

PHYTOCOMPOSITIONS OF AYURVEDIC MEDICINE IN THE RESTORATION OF MENSTRUAL HEALTH IN WOMEN OF EARLY REPRODUCTIVE AGE WHO HAVE SURVIVED MODERATE AND SEVERE FORM OF COVID-19

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INTRODUCTION

Menstruation is a healthy biological event that has recently been recognized as a vital sign of health [1, 2]. A healthy menstrual cycle (MC) in women of early reproductive age can be defined as MC lasting 24–38 days, changes in the duration of MC from the shortest to the longest variant $\leq 7-9$ days, menstrual bleeding for ≤ 8 days, and the volume of blood loss as light or moderate in the words of a woman [3]. Other authors also indicate that a healthy MC should be ovulatory [4]. Recently, a multi-step process led by the Global Menstrual Collective Terminology Action Group (www.globalmenstrualcollective.org) introduced the term menstrual health, which was defined from a more holistic perspective than healthy MC. Menstrual health, according to this definition, is defined as a state of complete physical, mental and social well-being, and not simply the absence of disease or physical defects, in connection with MC [5]. MC-related disorders affect quality of life, including pain, physical discomfort, mental health effects, and abnormal uterine bleeding (AUB). They can occur in the absence of violations of the quantitative characteristics of MC [5].

COVID-19 (abbreviation from the COronaVirus Disease 2019) is a coronavirus disease of 2019, which can take the form of an acute respiratory viral infection of mild, moderate and severe severity. The virus is capable of affecting various organs through direct infection or through the body's immune response [6–8]. In the period from March 2020 to June 2023, 5,526,748 cases of the disease were officially registered in Ukraine, and 112,478 people died. The specific gravity of patients with COVID-19 aged 18–29 years in Ukraine is 11%, and the share of women among those infected is 60% [9]. According to global studies of the last 3 years, COVID-19 leads to menstrual health disorders [10].

The key factor in the virulence of the SARS-CoV-2 virus is the interaction of the receptor-binding domain (RBD) of protein S, located on its outer membrane, with the angiotensin-converting enzyme 2 receptors (ACE2), which is activated by human transmembrane serine proteases (transmembrane protease, ser-

ine 2, TMPRSS2) [11–16]. ACE2 and TMPRSS2 are expressed in several endocrine tissues, namely the hypothalamus, pituitary gland, thyroid gland, adrenal glands, gonads, and pancreatic islets [17, 18].

SARS-CoV and SARS-CoV-2 express specific amino acid sequences that show striking homology to adrenocorticotrophic hormone (ACTH) residues. It has been suggested that the host response to SARS-CoV (and SARS-CoV-2) may lead to the production of cross-reactive antibodies that inactivate or destroy endogenous ACTH [17, 19]. This may be an adaptive mechanism by which the virus avoids the ACTH response, as an immune invasive strategy aimed at suppressing the host's cortisol response [20]. On the other hand, this mechanism can be a trigger factor for secondary adrenal insufficiency.

SARS-CoV-2 can cause damage and dysfunction of the thyroid gland [21–23], including causing subclinical and atypical thyroiditis [24, 25]. There are isolated data that the main accompanying hormonal dysfunctions after 3 months after recovery from the transferred coronavirus infection, there is central hypocorticism (39%) and central hypothyroidism (5%) [26].

The severe stress caused by the new coronavirus infection, as well as the state of emergency during the pandemic, can also have a significant impact on the reproductive system. There is a reciprocal relationship between the hypothalamic-pituitary-adrenal axis, which ensures the formation of the response to stress, and the hypothalamic-pituitary-ovarian axis, in which the activation of one axis leads to the suppression of the other. Chronic activation of reactions in response to stress suppresses the production of estrogens and norepinephrine, which contributes to MC disturbances and the appearance of anovulatory cycles [27]. According to statistical data, menstrual health disorders caused by psychogenic factors are observed much more often in teenagers and young women under the age of 25, so special attention should be paid to this category of patients [28].

Intra-family conflicts, which may be exacerbated by self-isolation during a pandemic, also potentially provoke menstrual health disorders [29].

The extrapulmonary presence of SARS-CoV-2 was also detected in cholangiocytes. Possible factors of liver damage include virus-induced exposure, systemic inflammation («cytokine storm»), hypoxia, hypovolemia, hypotension in shock, drug hepatotoxicity, etc. [30]. Therefore, drugs used for post-COVID rehabilitation should be optimally safe. In the case of the first line of post-convulsive rehabilitation of women with menstrual health disorders, the use of ayurvedic herbal preparations to restore the indicators of menstrual function seems appropriate.

Research objectives: to evaluate the effectiveness of phytotherapy in the treatment of menstrual health disorders in women of early reproductive age after a moderate and severe form of the new coronavirus disease.

MATERIALS AND METHODS

104 women of early reproductive age with menstrual health disorders that occurred 3 months later after moderate or severe COVID-19 were under observation, and 34 gynecologically and somatically healthy women of the control group who did not suffer from COVID-19. The patients were examined and treated in women's consultations of the Maternity Hospital No. 7 of the Odesa City Council, Odesa Profile Hospital AIRMED, Odesa Clinic of Reproductive Medicine «Hope-Odesa», Odesa Medical Center «Odesa Cardyka Assistance», Lviv Regional Children's Clinical Hospital «OKHMATDYT» of the Lviv Regional Council in the period from 2020 to 2022.

