapse rate after treatment in group 1 was significantly lower for all types of disorders: polymenorrhea – 13.3% vs. 73.3%, hypomenorrhea – 8.7% vs. 69.6%, opsoligomenorrhea – 16% vs. 56%, menometrorrhagia – 23.5% vs. 76.5%, amenorrhea – 20% vs. 80%. Complete normalization of menstrual function was observed in 72–84% of women in the main group compared with 33–52% in the control group. A decrease in the need to modify the therapeutic regimen and a significant improvement in treatment tolerability were also recorded ($P < 0.05$). Pathogenetically based personalized therapy for menstrual cycle disorders in women after COVID-19 provides significantly better outcomes than standard protocols. Elimination of vascular, immune, and neuroendocrine consequences of COVID-19 is a key factor in the effective restoration of menstrual function in women of reproductive age with post-COVID menstrual disorders.

Key words: Long-COVID; post-COVID syndrome; menstrual cycle disorders; reproductive health; vitamin and micronutrient supplementation; folic acid; quality of life; endothelial dysfunction.

INTRODUCTION

The post-COVID-19 condition (Long COVID) has been officially recognized by the World Health Organization (WHO) as a state characterized by symptoms that usually begin within three months after the acute infection and last for at least two months, significantly limiting daily functioning and quality of life – particularly in women of reproductive age [1, 2].

An increasing body of evidence indicates an

association between post-COVID-19 condition and menstrual cycle alterations, ranging from changes in cycle length and regularity to abnormal uterine bleeding (AUB). Several clinical case series and systematic reviews report menstrual disturbances during the first cycles after infection, while newer population-based studies associate the post-COVID-19 condition with an elevated risk of AUB and greater variability of cycle-related symptoms. These findings highlight both the clinical relevance

and the systemic nature of the problem [3–5].

Pathophysiologically, COVID-19 is considered a multisystem disease, in which endothelial dysfunction and microthrombosis play a central role, potentially impairing endometrial and myometrial microcirculation and contributing to both hypermenstrual and hypomenstrual disorders [6, 7].

Neuroendocrine mechanisms also contribute: dysregulation of the hypothalamic-pituitary-gonadal and hypothalamic-pituitary-adrenal axes under the influence of infection and/or chronic stress may explain reduced ovulatory function, oligo/amenorrhea, and cyclic variability of symptoms in women with post-COVID syndrome [8, 9].

At the same time, existing treatment protocols for amenorrhea, oligomenorrhea, or menorrhagia remain primarily focused on classical etiologies – ovulatory dysfunction in polycystic ovary syndrome (PCOS), hypothalamic suppression due to weight loss or stress, hormonal imbalance in hypothyroidism, and AUB management of structural and functional origin according to the PALM-COEIN (FIGO) classification [10, 11]. However, these approaches only partially address the virus-induced vascular, immune, and neuroendocrine pathways characteristic of the post-COVID state, potentially limiting the effectiveness of standard treatment schemes in certain patients. This creates a clinical need for pathogenetically oriented, multicomponent strategies that integrate hormonal, endothelial-protective/metabolic, and psychoendocrine correction.

Despite the growing evidence linking SARS-CoV-2 infection with menstrual disorders, there are still no standardized or consensus-based treatment guidelines specifically addressing post-COVID associated menstrual dysfunctions; most clinicians continue to apply conventional approaches to diagnosis and management [3, 4]. The existing gap between pathogenetic understanding – involving endothelial dysfunction, microthrombosis, neuroendocrine dysregulation, and chronic stress – and therapeutic practice underscores the need to develop and evaluate pathogenetically grounded, comprehensive treatment regimens.

The aim of our study was to assess the clinical efficacy and tolerability of a pathogenetically based, modified therapeutic approach for menstrual cycle disorders in women after COVID-19 compared with standard treatment protocols.

METHODS

The investigation was conducted during 2023–2024 in the Department of Minimally Invasive Surgery, State Scientific Institution “Scientific and Practical Center of Preventive and Clinical Medicine” of the State Administration of Affairs (Kyiv, Ukraine). All procedures involving human participants were performed in accordance with the ethical principles of the Declaration of Helsinki (WMA, 2000), the EEC Directive No. 609 (1986), and the ICH-GCP Guidelines (1996). The study also adhered to the national regulatory documents of the Ministry of Health of Ukraine (Orders No. 690 dated 23.09.2009, No. 944 dated 14.12.2009, and No. 616 dated 03.08.2012). Each participant provided written informed consent for participation and data processing. Ethical approval for this study was obtained from the Ethics Committee of the hosting institution (Protocol No. 1, dated 31.01.2022).

