

FEMICYCLE - EFFECTIVE AND SAFE CORRECTION OF MENSTRUAL IRREGULARITIES

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SUMMARY

Menstrual irregularities are one of the most common pathological conditions of the reproductive system, occurring in all age periods - from menarche to menopause. In the last decade, a steady increase in this pathology is observed despite the great adaptive capabilities of the female body. So, according to the results of epidemiological studies, menstrual irregularities are the cause of women going to a gynecologist in 40-60% of cases [1, 2]. 30% of cases are directly associated with gynecological diseases, 20% with extragenital pathology, 15% with stressful situations, and 9% with surgical treatment of the reproductive organs [1, 3].

INTRODUCTION

Menstrual irregularities cause deterioration in the reproductive function of women, uterine bleeding, anaemia, psychoemotional disorders, and a significant decrease in working capacity and quality of life [4]. Also, according to different studies, menstrual irregularities associated with hormonal homeostasis disorders increase the risk of developing breast cancer and endometrial adenocarcinoma [5].

All this determines the relevance of this problem and dictates the need for early diagnosis, effective treatment and prevention of menstrual irregularities.

PHYSIOLOGY AND REGULATION OF MENSTRUAL CYCLE

The menstrual cycle is cyclically repeated changes in a female body, mainly in the parts of the reproductive system, the external manifestation of which is blood discharge from the genital tract - menstruation [6]. The menstrual cycle occurs after the menarche (first menstruation) and persists throughout the reproductive period of a woman's life. The cyclic changes in a woman's body are biphasic. The first (follicular) phase of the cycle is determined by the maturation of the follicle and the ovum in the ovary, followed by the follicle rupture and the ovum release - ovulation. The second (luteal) phase is associated with the formation of the corpus luteum. At the same time, the cyclic regeneration and proliferation of the functional layer followed by the secretory activity takes place in the endometrium. Such changes in the endometrium cause rejection of the functional layer, known as menstruation [7].

The standard parameters of the menstrual cycle are as follows [3]:

- duration is 21 to 35 days (for 60% of women, the average cycle is 28 days);
- duration of menstrual discharge is 2 to 7 days;
- amount of blood loss within menstrual days is 40-60 ml (an average of 50 ml).

The processes providing the normal course of the menstrual cycle are regulated by the functional neuroendocrine system, which includes the central regions and peripheral structures with a certain number of intermediate links. In accordance with their hierarchy (from higher regulatory structures to directly executive bodies) in neuroendocrine regulation, 5 levels interacting on the principles of direct and inverse positive and negative interactions can be distinguished [8, 9].

The first (highest) levels of regulation of the reproductive system functioning are the cerebral cortex and extrahypothalamic cerebral structures: limbic system, hippocampus and amygdala. The balance of synthesis and metabolic transformations of neurotransmitters, neuropeptides and neuromodulators in brain neurons and in suphypothalamic structures provides the normal course of processes associated with ovulatory and menstrual function [10].

The second level of regulation of reproductive function is the hypothalamus. The activity of neurosecretion in the hypothalamus is regulated by sex hormones coming from the bloodstream, and by neurotransmitters and neuropeptides formed in the cerebral cortex and suphypothalamic structures [9, 10].

The third level of regulation of reproductive function is the anterior pituitary gland, in which gonadotropic hormones, such as follicle-stimulating (FSH), luteinizing (LH), prolactin, adrenocorticotrophic hormone (ACTH), somatotrophic hormone (STH) and thyroid-stimulating hormone (TSH), are secreted. The normal functioning of the reproductive system is possible only with a balanced release of each of these hormones. FSH stimulates the growth and maturation of follicles in the ovary, the proliferation of granulosa cells, the formation of FSH and LH receptors on granulosa cells, the activity of aromatases in the maturing follicle that enhances the conversion of androgens to estrogens, the production of inhibin, activin and insulin-like growth factors [8, 10].

LH promotes the formation of androgens in theca cells, ovulation (along with FSH), remodeling of granulosa cells during luteinization, and the synthesis of progesterone in the corpus luteum.

Prolactin has a diverse effect on the woman's body. The main biological role of prolactin is to stimulate the growth of mammary glands and regulate lactation. Also, by activating the formation of LH receptors, prolactin regulates corpus luteum progesterone secretion. During pregnancy and lactation, the inhibition of prolactin synthesis stops, as a result blood prolactin concentration increases.