The study was approved by the Bioethics Committee of Odessa National Medical University and was carried out within the framework of the planned research topic of the Department of Obstetrics and Gynecology of Odessa National Medical University «Improving methods of prevention, diagnosis and treatment of diseases of the female reproductive system using the latest medical technologies» (state registration number 0117U007494). All patients gave informed consent to participate in the study.

Inclusion criteria: age 18–25 years; the case had to be diagnosed as having transmitted COVID-19 with a positive reverse transcription polymerase chain reaction for SARS-CoV-2 or typical computed tomography findings of viral pneumonia; complaints of menstrual health disorders, provided that COVID-19 is indicated as the cause of these disorders; absence of menstrual function disorders and use of hormonal therapy for at least 6 months until the onset of the disease with COVID-19; lack of taking psychotropic drugs; normal body mass index. **Exclusion criteria:** refusal of the proposed treatment; organic diseases of the reproductive system as a cause of menstrual health disorders; endocrinopathy; congenital chromosomal, genetic diseases or malformations of genital organs associated with menstrual health disorders; pregnancy or breastfeeding; diagnosis of ovarian dysfunction in the anamnesis 6 months before the onset of COVID-19; previous surgery on the internal genitalia.

The performed examination included: study of complaints, general and gynecological anamnesis, physical and gynecological examination, ultrasound examination of the pelvic organs on expert class devices using convex sensors with a frequency of 3.5–5.0 MHz, immunochemical with electrochemiluminescence detection determination of serum levels of anti-Mullerian

hormone (AMH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), thyroid-stimulating hormone (TSH), estradiol (E_2), dehydroepiandrosterone sulfate (DHEAS), cortisol with the help of kits from Roche Diagnostics GmbH (Switzerland) on analyzers Cobas 6000 (e 601 module), immunochemical with chemiluminescence detection determination of ACTH, free testosterone (Tf), androstenedione (AS) using the analyzer and test systems Immulite (Siemens AG) (Germany), immunoenzymatic analysis of serum content 17(OH)-progesterone using the analyzer and test systems EUROIMMUN, De-meditec (Germany).

All patients with COVID-19 received a comprehensive rehabilitation program, which included diet therapy, vitamin-mineral complexes, and psychotherapy. Patients with COVID-19 were randomly divided into two groups - the main group (n=53) and the comparison group Cm (n=51). In addition to the comprehensive rehabilitation program, main group patients received 6 months of ayurvedic phytocompositions Femicycle or Femimens.

In this study women with a normal level of PRL were prescribed the phytopreparation Femicyc I1–2 capsules per day for 6 months while eating, which consisted of such active substances as the extract of *Symplocos racemosa* – 125 mg; *Asparagus racemosus* extract – 100 mg; *Indian saraca* extract – 100 mg; *Glycyrrhiza glabra* extract – 50 mg; *Curcuma longa* extract – 40 mg.

The extract of *Symplocos racemosa* contributes to the restoration of the functioning of the axis «pituitary – hypothalamus – ovaries» [43]: it normalizes the content of FSH and LH, maintains the ratio of estrogens and progesterone in blood serum [44]; has a hemostatic effect; has a pronounced anti-inflammatory, antibacterial effect; improves the morphofunctional properties of hepatocytes [45]; restores the levels of liver transaminases, alkaline phosphatase, bilirubin, albumin, total proteins and antioxidant balance [43].

Asparagus racemosus extract has phytoestrogenic properties, normalizes hormonal imbalance in women by restoring the FSH/LH balance in the hypothalamic-pituitary system, affects the synthesis of progesterone in the ovaries and intervenes in the process of biotransformation of estrogens, promotes the stimulation of the conversion of E_2 into low-active estrone [46]; shows a competitive effect with estrogens by binding to the ligand-binding domain of estrogen receptors [47]; contributes to the growth and development of follicles, improving the quality of oocytes by reducing the level of oxidative stress and increasing the activity of the endogenous antioxidant system [48–51]; suppresses pro-inflammatory cytokines, has antitoxic, antistress, antioxidant, anti-inflammatory and antibacterial properties [50, 52].

Saraca indica stimulates the production of estrogens and folliculogenesis in the ovary: accelerates the regeneration of the endometrium, increases the secretory function of the ovaries. It has hemostatic, blood purifying, anti-inflammatory, detoxifying, antispasmodic, diuretic, analgesic, antidote properties, reduces vaginal secretion. Procyanidin, which is part of *Saraca indica*, has a pronounced antioxidant effect, according to some data, it is much more powerful than ascorbic acid and vitamin E. Procyanidin reduces the level of pro-inflammatory

cytokines (interleukins), which ensure the mobilization of the inflammatory response [53, 54].

Glycyrrhiza glabra shows a powerful immunomodulatory ability [55, 56], which is a synergist of glucocorticoid receptors; affects the level of estrogens in a woman's body and has a high affinity for estrogen receptors, is a powerful E₂ antagonist [57]; has antispasmodic, antibacterial, antitumor, antiestrogenic activity [58].

