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Pathogenetically targeted restoration of the menstrual cycle in women after COVID-19

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Menstrual disorders are increasingly being observed in women recovering from COVID-19. Mechanisms include neuroendocrine suppression, endothelial dysfunction, and systemic inflammation, which may transiently impair hypothalamic-pituitary-ovarian axis activity and endometrial perfusion. The aim of our study was to substantiate and evaluate the effectiveness of a pathogenetically targeted personalized rehabilitation program for restoring menstrual function in women after COVID-19. Women of reproductive age (n = 82) with menstrual disorders that developed within six months after COVID-19 participated in the study. The personalized protocol included hormonal correction (dopamine agonists, levothyroxine, estrogen-progestagen therapy according to indications), metabolic and antioxidant support (vitamin D_3, N-3 PUFAs, folic acid and vitamin B_{12}, magnesium-B_6 complex), as well as chronobiotic and psychological regulation (melatonin, cognitive-behavioral therapy, sleep hygiene). The primary endpoint was the restoration of a regular cycle (21-35 days); secondary endpoints were hormonal normalization and improvement in SF-36 quality of life. Regular menstrual cycles were restored in 90.2% of women within 3.9 ± 1.6 months. Hormonal normalization (euthyroid state, normoprolactinemia, physiological level of sex hormones) was achieved in 80.5%. Total Short Form-36 Health Survey questionnaire *scores (SF-36) increased from 58.4 ± 12.7 to 83.8 ± 8.9. Side effects were mild and transient (9.8%). Personalized rehabilitation, including hormonal, metabolic, antioxidant, and psychoneuroendocrine correction, significantly improved reproductive recovery after COVID-19. Vitamin and micronutrient supplementation, particularly folic acid, magnesium, melatonin, and vitamin D_3 is pathogenetically justified and promotes faster normalization of menstrual and hormonal function in women of reproductive age.*

Key words:SARS-CoV-2; COVID-19; post-COVID syndrome; menstrual cycle disorders; reproductive health; vitamin and micronutrient supplementation; folic acid; quality of life.

INTRODUCTION

Menstrual disorders are notably more prevalent among post-COVID women than in the general population. For example, a 2023 study in China showed that 51% of women reported menstrual irregularities within three months post-infection [1, 2]. Other international data confirm changes such as cycle lengthening, delayed or early menses, and altered bleeding patterns, particularly in severe or long COVID cases, where prevalence may exceed 80% [3, 4]. Though often transient, these disturbances may persist for several cycles [5, 6]. The pathogenesis of COVID-related menstrual disorders is multifactorial, involving several interrelated pathways.

Neuroendocrine mechanism. Severe COVID-19 triggers systemic inflammation and stress responses, leading to elevated pro-inflammatory cytokines (e.g., ILs, TNF-α) and cortisol levels, which suppress hypothalamic GnRH secretion [7]. This reduces LH and FSH pulse activity, causing transient hypogonadotropic hypogonadism. Clinically, this mimics functional hypothalamic amenorrhea — an adaptive, reversible response to stress. Infected women often show temporary anovulation and luteal phase deficiency [8], with decreased estradiol and progesterone during acute illness [7]. However, ovarian reserve markers (AMH, FSH, inhibin B) typically remain age-appropriate [5–7],

indicating that SARS-CoV-2 likely disrupts neuroendocrine regulation without depleting the follicular pool.

Immunovascular mechanism. SARS-CoV-2 provokes systemic inflammation and direct endothelial injury, resulting in endothelial dysfunction and microvascular thrombosis. Elevated D-dimer and coagulopathy are common in acute COVID-19, with microthrombi found in multiple organs, including lungs, kidneys, and placenta. Similar processes may affect the endometrial and ovarian microvasculature [9–11], causing transient ischemia that disrupts endometrial maturation and ovulation. Although intra-ovarian thrombosis has not been directly confirmed, clinical data support a vascular contribution [12, 13]. Notably, acupuncture – known to enhance pelvic blood flow — reduced menstrual disorders in post-COVID women (41% vs 65%), highlighting the role of vascular and autonomic mechanisms in reproductive recovery [14].