Inclusion criteria: Women of reproductive age (18–45 years) with a documented history of COVID-19 and newly developed menstrual irregularities within six months after recovery. **Additional criteria** included regular menstrual cycles prior to infection, absence of pregnancy, and no hormonal contraceptive use within six months before enrollment. **Exclusion criteria:** Women with organic pelvic pathology, severe somatic diseases, or endocrine disorders capable of independently affecting menstrual function were excluded, as were those planning pregnancy during follow-up.

Group 2 ($n = 78$) received treatment according to the Unified Clinical Protocols of the Ministry of Health of Ukraine (Order No. 353 of April 13, 2016), the Clinical Guideline “Polycystic Ovary Syndrome (PCOS)” No.

00953, and FIGO recommendations (PALM-COEIN classification).

Group 1 ($n = 80$) received a modified comprehensive pathogenetic regimen that combined hormonal, vascular-metabolic, neuroendocrine, and micronutrient support. Patients with polymenorrhea received vitamin D₃, magnesium B₆, L-arginine, quercetin in addition to standard recommendations; patients with hypomenorrhea - combined oral contraceptive (COC) based on natural estrogens, melatonin, vitamin D₃, folic acid and vitamin B₁₂, magnesium B₆; patients with menometrorrhagia - COC based on natural estrogens, vitamin D₃, magnesium B₆, L-arginine, quercetin, iron; patients with opsologomenorrhea - COC based on natural estrogens, melatonin, vitamin D₃, folic acid and vitamin B₁₂, magnesium B₆, L-arginine; patients with amenorrhea - melatonin, vitamin D₃, folic acid and vitamin B₁₂, magnesium B₆, L-arginine, quercetin, COC based on natural estrogens. Administration of vitamin D₃ was carried out under laboratory monitoring of serum 25(OH)D concentrations. The follow-up period after treatment ranged from 3 to 6 months.

Data were processed using Statistica 13.0 (StatSoft Inc., USA) and SPSS v.26.0 (IBM Corp., USA). Descriptive statistics were

applied, as well as methods for comparing frequencies (χ^2 test or Fisher's exact test), mean values (Student's t -test), and calculating 95% confidence intervals (95% CI). Differences between groups were considered statistically significant at $P < 0.05$.

RESULTS

According to the obtained data, the clinical outcomes of treatment for different types of menstrual disorders in women with post-COVID syndrome in group 1 (who received pathogenetically based therapy) and group 2 (who received treatment according to standard protocols) were as follows.

In women with polymenorrhea (Fig. 1) who received personalized therapy (group 1), the recurrence rate was only 13.3%, compared to 73.3% in group 2 (standard treatment). Complete normalization of the menstrual cycle was observed in 80% of patients in the main group, which is more than twice as high as in the control group (33.3%). The need to modify the treatment regimen occurred in only 20% of women receiving personalized therapy, while in the standard treatment group this rate reached 93.3%. Adverse effects (edema, mastodynia,

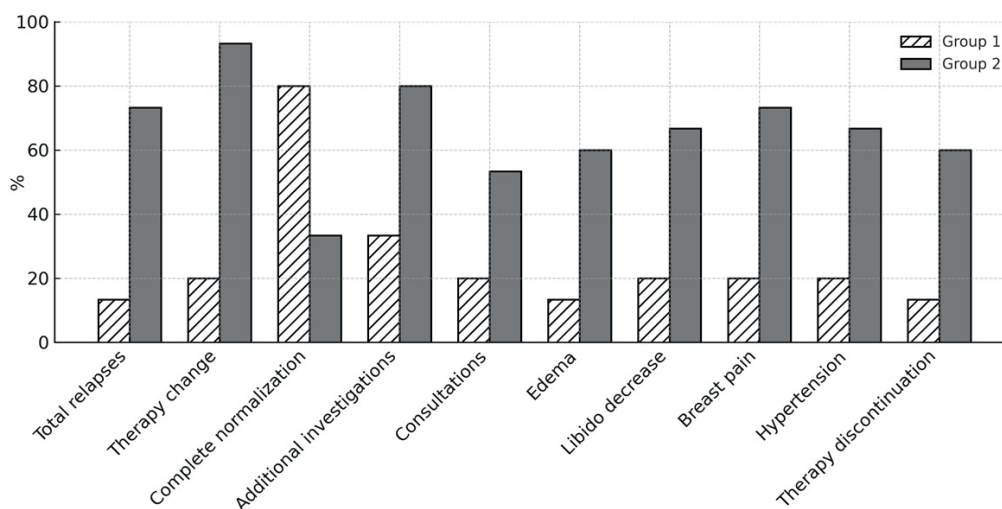


Fig. 1. Comparative clinical outcomes and therapy-related complications in women with polymenorrhea and post-COVID syndrome.