Curcuma longa L extract has a pronounced anti-inflammatory [59] and neuroprotective effect [60]; reduces swelling, improves blood circulation, stimulates the formation of erythrocytes, reduces platelet aggregation, regulates metabolism, correcting both excess and deficiency of metabolic processes, and promotes protein assimilation [61]. *Curcuma longa* L. is a herbal medicine used by the Chinese and Malaysians to treat amenorrhea [62].

Women with menstrual health disorders, primarily with dysmenorrhea, premenstrual syndrome (PMS), and with an elevated level of PRL, were prescribed the phytocomposition Femimens 1–2 capsules per day during meals, which includes extracts of *Vitex agnus castus* – 125 mg; *Withania somnifera* extract – 100 mg; *Zingiber officinale* – 35 mg; *Trigonella foenum-graecum* L. – 30 mg.

Vitex agnus castus restores the physiological cycle of secretion of gonadotropic hormones, reduces the level of PRL. One mechanism of action may be through dopamine receptors, which reduce TSH and PRL levels, alleviating PMS symptoms. An alternative mechanism has been reported as an opiate receptor agonist [63]. *Vitex agnus castus* increases the level of progesterone in the blood [64–67], normalizes the balance between estrogen and progesterone, and reduces the reaction of mammary glands to MC phases. It restores the duration of the luteal phase of the MC, raises the prolactin and 17β-estradiol levels in the middle of the luteal phase [68] during the window of implantation. The extract has antioxidant, anti-inflammatory and anti-proliferative properties, and is able to alleviate the symptoms of premenstrual dysphoric disorders and PMS [63, 69].

Withania somnifera a extract has a calming, anti-inflammatory, adaptogenic, cognitive, antitumor, antioxidant, antibacterial, immunomodulatory effect, normalizes the sleep cycle, and improves female sexual health [70, 71]. *Withania somnifera* is considered an «adaptogen» because it protects the body from stress and helps the body recover from the effects of stress. It reduces the level of cortisol in blood serum in patients with chronic stress, restores the functions of the adrenal glands and normalizes the sympathetic nervous system [72]. Animal studies have confirmed the effect of *Withania somnifera* on the production of sex hormones, as evidenced by its effect on LH, FSH, testosterone and progesterone [71, 72, 73]. Plant phytochemicals in combination with drugs or other clinical treatments can be used for therapeutic purposes, including the treatment of SARS-CoV-2 infection [74]. Chemical components of the genus *Withania somnifera* include withanolides. The bioactive steroid withaferin A reduces the secretion of various proinflammatory cytokines, such as tumor necrosis factor α, interleukin (IL)-6, IL-8, and IL-18 [75], while withanone blocks

the entry of SARS-CoV by reducing the electrostatic component of the ACE2-RBD complex [76], and it interferes with the activity and regulation of the cell surface receptor protein TMPRSS2 and the viral replicative protease M pro [77, 78]. *Withania somnifera* can inhibit the replication of the COVID-19 virus due to its ability to regulate the cytotoxicity of NK cells of T cell differentiation [79]. Several withanolides cause down-regulation of the expression of the viral envelope (E-gene) and nucleoplasmic sequences (N-gene). The organ-preserving results of *Withania somnifera* are used to reduce systemic inflammation, which protects against the severity of inflammation-induced organ damage. In addition to these antiviral actions, *Withania somnifera* has a confirmed sedative role in supporting mental health, which may be very useful in the control and treatment of COVID-19 [80]. Since the interaction of SARS-CoV-2 S-protein RBD and ACE2 receptor is very important for viral entry into host cells during infection, thus bioactive compounds of *Withania somnifera* such as withanone and withaferin A may be involved in the management and treatment of COVID-19 [81].

Zingiber officinale root extract has anti-inflammatory and analgesic properties, is effective in dysmenorrhea [82, 83] and PMS [84]. Elinoid, which is a component of ginger, inhibits lipoxygenase and cyclooxygenase-1,2 enzymes, slows down or prevents the formation of prostaglandins from arachidonic acid, and inhibits leukotriene production by inhibiting 5-lipoxygenase [85]. Analgesic activity of *Zingiber officinale* extract is comparable to the effectiveness of ibuprofen and mefenamic acid [82, 85, 86]. It is able to activate estrogen receptors with the same power as licorice.

Trigonella foenum-graecum L. extract has compounds, including linoleic acid, that lower LH levels, reduce the release of leptin, nitric oxide, and gonadotropin-releasing hormone [87–89]. *Trigonella foenum-graecum* L. normalizes the level of testosterone, E₂ in women, thereby normalizing libido. It has an analgesic, antipyretic, antitumor effect. *Trigonella foenum-graecum* L. extract contains diosgenin, which normalizes progesterone levels, has a neuroprotective, hepatoprotective, hypoglycemic, antiatherogenic effect, significantly reduces the secretion of various inflammatory factors, including tumor necrosis factor α, IL-1β, and IL-6 [43, 90, 91].