Direct effects on reproductive organs. SARS-CoV-2 uses ACE2 receptors – expressed in the ovaries, uterus, and thyroid – to enter host cells, suggesting potential viral tropism during viremia [15]. Although widespread ovarian infection hasn't been confirmed, case reports and *in vitro* studies indicate viral-induced alterations. In granulosa cells from post-COVID women, inflammatory gene expression was altered, suggesting a disrupted follicular environment that may affect oocyte maturation and steroidogenesis [5, 7, 8]. These changes appear reversible and unlikely to reduce ovarian reserve but may temporarily impair fertility. More clearly established is the virus's impact on endocrine glands: meta-analyses show thyroid dysfunction in ~15% of acute COVID-19 cases, especially severe ones, due to thyroiditis or non-thyroidal illness syndrome [15]. Even mild hypothyroidism can cause menstrual disturbances, including anovulation and amenorrhea. Thus, COVID-19 may act as a multifactorial trigger for endocrine dysregulation affecting reproductive function.

Currently, there are no official clinical guidelines for managing menstrual disorders following COVID-19, and existing research remains limited. Therefore, further studies are urgently needed to consolidate available evidence and develop evidence-based diagnostic and therapeutic strategies for reproductive rehabilitation in affected women.

The aim of this study to substantiate a pathogenetically targeted treatment strategy aimed at restoring the menstrual cycle in women after COVID-19.

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.

The study group consisted of 82 women (mean age 31.4 ± 6.8 years; P = 0.523). All participants underwent a comprehensive clinical and laboratory evaluation including: anamnesis with assessment of COVID-19 severity and recovery course; anthropometric measurements (height, weight, BMI); general and gynecological examination; transvaginal ultrasonography of pelvic organs; laboratory testing, including hormonal profiling: luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, progesterone, prolactin, thyroid-stimulating hormone (TSH), and free thyroxine (fT4).

A pathogenetically based individualized rehabilitation program was implemented, comprising three major components:

1. Hormonal correction therapy was individualized according to the menstrual disorder type and hormonal profile:

Hypoestrogenism – low-dose estrogens and progestogens;

Hyperprolactinemia – dopamine receptor agonists (bromocriptine 2.5-5 mg/day or cabergoline 0.25 mg 1-2 times/week);

Subclinical hypothyroidism – levothyroxine 25-50 µg/day under TSH monitoring.

2. Metabolic and mitochondrial support

Lifestyle and metabolic management: individualized nutrition and physical activity programs;

Insulin resistance: metformin 500-1000 mg twice daily;

Antioxidant therapy: vitamin D_3 (2000-4000 IU/day), n-3 polyunsaturated fatty acids (1000 mg/day), α-lipoic acid (600 mg/day);

Folate complex: folic acid 1000 µg and vitamin B_{12} 200 µg/day to enhance methylation and endothelial function;

Magnesium-B_6 complex: 1-2 tablets/day (providing ≈ 300-400 mg Mg) for neuroendocrine stabilization and prolactin regulation.

3. Chronobiotic and psychoneuroendocrine regulation

Melatonin 3-6 mg nightly (1-2 h before sleep) for circadian rhythm normalization, antioxidant protection, and LH-FSH axis stabilization;

Psychological support: cognitive-behavioral therapy (CBT) and relaxation techniques;

Sleep hygiene: consistent bedtime, reduced screen exposure, and avoidance of stimulants.

The primary endpoint was restoration of a regular menstrual cycle (21-35 days) within 6 months. Secondary endpoints included normalization of hormonal parameters (prolactin, TSH, estradiol, progesterone), reduction in post-COVID symptom burden, and improvement in quality of life assessed by the Short Form-36 Health Survey questionnaire (SF-36).

Statistical analysis. Data were processed using SPSS v.26.0. For continuous variables, the two-tailed Student's t-test was used. Differences were considered statistically significant at $P < 0.05$.