Notes: Differences were statistically significant at $P < 0.05$

increased blood pressure) were observed only in isolated cases (15%) in group 1, compared with 60-70% in the control group.

Among women with hypomenorrhea (Fig. 2), relapses occurred in only 8.7% of cases in group 1, compared with 69.6% in group 2. Complete normalization of the menstrual cycle was achieved in 82.6% of patients in the main group versus 47.8% in the control group. The need to modify the therapy was observed in 47.8% of women in group 1 and 87% in group 2. Adverse reactions (edema, breast tenderness, hypertension) were reported in 15-20% of cases in group 1 compared with 60-70% in group 2.

In women with opsooligomenorrhea (Fig. 3), the recurrence rate in group 1 was 16%, compared to 56% in group 2. Complete normalization of the menstrual cycle was observed in 84% of patients in the main group versus 52% in the control group. The need to modify therapy was noted in only 12% of cases in group 1, while in group 2 this indicator reached 64%.

The incidence of hormonal therapy-related complications (edema, breast pain, increased blood pressure) was 18% in group 1 and exceeded 60% in group 2.

In patients with menometrorrhagia (Fig. 4), post-treatment recurrences were recorded in

23.5% of women in group 1 and in 76.5% of those in group 2. Complete normalization of menstrual function was achieved in 76.5% of patients in the main group compared to 35.3% in the control group. The need to modify therapy decreased more than threefold – 29.4% versus 88.2%, respectively. The frequency of adverse effects (venous thrombosis, inflammation, breast pain, elevated blood pressure) was 20% in group 1 compared with 60-70% in group 2.

In patients with amenorrhea (Fig. 5), the recurrence rate in group 1 was 20%, compared to 80% in group 2. Complete normalization of menstrual function was achieved in 72% of patients in the main group versus 36% in the control group. The need to modify the therapeutic regimen was 16% in group 1 and 68% in the control group. The frequency of hormonal therapy-related adverse effects (decreased libido, breast tenderness, malaise, hypertension) was significantly lower in group 1 – 15-20%, whereas in group 2 it exceeded 60%.

DISCUSSION

According to the data presented in Figures 1-5, the recurrence rate after treatment in group 1 (pathogenetically based therapy) was significantly

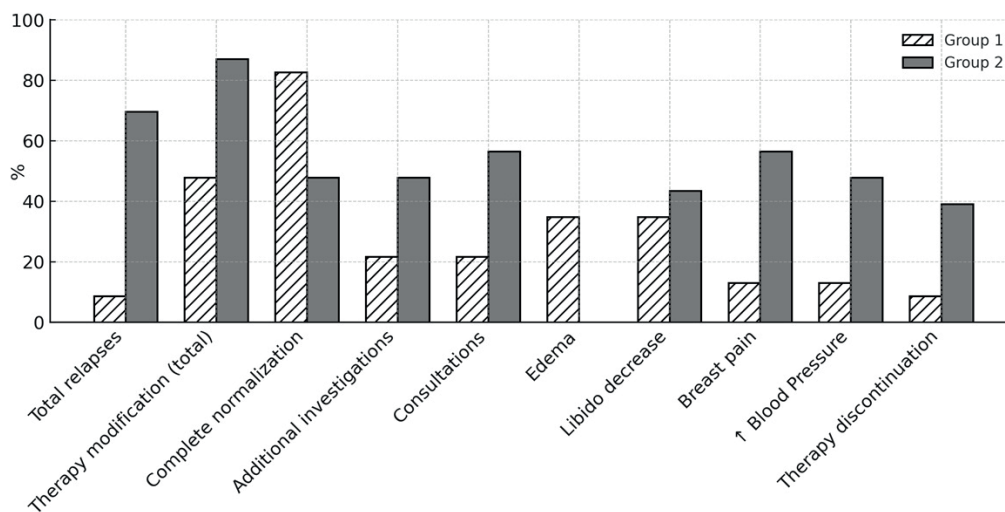


Fig. 2. Comparative clinical outcomes and hormonal therapy-related complications in women with hypomenorrhea and post-COVID syndrome.