Statistical analysis of the material was carried out using the statistical program «Microsoft Excel 2011». The calculation of parametric indicators is presented in the form of mean values and error of standard deviation (M ± SE). After confirming the fact of homoscedasticity, the unpaired Student's test was used, in case of non-confirmation of the assumption regarding the normality of the distribution of quantitative features, as well as when comparing reference groups by ordinal and discrete features, the non-parametric Wilcoxon-Mann-Whitney test was used. Comparison of non-parametric features was performed using the analysis of linkage tables using Pearson's χ² test, calculation of odds ratio (OR) and 95% confidence interval (95% CI), which was presented as OR [95% CI].

RESULTS AND DISCUSSION

The average age of the examined patients in the group with COVID-19 was 21.89 ± 0.20 years, in the main group – 21.96 ± 0.26

years, in the comparison group – 21.82 ± 0.33 years against 22.15 ± 0.41 years in the control group ($p > 0.05$). Body mass index, respectively, was 22.23 ± 0.26 , 22.09 ± 0.32 , 22.57 ± 0.42 kg/m² versus 21.18 ± 1.07 kg/m² ($p > 0.05$). All patients with transferred COVID-19 had the characteristics of a healthy MC before the disease.

The main complaints with which patients turned to a gynecologist after suffering from COVID-19 were: infrequent menstruation – 60.58% of cases ($p < 0.01$), amenorrhea – 14.42% ($p < 0.02$), scanty menstruation – 11.54% ($p < 0.04$), excessive menstruation – 17.31% ($p < 0.01$), intermenstrual bleeding – 10.58% ($p < 0.05$). In addition to AUB, in patients with a moderate and severe form of the new coronavirus disease, painful menstruation was observed in 44.23% of cases against 20.59% in the control group (OR 3.059 [1.223–7.653], $p < 0.01$), and 40.38% had PMS against 11.76% in the control group (OR 5.081 [1.667–15.484], $p < 0.01$).

Hormonal examination of patients on the 2nd–3rd day of independent or dydrogesterone induced MC showed that the levels of the studied hormones, with the exception of the levels of PRL and ACTH in some patients, were within the reference norm. But a comparison with the indicators of the control group revealed statistically significant deviations in the production of hormones that take part in ensuring menstrual health.

MC is regulated by a complex interplay of hypothalamic-pituitary-adrenal-ovarian and hypothalamic-pituitary-thyroid hormones that interact with the immune, vascular, and hemostatic systems, and these interactions can influence the nature, duration, regularity, volume, and severity of PMS [31, 32], which was demonstrated by a comprehensive study of the levels of hormones of the pituitary gland, thyroid gland, ovaries, and adrenal glands in women of early reproductive age with post-COVID AUB. SARS-CoV enters the brain through the ACE2 receptor located in the olfactory bulb [33]. In addition, SARS-CoV-2 is known to cause anosmia and ageusia, which may be associated with local or central pathology, such as hypothalamic damage leading to hormonal imbalance [34]. In women, a severe acute disease can change the function of the hypothalamus-pituitary-ovary axis, and, as a result, reduce the endogenous production of E₂ and progesterone [16, 35]. In our patients 3 months after moderate and severe form of COVID-19

the average level of LH was recorded by 1.13 times (5.01 ± 0.11 vs. 5.65 ± 0.21 mIU/ml, $p < 0.02$), E₂ – by 1.44 times (55.32 ± 0.68 vs. 79.81 ± 2.66 pg/ml) against the background of an increase in the average serum FSH content by 1.14 times (6.00 ± 0.10 vs. 5.28 ± 0.17 mIU/ml), PRL – 1.66 times (20.03 ± 0.79 vs. 12.06 ± 0.51 ng/ml, $p < 0.01$). Levels of AMH and Tf did not differ statistically significantly between groups (Table 2, Fig.).

It is known that hyperprolactinemia can occur in response to any form of stress, including infections [36]. It should be noted that the level of PRL was increased above the reference norm in 33 (31.73%) patients with post-COVID AUB after 3 months after the disease, while in 71 (68.27%) women it was within the reference norm. The average level of PRL in women with COVID-19 was 20.03 ± 0.79 ng/ml and was 1.66 times higher than that in the control group ($p < 0.01$).

Damage to the hypothalamus and pituitary gland in patients with atypical pneumonia was demonstrated by autopsy studies. For example, L. Wei et al. (2010) [37] examined autopsy pituitary specimens from four men and one woman with atypical pneumonia. They found that pituitary somatotrophic, thyrotrophic, and corticotrophic cells were reduced in number and showed changes indicative of acute injury, such as swelling and neuronal degeneration. It has been established that SARS-CoV affects the hypothalamic-pituitary-adrenal axis and causes transient hypocorticism [16], which develops gradually as a late complication several weeks after the onset of SARS infection.

Since the patients of early reproductive age examined by us were previously healthy and did not take corticosteroids, there is a high probability that SARS-CoV-2 was responsible for their decreased cortisol levels by 1.26 times (11.01 ± 0.15 vs. 13.91 ± 0.58 mg/dL, $p < 0.01$), AS – 1.56 times (1.51 ± 0.04 vs. 2.36 ± 0.11 ng/ml, $p < 0.01$), DHEAS – by 1.24 times (5.59 ± 0.07 vs. 6.93 ± 0.21 μmol/l, $p < 0.01$), 17(OH)-progesterone – by 1.33 times (0.46 ± 0.01 vs. 0.62 ± 0.02 ng/ml, $p < 0.01$). The average level of ACTH in patients with COVID-19 reached 20.15 ± 1.23 pg/ml and was 1.41 times lower than the similar level in controls (28.38 ± 1.92 pg/ml) ($p < 0.01$). However, the level of ACTH in 12.50% of women exceeded the reference norms.