RESULTS

The baseline clinical and demographic parameters were comparable between groups. The mean body mass index (BMI) was 24.6 ± 4.2 kg/m² vs 25.1 ± 4.8 kg/m² (P = 0.467). The severity of previous COVID-19 infection did not differ significantly: 34.1% of women had a mild course, 58.5% a moderate course, and 7.3% a severe course (P = 0.798).

The predominant menstrual irregularities observed were oligomenorrhea (37.8%), hypermenorrhea (26.8%), and dysmenorrhea (19.5%). Amenorrhea was recorded in 15.9% of participants. These disturbances correspond to the neuroendocrine and vascular sequelae commonly described in post-COVID reproductive dysfunction.

Restoration of regular menstrual cycles within 6 months of follow-up was achieved in 72 of 82 patients (90.2%). The mean time to cycle normalization was 3.9 ± 1.6 months, which was significantly shorter compared with standard-care data reported in the literature ($P < 0.001$). After 6 months of therapy, euthyroid status, normoprolactinemia, and normalization

of gonadal steroid levels were achieved in 80.5% of women. These findings confirm the clinical efficacy of the personalized multimodal approach. Key indicators of treatment effectiveness are summarized in Table 1.

A consistent positive trend was observed in all endocrine parameters. Prolactin levels decreased from 42.6 ± 18.3 ng/ml to 18.7 ± 8.4 ng/ml ($P < 0.001$). Thyroid-stimulating hormone levels decreased from 8.9 ± 4.2 mIU/l to 3.1 ± 1.6 mIU/l ($P < 0.001$). These changes reflect the recovery of hypothalamic–pituitary–ovarian–thyroid axis function following pathogenetically guided rehabilitation. Detailed hormonal data are presented in Table 2.

Table 1. Treatment outcomes after 6 months

Parameter	Intervention group (n = 82)
Restoration of regular cycles, n (%)	74 (90.2%)
Time to cycle recovery, months (M ± SD)	3.9 ± 1.6
Normalization of hormonal profile, n (%)	66 (80.5%)
Normalization of prolactin levels, n (%)	69 (84.1%)
Normalization of thyroid-stimulating hormone levels, n (%)	65 (79.3%)
Short Form-36 Health Survey total score (after 6 months, M ± SD)	83.8 ± 8.9
Adverse effects, n (%)	8 (9.8%)

According to the SF-36 Health Survey, the personalized rehabilitation program yielded a marked improvement in patients' perceived health status. The total SF-36 score increased from 58.4 ± 12.7 at baseline to 83.8 ± 8.9 post-treatment ($P < 0.001$), indicating significant enhancement in both physical and psychological domains of quality of life.

The comprehensive therapeutic protocol demonstrated good overall tolerability. Adverse effects were reported in 8 of 82 women (9.8%), all of which were mild or moderate in severity – most commonly transient dyspeptic symptoms. No patient discontinued therapy because of side effects.

DISCUSSION

The results of this study demonstrate the efficacy of a personalized, pathogenetically oriented rehabilitation program for restoring reproductive function after COVID-19. Restoration of regular menstrual cycles was achieved in 90.2% of patients, which exceeds the outcomes reported in the literature for conventional treatment approaches. Importantly, menstrual function recovery occurred on average within 4.2 months, a clinically significant finding for women of reproductive age planning pregnancy in the near future. These data underscore the necessity of early initiation of comprehensive rehabilitation once post-COVID menstrual disorders are detected.

Normalization of the hormonal profile, achieved in 80.5% of participants, confirms the pathogenetic validity of the proposed therapeutic strategy. Particularly noteworthy is the effective correction of hyperprolactinemia and thyroid dysfunction – key factors likely

Table 2. Hormone levels in patients

Parameter	Intervention (before treatment)	Intervention (6 months)	Reference range
Prolactin, ng/ml	44.8 ± 19.7**	17/2 ± 7/8**	5–25
Thyroid-stimulating hormone, mIU/l	9.2 ± 4.6**	2/8 ± 1/4**	0.4–4.0

Notes: $P < 0.001$ difference between pre- and post-treatment levels.

contributing to the development of post-COVID menstrual irregularities. Targeted pharmacologic correction with dopamine receptor agonists and levothyroxine promoted the restoration of normal hypothalamic–pituitary–ovarian rhythm in the majority of patients.