The fourth level of regulation of reproductive function includes peripheral endocrine organs (ovaries, adrenal glands, thyroid gland). The ovaries play the main role, and other glands perform their own specific functions, while maintaining the normal functioning of the reproductive system.

There are growth and maturation of follicles, ovulation, corpus luteum formation and sex steroids synthesis in the ovaries. In the reproductive period, the ovaries are the main source of estrogen. In addition, the ovaries produce progesterone and a certain amount of androgen.

The fifth level of regulation of reproductive function includes the internal and external parts of the reproductive system (uterus, fallopian tubes, vaginal mucosa) and mammary glands that are sensitive to sex steroid level imbalance [10]. Under the influence of sex hormones secreted by the ovaries, the tone, excitability and blood supply of the uterus are changed. Also cyclic changes occur in the functional layer of the endometrium (uterine cycle).

CLASSIFICATION OF MENSTRUAL IRREGULARITIES.

ETHIOLOGICAL AND PATHOGENETIC ASPECTS OF MENSTRUAL IRREGULARITIES

Menstrual irregularities are characterized by changes in the cycle, duration and volume of menstrual blood loss. According to the change in cyclicity, there are amenorrhea (absence of menstruation for 6 months or more), opsomenorrhea (rare menstruation, repeated after more than 35 days), spaniomenorrhea (extremely rare menstruation – 2 to 4 times a year), and promenomenorrhea (menstruation starts 21 or even fewer days after the onset of the previous one). The disturbed duration of menstruation is divided into oligomenorrhea (short menstruation up to 2 days) and polymenorrhea (duration of menstruation – 7 to 12 days). Changes in the amount of blood released during menstruation are represented by hypomenorrhea (mild volume of blood loss) and hypermenorrhea (excessive volume of blood loss). Anovulatory uterine bleeding (uterine bleeding that does not meet the parameters of normal menstruation in reproductive age) and dysmenorrhea (a cyclically repeated pain syndrome accompanying menstruation) are taken as a separate pathology.

Menstrual irregularities occur when one or more links in the neurohumoral regulation of the cycle are disturbed. The etiology of these disorders can be different [4, 12].

1. Ovarian diseases: impaired interaction with the pituitary gland; corpus luteum failure with decreased progesterone production; inflammatory diseases; injuries, surgery; cysts, polycystoses, ovarian tumours.
2. Chronic uterus inflammatory diseases, endometriosis, trauma, and tumours.
3. Violations of the hypothalamic-pituitary system in the critical periods of the development of the female body, especially during puberty and menopause. In this case, normal regulation of the cycle is disrupted due to insufficient secretion of FSH, LH, etc.
4. Acute and chronic infectious diseases that affect the hypothalamic-pituitary-ovarian system (parotitis, flu, tonsillitis, chronic tonsillitis, rheumatism, pneumonia) and the uterus (genital tuberculosis, sepsis); secondary immunological disorders that contribute to the development of autoimmune processes in the endometrium.
5. Chronic extragenital diseases: chronic pyelonephritis, chronic diseases of the gastrointestinal tract, hepatobiliary, cardiovascular and hematopoietic systems.
6. Conditions of acute and chronic stress (psychogeny). It is associated with the increased levels of ACTH, prolactin and, indirectly, cortisol, and the decreased level of LH cyclic secretion.
7. Hyperandrogenic conditions (chronic anovulation syndrome, PCOS). The condition is associated with a deficiency of the luteal phase, a persistent lack of the dominant follicle development and ovulation, respectively.
8. Unhealthy diet (hypovitaminosis), mental trauma, physical overwork.
9. Dysfunction of other endocrine glands (thyroid gland, adrenal glands).
10. Harmful environmental factors and occupational hazards.
11. Drug therapy: hormone replacement therapy, corticosteroids, anticoagulants, tranquilizers, antidepressants.
12. Genetic diseases.

As a rule, the pathogenesis of menstrual irregularities is determined by the level of damage to neuroregulation. The impaired follicular maturation, anovulation and infertility occur as a result of insufficient synthesis of follicle-stimulating and luteinizing hormones by the pituitary gland. In adolescent girls the menstrual irregularities are clinically manifested by a delayed menarche, irregular menstrual cycle, and primary or secondary amenorrhea in rare cases. In women of childbearing age, the menstrual irregularities are manifested by opsomenorrhea, oligomenorrhea, amenorrhea, menometorrhagia and/or infertility (primary or secondary). In addition, an insufficient level of follicle-stimulating hormone causes sexual dysfunction in women, such as decreased sexual desire and lack of orgasm [13].