The obtained data on the development of hypocorticism after COVID-19 are confirmed by other studies [7, 38]. Thus, M. K. Leow

Table 1. Nature of menstrual health disorders in the studied groups, n (%)

The nature of menstrual disorders	Groups of patients			
	A group of COVID-19 (n=104)	The main group (n=53)	Comparison group (n=51)	Control group (n=34)
Scanty menstruation	12 (11.54) ^c	7 (13.21) ^c	5 (9.80)	0 (0.00)
Abundant menstruation	18 (17.31) ^c	10 (18.87) ^c	8 (15.69) ^c	0 (0.00)
Rare menstruation	63 (60.58) ^c	30 (56.60) ^c	33 (64.71) ^c	0 (0.00)
Amenorrhea	15 (14.42) ^c	9 (16.08) ^c	6 (11.76) ^c	0 (0.00)
Intermenstrual bleedings	11 (10.58) ^c	6 (11.32) ^c	5 (9.80)	0 (0.00)
Dysmenorrhea	46 (44.23) ^c	24 (45.28) ^c	22 (43.14) ^c	7 (20.59)
PMS	42 (40.38) ^c	23 (43.40) ^c	19 (20.59) ^c	4 (11.76)

^cStatistically significant difference with the indicators of the control group ($p < 0.05$).

Table 2. Hormonal profile of peripheral blood serum on the 2nd–3rd day of MC 3 months after COVID-19, M ± SE

Hormone	Groups of patients		Reference interval
	The group with COVID-19 after 3 months. after illness (n=104)	Control group (n=34)	
LH, mIU/ml	5.01 ± 0.11 ^c	5.65 ± 0.21	1.6–9.3
FSH, mIU/ml	6.00 ± 0.10 ^c	5.28 ± 0.17	2.4–9.3
PRL, ng/ml	20.03 ± 0.79 ^c	12.06 ± 0.51	4.79–23.3
ACTH, pg/ml	20.15 ± 1.23 ^c	28.38 ± 1.92	6–58
TSH, μIU/ml	2.35 ± 0.05 ^c	1.91 ± 0.10	0.17–4.05
E ₂ , pg/ml	55.32 ± 0.68 ^c	79.81 ± 2.66	12.5–166.0
Tf, pg/ml	1.37 ± 0.05	1.59 ± 0.11	<9
AS, ng/ml	1.51 ± 0.04 ^c	2.36 ± 0.11	0.3–3.3
Cortisol, nmol/l	11.01 ± 0.15 ^c	13.91 ± 0.58	6.2–19.4
DHEAS, μg/dL	205.86 ± 5.81 ^c	256.12 ± 17.12	148.0–407.0
17(OH)-progesterone, ng/ml	0.44 ± 0.02 ^c	0.62 ± 0.03	0.1–0.8
AMH, ng/ml	3.81 ± 0.09	4.01 ± 0.12	1.88–7.29

^cStatistically significant difference with the indicators of the control group (p<0.05).

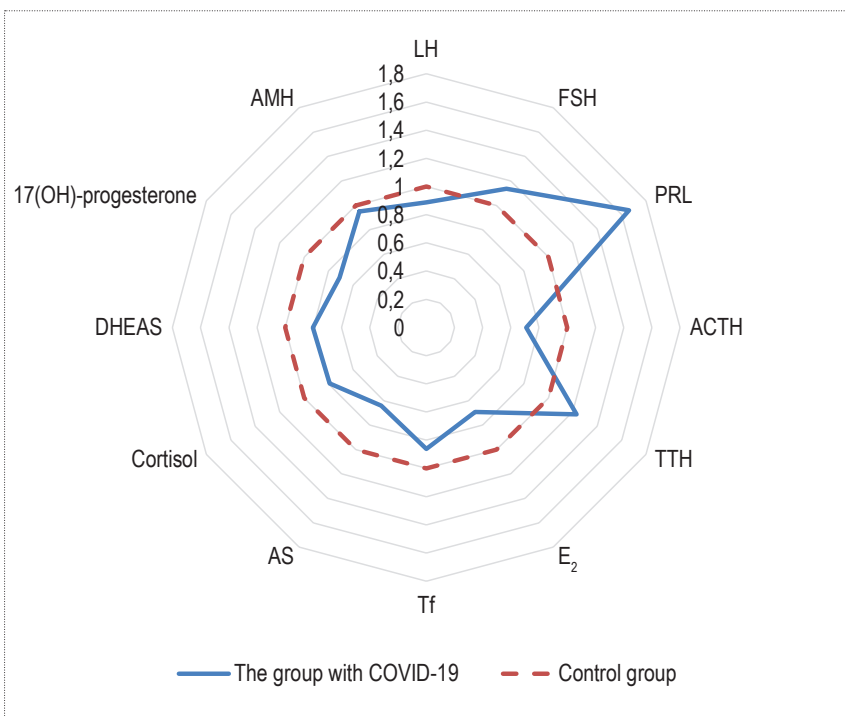


Figure. Displacement of hormone levels in patients with COVID-19 relative to similar indicators of the control group, taken as a unit