An additional marker of treatment effectiveness was the significant improvement in quality of life, which was more pronounced under the personalized therapeutic approach. This is crucial, as post-COVID reproductive dysfunction is often accompanied by psychoneuroendocrine disorders, reduced productivity, and impaired social functioning. The improvement in SF-36 scores reflects the multidimensional benefit of therapy – addressing not only physiological recovery but also emotional and psychosocial well-being.

Folic acid (vitamin B_6) plays a pivotal role in endothelial protection and metabolic regulation. It reduces homocysteine concentrations and increases nitric oxide (NO) bioavailability, thereby improving uterine–ovarian microcirculation and preventing abnormal uterine bleeding. Furthermore, folic acid enhances antioxidant defense by stimulating glutathione synthesis and lowering malondialdehyde (MDA) formation, a biomarker of oxidative stress. This contributes to reduced inflammation and improved follicular function. Supplementation with vitamin B_6 also improves glucose metabolism and insulin sensitivity, facilitating the restoration of regular ovulatory cycles in women with insulin resistance. Through its participation in methylation reactions affecting neurotransmitter synthesis, folate indirectly supports neuroendocrine stability, reducing hyperprolactinemia and improving emotional resilience [16]. Thus, folic acid helps mitigate endothelial dysfunction and microthrombosis characteristic of post-COVID vascular injury.

Melatonin, a pineal hormone with potent antioxidant, anti-inflammatory, and immunomodulatory properties, can attenuate the hyperinflammatory and oxidative stress response induced by SARS-CoV-2 and enhance mitochondrial function. These effects provide a clear pathogenetic rationale for its use to protect the ovaries from oxidative and ischemic injury following COVID-19. In patients with polycystic ovary syndrome (PCOS), adjunctive melatonin therapy significantly increased plasma total antioxidant capacity, reflecting a reduction in ovarian oxidative stress [17]. Normalization of circadian rhythms under melatonin supplementation promotes restoration of pulsatile gonadotropin secretion, regular menstrual cyclicity, improved sleep quality, and stabilization of mood and stress reactivity in women recovering from COVID-19.

Vitamin D is essential for reproductive health; its receptors are expressed in the ovaries, endometrium, and pituitary gland. Vitamin D deficiency disrupts ovulation and is associated with irregular menstrual cycles – population data indicate that each 10 ng/ml decrease in serum 25(OH)D is linked to nearly a twofold increase in the risk of menstrual irregularity. Mechanistically, vitamin D modulates anti-Müllerian hormone (AMH) synthesis and follicular development, promoting normal folliculogenesis and ovulation [18, 19]. Therefore, correction of vitamin D deficiency serves as an important component of post-COVID reproductive rehabilitation.

Magnesium acts as a cofactor in more than 300 enzymatic reactions, including those involved in steroidogenesis and glucose metabolism. Magnesium deficiency intensifies oxidative stress and chronic inflammation, both of which impair ovarian function, ovulation, and luteal phase sufficiency. Supplementation with magnesium provides antioxidant and metabolic support, improves oocyte quality, and enhances ovulatory function [20]. Clinical data also associate magnesium intake with reduction of premenstrual syndrome, dysmenorrhea, and menstrual migraines [21]. Since post-COVID states are frequently accompanied by stress and exhaustion, magnesium supplementation helps attenuate neuroendocrine stress responses, normalize prolactin levels, and accelerate menstrual cycle recovery.

Taken together, these findings confirm that pathogenetically individualized therapy–integrating hormonal, metabolic, antioxidant, and psychoneuroendocrine correction–provides a rational and effective strategy for restoring menstrual and reproductive function in women after COVID-19.