Notes: Differences were statistically significant at $P < 0.05$

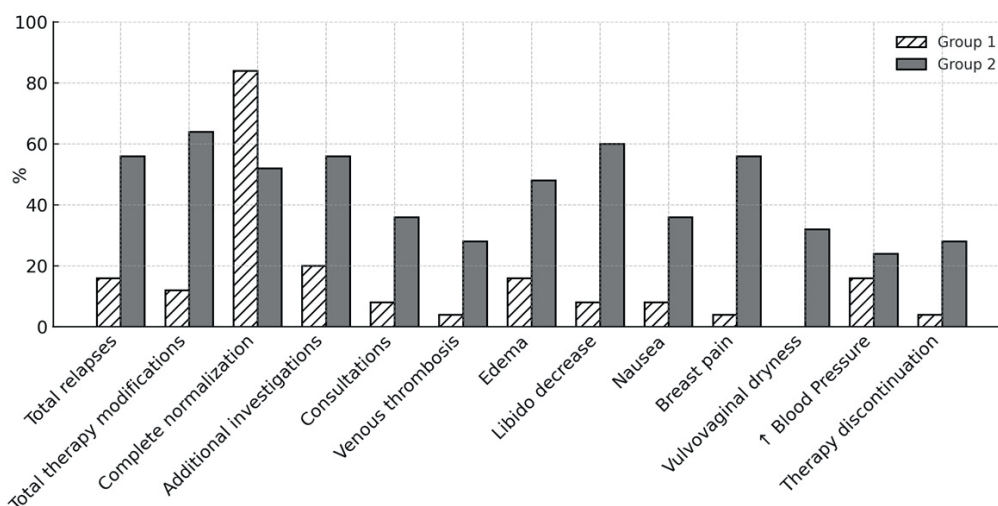


Fig. 3. Comparative clinical outcomes and hormonal therapy-related complications in women with opsooligomenorrhea and post-COVID syndrome.

Notes: Differences were statistically significant at $P < 0.05$

lower across all types of menstrual disorders: polymenorrhea – 13.3% vs. 73.3%, hypomenorrhea – 8.7% vs. 69.6%, opsooligomenorrhea – 16% vs. 56%, menometrorrhagia – 23.5% vs. 76.5%, and amenorrhea – 20% vs. 80%.

Complete normalization of menstrual function was observed in 72-84% of women in the main group receiving pathogenetically guided therapy, compared with 33-52% among those treated according to standard protocols. A reduced need for therapy

modification and a marked improvement in treatment tolerability were also recorded.

The obtained results demonstrate that pathogenetically based therapy for menstrual cycle (MC) disorders in women after COVID-19 provides significantly better clinical outcomes compared with standard treatment protocols.

According to the FIGO, ESHRE, and Ministry of Health of Ukraine guidelines, current standards for the management of amenorrhea, oligomenorrhea,

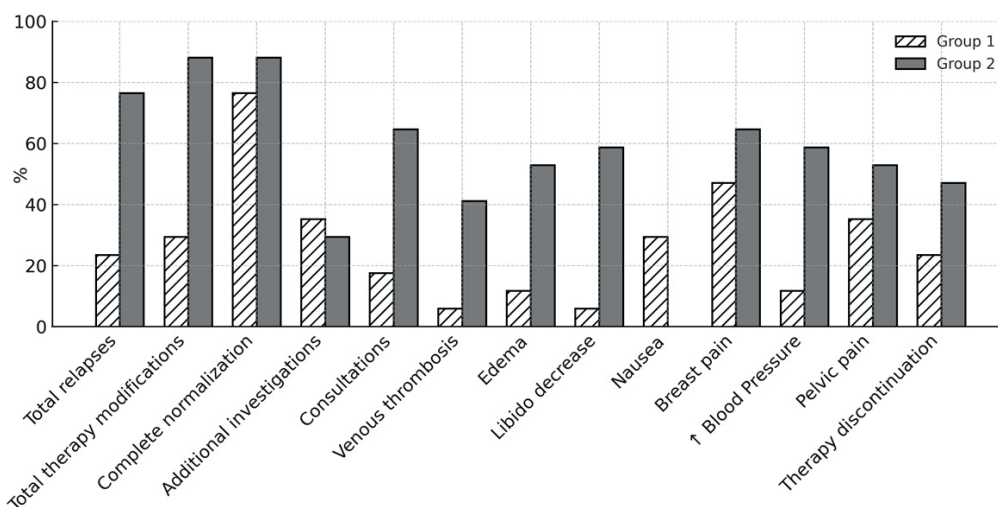


Fig. 4. Comparative clinical outcomes and hormonal therapy-related complications in women with menometrorrhagia and post-COVID syndrome.