et al. (2005) [7] studied hypocorticism in patients who recovered from SARS-CoV. The authors studied those patients who had an intact hypothalamic-pituitary-adrenal axis at the time of SARS-CoV infection and did not receive systemic steroids for treatment, which excluded the possibility of suppression of the

hypothalamic-pituitary-adrenal axis with the use of exogenous corticosteroids. Three months after recovery, almost half of the patients examined by the researchers had hypocorticism, most of whom had central hypocorticism, as evidenced by low ACTH levels. Interestingly, hypocorticism was transient and resolved in two thirds

of patients within a year [7]. Data obtained during the SARS epidemic in 2003 indicate that the amino acid sequence of the SARS virus shows molecular mimicry with ACTH; this could lead to host antibodies against viral antigens binding to ACTH receptors, limiting the response to corticosteroid stress [39]. Some studies have shown that in patients with hypocorticism that developed after COVID-19, the hypothalamic-pituitary-adrenal axis recovers within one year [39].

Less often, according to various data, with COVID-19, the hypothalamic-pituitary-thyroid axis is affected, which leads to secondary hypothyroidism [38]. Researchers consider reverse hypophysitis or a direct hypothalamic effect as possible factors [7]. In the conducted study, TSH levels were increased in examined patients with moderate and severe COVID-19 compared to controls by 1.23 times (2.35 ± 0.05 μIU/ml vs. 1.91 ± 0.14 μIU/ml), but were within the reference norm.

Menstrual health disorders in women who have experienced moderate or severe coronavirus disease are associated with the direct impact of the most recent coronavirus infection, exacerbation of chronic diseases, emotional stressors due to the transferred disease, metabolic stressors in the form of weight loss,

Table 3. Characteristics of menstrual health in the studied groups 6 months after the beginning of treatment, n (%)

The nature of menstrual disorders	The main group (n=53)	Comparison group (n=51)	OR [95% ДІ]
Scanty menstruation	1 (1.89)	3 (5.88)	0.308 [0.031–3.060]
Abundant menstruation	0 (0.00)	4 (7.84)	-
Rare menstruation	1 (1.89)	16 (31.37)	0.042 [0.005–0.332]
Amenorrhea	1 (1.89)	2 (3.92)	0.481 [0.042–5.470]
Intermenstrual bleeding	0 (0.00)	2 (3.92)	-
Dysmenorrhea	6 (11.32)	18 (35.29)	0.234 [0.084–0.653]
PMS	4 (7.55)	15 (29.41)	0.196 [0.060–0.640]

adherence to a diet, taking antibacterial drugs, antiviral, glucocorticoid drugs and low molecular weight heparins. In the conducted study, the structure of the COVID-dependent MC disorders was dominated by irregular menstruation. Interestingly, according to foreign researchers, infrequent menstruation and amenorrhea are the predominant variant of MC disorders in response to stress in the reproductive period of life [40, 41].

Menstrual health disorders are a pathology that requires

long-term treatment, so an important aspect when choosing a therapy is not only its effectiveness, but also its safety. Today, phytocompositions of ayurvedic medicine, which have been used for thousands of years in gynecological practice and have proven their effectiveness, possess such parameters. They significantly expand the possibilities of restoring menstrual health and are a worthy alternative to hormonal drugs, especially if there are contraindications for the latter [42].

Table 4. Hormonal profile of peripheral blood serum on the 2nd-3rd day from the beginning of the MC before and after 6 months of treatment, M ± SE

Hormone	The time of examination after a transfer of COVID-19	Groups of patients*		
		The main group (n=53)	Comparison group (n=51)	Control group (n=34)
FSH, mIU/ml	in 3 months	5.07 ± 0.15 ^c	4.95 ± 0.15 ^c	5.65 ± 0.21
	in 9 months	5.59 ± 0.13 ^{cm}	5.10 ± 0.08 ^{cm}	
LH, mIU/ml	in 3 months	5.94 ± 0.13 ^c	6.06 ± 0.20 ^c	5.28 ± 0.17
	in 9 months	5.36 ± 0.13 ^{cm}	5.95 ± 0.15 ^{cm}	
PRL, ng/ml	in 3 months	0.89 ± 0.03 ^c	0.85 ± 0.03 ^c	1.10 ± 0.04
	in 9 months	1.11 ± 0.04 ^{cm}	0.91 ± 0.03 ^{cm}	
ACTH, pg/ml	in 3 months	20.57 ± 1.06 ^c	19.47 ± 1.20 ^c	12.06 ± 0.51
	in 9 months	12.46 ± 0.47	18.29 ± 0.77	
TSH, μIU/ml	in 3 months	19.55 ± 1.64 ^c	20.79 ± 1.85 ^c	28.38 ± 1.92
	in 9 months	27.79 ± 0.75 ^{cm}	24.85 ± 1.56 ^{cm}	
E ₂ , pg/ml	in 3 months	2.31 ± 0.06 ^c	2.39 ± 0.07 ^c	1.91 ± 0.10
	in 9 months	1.98 ± 0.06 ^{cm}	2.28 ± 0.07 ^{cm}	
Tf, pg/ml	in 3 months	56.03 ± 1.01	54.58 ± 0.89	79.81 ± 2.66
	in 9 months	77.23 ± 1.01	67.26 ± 0.89	
AS, ng/ml	in 3 months	1.33 ± 0.07 ^c	1.41 ± 0.08 ^c	1.59 ± 0.11
	in 9 months	1.53 ± 0.08 ^{cm}	1.46 ± 0.06 ^{cm}	
TSH, μIU/ml	in 3 months	1.43 ± 0.05 ^c	1.59 ± 0.05 ^c	2.36 ± 0.11
	in 9 months	2.10 ± 0.06 ^{cm}	1.81 ± 0.05 ^{cm}	
Cortisol, nmol/l	in 3 months	11.18 ± 0.18 ^c	10.83 ± 0.24 ^c	13.91 ± 0.58
	in 9 months	13.74 ± 0.18 ^{cm}	12.48 ± 0.24 ^{cm}	
DHEAS, μg/dL	in 3 months	209.46 ± 8.29 ^c	202.11 ± 8.21 ^c	256.12 ± 17.12
	in 9 months	243.64 ± 8.29 ^{cm}	208.05 ± 6.50 ^{cm}	
17(OH)-progesterone, ng/ml	in 3 months	0.48 ± 0.01 ^c	0.41 ± 0.02 ^c	0.62 ± 0.03
	in 9 months	0.57 ± 0.03 ^{cm}	0.44 ± 0.02 ^{cm}	