The disturbance of the follicular phase of the menstrual cycle, often accompanied by premature atresia of the follicle, hypo-, oligo- and opsomenorrhea, develops due to the impaired synthesis of estrogen. Also, estrogen deficiency may be accompanied by hypoplasia of the mammary glands and uterus. This causes atrophic vaginal processes that lead to dryness of the vaginal mucosa, pain, difficulty in sexual intercourse and refusal of sexual life [14].

The decreased secretion of progesterone synthesized in the corpus luteum of ovaries underlies the development of the luteal phase deficiency of the menstrual cycle, the decrease in the ovulatory levels of the luteotropic hormone, the synthesis of prostaglandins, oxytocin and lysosomal enzymes in the follicle.

The decreased level of progesterone causes involutive processes in the mammary glands and the uterus: fibrocystic mastopathy and uterine hypoplasia [15].

The imbalance of the estrogen / progesterone ratio is characterized by severe premenstrual syndrome, the painful menstrual cycle, the changes of the duration of menstrual cycle of less than 21 or more than 35 days, vaginal dryness, infertility and discomfort during intercourse [14, 15].

FEMICYCLE IS AN EFFECTIVE AND SAFE CORRECTION OF MENSTRUAL IRREGULARITIES

Menstrual irregularities are a pathology requiring a long-term treatment. Therefore, an important aspect when choosing a therapy is not only effectiveness, but also safety. Today phytocompositions (herbal preparations) have such parameters. They significantly expand the possibilities of treating menstrual irregularities and are the best alternative to hormonal drugs, especially if they are contraindicated.

FEMICYCLE is a phytocomposition designed for the correction and prevention of menstrual irregularities. Each capsule contains 5 components: *Symplocos racemosa* extract - 125 mg, *Asparagus racemosus* extract - 100 mg, *Saraca indica* extract - 100 mg, *Glycyrrhiza glabra* extract - 50 mg, *Curcuma longa* extract - 40 mg. A large scientific evidence base has been collected regarding the plant extracts contained in the phytocomposition of Femicycle.

Symplocos racemosa

Symplocos racemosa extract contains a large number of phenolic glycosides, such as simplocoside, triterpenoids (betulinic, acetyloleanic, oleanolic acids) and quercetin-like flavonoids, which determine its pharmacological properties [6]. *Symplocos racemosa* has a long history of use in the treatment of diseases of female reproductive organs, and the results of numerous modern studies confirm its effectiveness and safety. It normalizes the hypothalamic-pituitary-ovarian levels of regulation of the female reproductive system, and has anti-blastoma, antioxidant, antiandrogenic and anti-inflammatory effects [16].

A study by M. Jung et al. (2014) [17], has established that isoflavone glycoside pesidobatigenin-7O- [bd-apitofuranosyl] simplocoside provides the main pharmacological action of *Symplocos racemosa* extract, namely normalization of the hormonal activity of the hypothalamic-pituitary system, which, in turn, restores the ovarian cycle of estrogen hormones.

Similar results have been shown in a study by N. Acharya (2016) [16]. The study has demonstrated the effectiveness of the biologically active substances of *Symplocos racemosa*, such as simplocoside, betulinic, acetyloleanic and oleanolic acids, in normalizing the hormonal activity of the hypothalamic-pituitary system, and restoring the levels of estrogen and progesterone as well. Also, there were established the additional properties of *Symplocos racemosa*, such as antiandrogenic and antioxidant effects.

A study by A.M. Durkar et al. (2014) [19] has revealed the hypolipidemia and antioxidant activity of ethanolic *Symplocos racemosa* extract under the experimentally created hyperlipidemia. The oral administration at doses of 200 and 400 mg/kg helped to restore the levels of high-density lipoprotein, improved the antiatherogenic index, prevented the increased formation of hepatic malondialdehyde and restored its depleted enzymatic and non-enzymatic antioxidant systems. The activity of glutathione, superoxide dismutase and catalase were increased, and cholesterol was decreased to the physiological norm. In addition, *Symplocos racemosa* extract significantly improved hepatocytes histoarchitectonics. A study by D. Wakchaure et al. (2011) [20] has found a pronounced hepatoprotective effect of simplocos extract, manifested by the restoration of marker enzymes of cytolysis (alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase). Also, against the background of toxic acute hepatitis, normalization of the levels of bilirubin, albumin, total proteins and antioxidant balance was reported.