Notes: Differences were statistically significant at $P < 0.05$

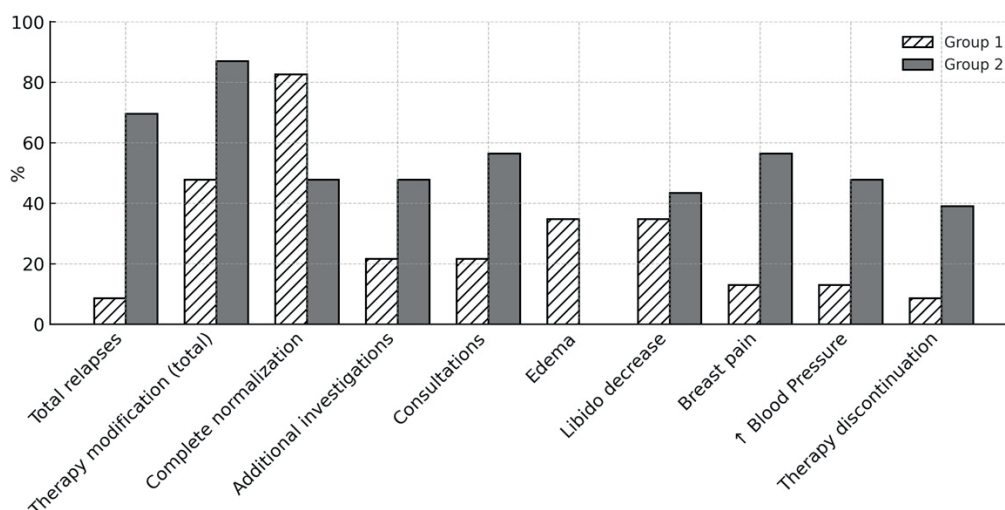


Fig. 5. Comparative clinical outcomes and hormonal therapy-related complications in women with amenorrhea and post-COVID syndrome.

Notes: Differences were statistically significant at $P < 0.05$

or menometrorrhagia are primarily focused on classical endocrine or structural causes such as PCOS, hypothyroidism, hyperprolactinemia, uterine fibroids, and polyps [10–13]. However, these protocols do not consider virus-induced mechanisms—including endothelial dysfunction, hypercoagulability, and cytokine-mediated inflammation—which are closely linked to the development of menstrual disturbances during the post-COVID period.

It has been proven that SARS-CoV-2 causes generalized endothelial dysfunction—damage to the vascular endothelium, activation of thrombin, and formation of microthrombi—which disrupts endometrial perfusion and leads to hypomenstrual or hypermenstrual disorders [14]. Moreover, due to the expression of ACE2 receptors in the hypothalamus and pituitary gland, the virus can directly affect cells of the hypothalamic–pituitary–ovarian axis, resulting in central hypogonadotropic amenorrhea [8].

It is also well established that after COVID-19, endocrine dysregulation frequently occurs, including elevated prolactin levels, reduced T_3/T_4 with elevated TSH, and autoimmune activation of the thyroid gland, as confirmed by recent endocrinological studies [15, 16]. Furthermore, chronic psychoemotional stress

contributes to hypothalamic–pituitary–gonadal axis dysfunction through excessive secretion of CRH and cortisol, which suppress GnRH pulsatility and ovulation [9].

Thus, in post-COVID patients, a comprehensive, multifactorial therapeutic approach is required—aimed not only at restoring hormonal balance but also at correcting endothelial dysfunction, oxidative stress, and neuroendocrine imbalance [17]. The combination of hormonal therapy with antioxidants and adaptogens (vitamin D_3 , magnesium, melatonin, L-arginine, quercetin, folic acid, etc.) significantly accelerates the recovery of regular menstrual cycles. In addition, the use of natural estrogen formulations rather than high-dose synthetic estrogens reduces the risk of thrombotic complications.