*statistically significant difference between the main and comparison groups 3 months after COVID19 was not detected;

^{m, cm, c} A statistically significant difference with the main, comparison and control groups (p<0.01).

Ayurvedic phytocompositions can be used as monotherapy or in combination with hormonal drugs.

Over time after COVID-19 the MC began to return to the characteristics that were before the disease, but 6 months after the beginning of treatment indicators of menstrual health in the main group recovered faster and were better than in the comparison group (Table 3).

After 6 months from the beginning of treatment in main group there was a statistically significant smaller number of women with infrequent menstruation (OR 0.042 [0.005–0.332]), with manifestations of dysmenorrhea (OR 0.234 [0.084–0.653]) and PMS (OR 0.196 [0.060–0.640]).

Such results can be explained by the faster and more effective recovery of the hypothalamic-pituitary-adrenal-ovarian and hypothalamic-pituitary-thyroid systems, as evidenced by the results of studies of the hormonal profile in the dynamics of treatment (Table 4).

In the main group women had no side effects from taking herbal preparations and showed high compliance.

CONCLUSIONS

1. The moderate and severe course of the coronavirus infection affects the state of the reproductive system of women of early reproductive age and leads to menstrual health disorders, which are dominated by irregular menstruation, PMS, and dysmenorrhea.

2. Levels of pituitary, adrenal, ovarian and thyroid serum hormones are in most cases within the reference norm, but have statistically significant deviations from similar indicators of healthy control women who did not suffer from COVID-19. One third of women of early reproductive age after moderate to severe COVID-19 have elevated prolactin levels

3. Ayurvedic phytocompositions Femicycle and Femimens, which are widely used in gynecological practice for the treatment of functional disorders and organic pathology, are effective and safe naturopathic drugs for restoring the menstrual health of women of early reproductive age after moderate and severe COVID-19.

4. Since plant extracts are multicomponent mixtures, different phytoconstituents can interact with each other, resulting in additive, synergistic, and/or antagonistic effects. Thus, the activity of extracts may not be due to just one or two compounds, but many compounds may be involved. Due to the complexity of analyzing the various interactions between phytoconstituents in plant extracts, these effects have not been well studied, and additional pharmacological and clinical research is needed in this area.

Conflict of interest

There is no conflict of interest.

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ФІТОКОМПОЗИЦІЇ АЮРВЕДИЧНОЇ МЕДИЦИНИ У ВІДНОВЛЕННІ МЕНСТРУАЛЬНОГО ЗДОРОВ'Я ЖІНОК РАНОГО РЕПРОДУКТИВНОГО ВІКУ, ЯКІ ПЕРЕНЕСЛИ СЕРЕДНЬОТЯЖКУ ТА ТЯЖКУ ФОРМУ COVID-19

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Мета дослідження: оцінити ефективність фітотерапії при лікуванні розладів менструального здоров'я жінок раннього репродуктивного віку, які перенесли середньотяжку та тяжку форму коронавірусного захворювання.

Матеріали та методи. Під спостереженням знаходилося 104 жінки раннього репродуктивного віку з розладами менструального здоров'я, які виникли не пізніше, ніж через 3 місяці після перенесеного COVID-19 середньої тяжкості або важкого ступеня, і 34 гінекологічно і соматично здорових жінки контрольної групи, які не хворіли на COVID-19. Пацієнтки з перенесеним COVID-19 були випадковим методом розділені на дві групи: основна група (n=53) і група порівняння (n=51). Обстеження включало: вивчення скарг, загального та гінекологічного анамнезу, фізикальний і гінекологічний огляд, ультразвукове дослідження органів малого таза, визначення гормонального профілю.