A study by S.K. Panda (2017) has revealed the cytotoxic effect of biologically active substances of *Symplocos racemosa* extract on cancer cells of the cervix [22]. A study by U. Farooq et al. (2017) has revealed a high antibacterial activity of simplequinones, included in the composition of *Symplocos racemosa*, against methicillin-resistant strains of *Staphylococcus aureus* and *Proteus mirabilis* [22].

Asparagus racemosus

The main active components of *Asparagus racemosus* extract are steroidal saponins, namely shatavarins. A study by S. Kaviarasan et al. (2007) has shown the effectiveness of shatavarin-I and shatavarin IV in reducing lipid peroxidation activity and their pronounced antioxidant effect [23].

A study by S.S. Smita et al. (2017) has proved that shatavarins of *Asparagus racemosus* affect the hypothalamic-pituitary system. They also increase dopamine level, reduce alpha synuclein aggregation, and significantly increase mRNA expression of stress sensitive genes, which indicates a pronounced antioxidant effect of shatavarins [25].

A study by R. Singh et al. (2016) [26] has found that saponins and flavonoids of *Asparagus racemosus* are capable to exert the following positive pharmacological effects aimed at normalizing the functions of the female reproductive system: restoration of the ratio of follicle-stimulating and luteinizing hormones, improvement of folliculogenesis, ovulation and estrogen metabolism, and acceleration of the conversion of estradiol to low activity estrone. In addition, they have a pronounced progestogen effect by stimulating the synthesis of progesterone in the ovaries. All this facts contributes to the normalization of the menstrual cycle.

A study by N. Tiwari et al. (2017) [26] has found that the biologically active substances of *Asparagus racemosa* extract stimulate cellular and humoral immunity, as evidenced by the increased levels of pro-inflammatory cytokines (IL-6 and TNF), IgE, and IgG, respectively. A study by N. Plangsombat et al. (2016) has proved that *Asparagus racemosa* extract has an anti-inflammatory effect, which is manifested by 52% inhibition at a concentration of 1 µg / ml TNF-α that corresponds to the reference anti-inflammatory drugs [27].

Glycyrrhiza glabra

Glycyrrhiza glabra extract contains triterpene saponins (glycerizinic, glyceretic and uralenic acid, methyl esters and glucuronides) and flavonoids (liquiritigenin, neoliquiritin, uraloside). Biologically active substances (glycetrone and isoliquiritigenin), which are part of *Glycyrrhiza glabra* extract, increase the level of estrogen in the woman's body, which is important when the menstrual cycle is disturbed.

A study by S. Tamir et al. (2001) has found that isoliquiritigenin has a high affinity for estrogen receptors and is a potent antagonist of estradiol, which explains its high antiproliferative activity in the treatment of estrogen-dependent breast cancer. Inhibition of estrogen receptors in breast tissue with isoliquiritigenin allows for an antitumor effect [28].

A study by X. Li et al. (2013) has proved the antioxidant activity of *Glycyrrhiza glabra* flavonoids and their antiulcer activity [29]. Also, *Glycyrrhiza glabra* is characterized by a hypolipidemic effect, caused by triterpenoids, which ensures its effectiveness in the treatment of metabolic syndrome and obesity [30].

Two studies by J.K. Kim et al. (2006) and P. Thiyagarajan et al. (2011) have shown that glycopeptides of glycerizinic acid have anti-inflammatory properties [31, 32]. A study by X. Not et al. (2011) and V.R. Yadav et al. (2011) have revealed that

glycerol of glyceric acid has a powerful immunomodulating ability [33, 34] that can be used in the treatment of immunomediated diseases.

In addition, glyceric acid and its derivatives, such as glyceretic acid and uralenic acid from the group of triterpene saponins have a pronounced antiviral effect against herpes simplex virus [35].

A study by Y.X. Jiang [36] has proved that licorice extracts have anti-inflammatory and antitumor effects against estrogen-dependent breast cancer, which is due to pronounced inhibition of iNOS. Researchers also reported on the antispasmodic and calming effect of *Glycyrrhiza glabra* [37].