CONCLUSIONS

Women who experienced severe COVID-19 or long COVID exhibit menstrual dysfunctions more frequently and for a longer duration than those with mild disease. The pathogenesis of post-COVID menstrual disorders involves a combination of neuroendocrine suppression and vascular-inflammatory mechanisms. Transient hypercortisolemia and cytokine storm inhibit pituitary gonadotropin secretion, leading to functional anovulation – a mechanism analogous to stress-induced amenorrhea. Endothelial injury and microthrombosis may impair uterine and ovarian perfusion, contributing to endometrial and ovarian dysfunction, while in some cases, direct viral effects on endocrine organs (e.g., transient thyroiditis) further disrupt menstrual rhythm. Most of these alterations are reversible, with spontaneous restoration of hormonal balance and menstrual function after recovery.

For women with post-COVID menstrual disorders, an individualized management strategy is essential. Incorporating hormonal, metabolic, antioxidant, and psychological interventions into a personalized rehabilitation protocol resulted in more complete endocrine normalization (euthyroid status, reduced prolactin levels) and improved overall well-being. The personalized approach significantly enhanced quality of life, as evidenced by a 39% increase in SF-36 scores.

Vitamin and micronutrient supplementation, particularly folates, magnesium, melatonin, and vitamin D_3 in the personalized rehabilitation program is pathogenetically justified, targeting key post-COVID pathophysiological links – endothelial and hormonal dysregulation, oxidative stress, and metabolic imbalance – which collectively promote faster recovery of regular menstruation, hormonal homeostasis, and overall reproductive health.

Thus, a personalized, multidisciplinary rehabilitation approach, grounded in the pathophysiology of post-COVID changes, can be recommended as an effective clinical strategy for restoring reproductive function in women following COVID-19.

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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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ПАТОГЕНЕТИЧНО СПРЯМОВАНЕ ВІДНОВЛЕННЯ МЕНСТРУАЛЬНОГО ЦИКЛУ У ЖІНОК ПІСЛЯ ПЕРЕНЕСЕНОГО COVID-19

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Порушення менструального циклу все частіше спостерігаються у жінок, які одужують від COVID-19. Механізми включають нейроендокринну супресію, ендотеліальну дисфункцію та системне запалення, які можуть тимчасово порушувати активність гіпоталамо-гіпофізарно-яєчникової осі та перфузію ендометрію. Метою нашого дослідження було обгрунтувати та оцінити ефективність патогенетично спрямованої персоналізованої реабілітаційної програми для відновлення менструальної функції у жінок після COVID-19. У дослідженні взяли участь 82 жінки репродуктивного віку (18–45 років) з порушеннями менструального циклу, що розвинулися протягом шести місяців після COVID-19. Персоналізований протокол

включав гормональну корекцію (агоністи дофаміну, левотироксин, естроген-прогестагенна терапія за показаннями), метаболічну та антиоксидантну підтримку (вітамін D_3, n-3 ПНЖК, фолієва кислота і вітамін B_{12}, комплекс магнію-B_6), а також хронобіотичну та психологічну регуляцію (мелатонін, когнітивно-поведінкова терапія, гігієна сну). Первинною кінцевою точкою було відновлення регулярного циклу (21–35 днів); Вторинними кінцевими точками були гормональна нормалізація та покращення якості життя за шкалою Short Form-36 Health Survey. Регулярні менструальні цикли відновилися у 90,2% жінок протягом 3,9 ± 1,6 міс. Гормональна нормалізація (еутиреоїдний стан, нормопролактинемія, фізіологічний рівень статевих гормонів) була досягнута у 80,5%. Загальний бал за шкалою SF-36 збільшився з 58,4 ± 12,7 до 83,8 ± 8,9. Побічні ефекти були легкими та тимчасовими (9,8%). Персоналізована реабілітація, що включає гормональну, метаболічну, антиоксидантну та психонейроендокринну корекцію, значно покращила репродуктивне відновлення після COVID-19. Дотація вітамінів і мікроелементів, зокрема фолієвої кислоти, магнію, мелатоніну та вітаміну D_3 є патогенетично виправданим та сприяє швидшій нормалізації менструальної та гормональної функції у жінок репродуктивного віку.

Ключові слова: SARS-CoV-2; COVID-19; постковідний синдром; порушення менструального циклу; репродуктивне здоров'я; дотація вітамінів і мікроелементів; фолієва кислота; якість життя.

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