The results of our study confirm the leading role of the above factors in the development of menstrual disorders and prove the key role of an individualized, multicomponent approach in restoring women's reproductive health in the post-COVID period.

CONCLUSION

Women with menstrual disorders after COVID-19 demonstrate a more complex and recurrent

clinical course, with an increased number of medical interventions, therapy adjustments, and adverse reactions to standard treatment.

The more complex or clinically unstable the type of menstrual disorder, particularly menometrorrhagia compared to polymenorrhea, the lower the likelihood of achieving full cycle normalization after a standard course of treatment.

Furthermore, women with menstrual disorders in women with post-COVID syndrome treated with standard protocols demonstrate higher rates of complications, relapses, therapeutic instability, and greater need for clinical support, highlighting the importance of individualized, pathogenetically informed treatment approaches.

Modified treatment approaches taking into account the key pathogenetic mechanisms of menstrual cycle disorders, endothelial, immune and endocrine, which combine hormonal, vascular-metabolic and psycho-emotional support (hormonal correction with the use of natural estrogens (estetrol and drospirenone); vascular-metabolic support (L-arginine, quercetin, vitamin D₃); neuroendocrine stabilization (melatonin, magnesium-B₆, folic acid, vitamin B₁₂); psycho-emotional support (psychotherapy, sleep normalization, relaxation practices) are more effective than standard protocols.

The developed approach may serve as a foundation for updating clinical guidelines on the management of menstrual disorders in women with post-COVID syndrome.

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The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or

financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of co-authors of the article.

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ЕФЕКТИВНІСТЬ МОДИФІКОВАНОЇ ТЕРАПІЇ ПОСТКОВІДНИХ ОВАРІАЛЬНО-ЕНДОМЕТРІАЛЬНИХ ДИСРЕГУЛЯТИВНИХ РОЗЛАДІВ ЦИКЛУ

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Постковідний синдром впливає на жінок репродуктивного віку, спричиняючи порушення менструального циклу, які патофізіологічно зумовлені мультисистемними наслідками COVID-19, зокрема ендотеліальною дисфункцією, мікротромбозом і нейроендокринними порушеннями, що впливають на функціонування осі гіпоталамо-гіпофізарно-гонадної та гіпоталамо-гіпофізарно-наднирковозалозної. Наявні протоколи лікування орієнтовані переважно на класичні причини – гормональний дисбаланс і структурні зміни – проте часто не враховують судинно-імунні та нейроендокринні механізми, індуковані вірусом SARS-CoV-2. Метою нашого дослідження було оцінити клінічну ефективність та переносимість патогенетично обґрунтованої модифікованої терапії порушень менструального циклу у жінок після перенесеного COVID-19 порівняно зі стандартними протоколами лікування. У дослідження включено 158 жінок репродуктивного віку з менструальними порушеннями у постковідному періоді. Пацієнтки 1-ї групи (n = 78) отримували лікування відповідно до уніфікованих клінічних протоколів МОЗ України, клінічних настанов та рекомендацій, а 2-ї (n = 80) – модифіковану комплексну патогенетичну схему, що включала гормональну, судинно-метаболическу, нейроендокринну та мікронутрієнтну підтримку. Схеми лікування адаптовано залежно від типу порушення (поліменорея, гіпоменорея, менометрорагія, олігоопсоменорея, вторинна аменорея). За результатами дослідження частота рецидивів після лікування у 1-ї групі була достовірно нижчою для всіх типів порушень: поліменорея – 13,3 щодо 73,3%, гіпоменорея – 8,7 щодо 69,6%, опсоолігоменорея – 16 щодо 56%, менометрорагія – 23,5 щодо 76,5%, аменорея – 20 щодо 80%. Повна нормалізація менструальної функції спостерігалась у 72–84% жінок основної групи щодо 33–52% у контрольній. Також зафіксовано зниження потреби у зміні терапевтичного режиму та покращення переносимості лікування. Патогенетично обґрунтована персоналізована терапія порушень менструального циклу у жінок після перенесеного COVID-19 забезпечує достовірно кращі результати, ніж стандартні протоколи. Усунення судинних,

імуних та нейроендокринних наслідків COVID-19 є ключовим чинником ефективного відновлення менструальної функції у жінок репродуктивного віку з постковідними менструальними розладами.

Ключові слова: постковідний синдром; порушення менструального циклу; репродуктивне здоров'я; дотація вітамінів і мікроелементів; фолієва кислота; якість життя; ендотеліальна дисфункція.

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