Saraca indica

Saraca indica extract contains tannin, catechol, phytosterols and organic calcium compounds. The biologically active substances of *Saraca indica* stimulate the secretion of estrogen, provide endometrial regeneration, and have pronounced anti-inflammatory and antispasmodic properties. Due to this, the menstrual cycle is restored and the pain caused by algodismenorrhea decreases. *Saraca indica* has a wide spectrum of antibacterial activity against several gram-positive and gram-negative pathogenic bacteria [43].

Procyanidin, included in *Saraca indica* composition, has a pronounced antioxidant property. According to some data procyanidin is much more powerful than ascorbic acid and vitamin E [44].

It is suggested that procyanidin can reduce the level of proinflammatory cytokines (interleukins) that mobilize the inflammatory response. Ergosterol, which is a substance that, under the influence of sunlight, turns into vitamin D, the metabolites of which regulate calcium transportation in the body, is also reported. In addition, the antitumor effect of *Saraca indica* has been proved [44].

Curcuma longa

Curcuma longa extract has a pronounced anti-inflammatory effect, comparable to the effect of hydrocortisone or phenylbutazone. The effect is due to *Curcuma longa* ability to inhibit the biosynthesis of inflammatory prostaglandins from arachidonic acid and activate the function of neutrophils in inflammatory conditions [39].

Curcuma longa extract has an antitumor effect. Moreover, curcumin, which is part of *Curcuma longa*, inhibits carcinogenesis at all three stages, such as tumour formation, angiogenesis and tumour growth. It is believed that such effect of *Curcuma longa* and curcumin is due to a direct antioxidant effect that reduces the production of reactive oxygen species, MDA, and caspase-3 and caspase-9 [40].

Curcuma longa extract also has antimicrobial and antifungal effects. It has a hepatoprotective effect, similar to the action of silymarin (milk thistle). The results of new studies confirm that curcuminoids (curcumin, bisdemetoxicurcumin and demethoxycurcumin) contained in *Curcuma longa* extract, normalize fatty acid metabolism and the process of hexosamine biosynthesis [41]. In addition, when applying *Curcuma longa* for a long time, a significant improvement in lipid profiles was recorded compared to placebo. Low-density lipoprotein cholesterol (LDL) was decreased, and high-density lipoprotein cholesterol (HDL) was increased. As a result a significant improvement of LDL/HDL ratio is observed [42].

CONCLUSIONS

Menstrual irregularities are a frequent pathological condition of the female reproductive system. FEMICYCLE phytocomposition is recommended as effective remedy for the correction and prevention of menstrual irregularities. FEMICYCLE consists of 5 components: *Symplocos racemosa* extract – 125 mg, *Asparagus racemosus* extract – 100 mg, *Saraca indica* extract – 100 mg, *Glycyrrhiza glabra* extract – 50 mg, *Curcuma longa* extract – 40 mg. The multicomponent composition of FEMICYCLE phytocomposition provides a polymodal pharmacological effect on all main pathogenetic links in case of menstrual irregularities. *Symplocos racemosa* extract restores the levels of FSH, LH, and estrogen, and maintains a normal ratio of FSH/LH in blood serum. It has an anti-inflammatory effect, and exhibits antioxidant activity. *Asparagus racemosus* extract has phytoestrogenic properties, and exhibits immunomodulatory, anti-inflammatory, antispasmodic, antioxidant and antibacterial effects. *Glycyrrhiza glabra* extract exhibits anti-inflammatory, antispasmodic and calming effects. *Saraca indica* extract has antispasmodic and antibacterial effects. *Curcuma longa* extract provides antioxidant, anti-inflammatory and antimicrobial effects.

The uniqueness of FEMICYCLE is the good tolerance and safety. FEMICYCLE is recommended for the correction and prevention of menstrual irregularities of various origins and infertility, and for the prevention of estrogen-dependent diseases as well (fibromyomas, mastopathy, endometriosis, cervical erosion).

Femicycle is used in the following dose:

1 capsule twice daily after meals; the duration of use is 3 to 6 months, depending on the severity of the disease and reduction of symptoms.

Food supplement. It is not a medicinal preparation.

For detailed information, contact Evitas Ltd.,

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References are in editorial office