Усі пацієнтки з перенесеним COVID-19 після звернення отримували комплексну програму реабілітації, яка включала дієтотерапію, вітамінно-мінеральні комплекси та психотерапію.

Пацієнтки основної групи додатково до комплексної програми реабілітації отримували впродовж 6 місяців аюрведичні фітокомпозиції Феміцикл або Феміменс.

Результати. Встановлено, що середньотяжкий та важкий перебіг коронавірусної інфекції впливає на стан репродуктивної системи жінок раннього репродуктивного віку і призводить до розладів менструального здоров'я, серед яких домінують рідкі менструації, передменструальний синдром та дисменорея. Рівні гіпофізарних, надниркових, яєчникових та тиреоїдних гормонів у більшості випадків знаходилися в межах референтної норми, але мали статистично вірогідні відхилення від аналогічних показників здорових жінок групи контролю, які не хворіли на COVID-19. Одна третина жінок раннього репродуктивного віку після середньотяжкого та важкого COVID-19 мала підвищені рівні пролактину. Застосування аюрведичних фітокомпозицій Феміциклу та Феміменсу в комплексній програмі реабілітації постковідних розладів менструального здоров'я сприяло більш швидкому відновленню менструального здоров'я і повноцінному відновленню гормонального фону.

Висновки. Аюрведичні фітокомпозиції Феміцикл та Феміменс є ефективними та безпечними натуропатичними препаратами для відновлення менструального здоров'я жінок раннього репродуктивного віку після перенесеного середньотяжкого та важкого COVID-19.

Ключові слова: COVID-19, менструальне здоров'я, менструальний цикл, дисменорея, передменструальний синдром, Феміцикл, Феміменс.

PHYTOCOMPOSITIONS OF AYURVEDIC MEDICINE IN THE RESTORATION OF MENSTRUAL HEALTH IN WOMEN OF EARLY REPRODUCTIVE AGE WHO HAVE SURVIVED MODERATE AND SEVERE FORM OF COVID-19

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Research objectives: to evaluate the effectiveness of phytotherapy in the treatment of menstrual health disorders in women of early reproductive age after a moderate and severe form of the coronavirus disease.

Material and methods. 104 women of early reproductive age with menstrual health disorders that occurred 3 months later after moderate or severe COVID-19 were under observation and 34 gynecologically and somatically healthy women of the control group who did not suffer from COVID-19. Female patients with COVID-19 were randomly divided into two groups: the main group (n=53) and the comparison group (n=51). The performed examination included: study of complaints, general and gynecological anamnesis, physical and gynecological examination, ultrasound examination of pelvic organs, determination of hormonal profile.

All patients with COVID-19 received a comprehensive rehabilitation program, which included diet therapy, vitamin and mineral complexes, psychotherapy. In addition to the complex rehabilitation program patients of the main group received ayurvedic phytocompositions Femicycle or Femimens for 6 months.

Results. It has been established that the moderate and severe course of the coronavirus infection affects the reproductive system of early reproductive aged women and leads to menstrual health disorders, among which irregular menstruation, premenstrual syndrome and dysmenorrhea dominate. Levels of pituitary, adrenal, ovarian and thyroid serum hormones were within the reference norm in most cases, but have statistically significant deviations from similar indicators of healthy control women who did not have COVID-19. One-third of women of early reproductive age after moderate to severe COVID-19 had elevated prolactin levels.

Ayurvedic phytocompositions Femicycle and Femimens in a comprehensive rehabilitation program for post-COVID menstrual health disorders led to a faster recovery of menstrual health and a full hormonal recovery.

Conclusions. Ayurvedic phytocompositions Femicycle and Femimens are effective and safe naturopathic drugs for restoring menstrual health in women of early reproductive age after experiencing moderate to severe COVID-19.

Keywords: COVID-19, menstrual health, menstrual cycle, dysmenorrhea, premenstrual syndrome, Femicycle, Femimens.

РОЗЛАДИ МЕНСТРУАЛЬНОГО ЗДОРОВ'Я:

Рідкі менструації

Передменструальний синдром

Дисменорея²

ФЕМІМЕНС капсули № 30

Екстракт Прутьяку звичайного – 125 mg
Екстракт Вітанії заспокійливої – 100 mg
Екстракт Імбиру – 35 mg
Екстракт Пажитника – 30 mg

ФЕМІМЕНС

ФЕМІМЕНС і ФЕМІЦИКЛ – ефективні та безпечні натуропатичні засоби для відновлення менструального здоров'я жінок раннього репродуктивного віку після перенесеного середньотяжкого та важкого COVID-19²



по 1 капсулі 2 рази на день після їжі, від 3 до 6 місяців¹

ФЕМІЦИКЛ

ВСЕ ЗА КАЛЕНДАРЕМ!

РЕЗУЛЬТАТИ: більш швидке та ефективне відновлення роботи гіпоталамо-гіпофізарно-наднирничково-яєчникової та гіпоталамо-гіпофізарно-тиреоїдної системи²

ФЕМІЦИКЛ капсули № 30

Екстракт Симплокоса кистевидного – 125 mg
Екстракт Спаржі кистевидної – 100 mg
Екстракт Сараки індійської – 100 mg
Екстракт Солодки голої – 50 mg
Екстракт Куркуми довгої – 40 mg

