Effectiveness of vitex agnus castus extract in the treatment of primary dysmenorrhea

Abstract. Background. Primary dysmenorrhea (PD) is one of the most common types of gynecological pathology and is observed in 31–52 % of young women, in 10 % of them the pain is so intense that leads to disability. In the pathogenesis of PD consider a representative of eicosanoids — thromboxane A2 with a pronounced vasoconstrictor effect. The article presents the results of clinical and hormonal examination of women with PD and developed on this basis a method of treatment. The purpose was to develop and evaluate the effectiveness of treatment of PD, taking into account the multicomponent pathogenesis of the disease. Materials and methods. There were 60 women observation, randomly divided into two groups: 30 women with PD (main group) and 30 healthy women (control group). PD was diagnosed on the basis of patients’ complaints of painful menstruation and related symptoms, excluding organic gynecological pathology and diseases of the internal organs in consultation with a physician and endocrinologist. Treatment of patients with PD was performed with a combined drug, which includes a standardized extract of Vitex agnus castus L., indole-3-carbinol, 3,3-diindolyl-methane, passionflower extract, California escholzia extract. Results. As a result of treatment in patients with PD significantly reduced the intensity of pain, and 60 % completely disappeared pain, all disappeared fear of waiting for the next menstruation, significantly reduced the manifestations of autonomic vascular (from 17 % of patients to 3 %), autonomic (from 10 % of patients to 0 %), metabolic and endocrine (from 13 % of patients to 0 %) disorders and disorders of the emotional and mental sphere (from 23 % of patients to 7 %), no patient had a combination of symptoms. Conclusions. Given the safety, high therapeutic efficacy, the drug based on Vitex agnus castus extract can be recommended for the treatment of young patients with PD lasting at least 3 months.

Keywords: menstrual pain; hormonal balance; primary dysmenorrhea

Introduction

Primary dysmenorrhea (PD) is defined as pain during the menstrual cycle in the absence of an identifiable cause. It is one of the most common causes of pelvic pain in women. PD is violation of the menstrual cycle (MC), which is manifested by cramping, less often aching pain in the lower abdomen, buttocks, lower back during menstruation and is accompanied by general malaise. PD is one of the most common types of gynecological pathology and is observed in 31–52 % of young women, in 10 % of them the pain is so intense that leads to disability [1]. Monthly pains, their expectations are reflected in the general well-being, emotional and mental spheres and disrupt intra-family and labor relations [2]. Therefore, PD is considered not only as a medical but also as a social problem.

The etiology of PD has not been established to date. Prostaglandin theory, dysfunction of the hypothalamic-pituitary-adrenal system and involvement in the process of female sex hormones [3]. The time discrepancy between the peak of contraction and the maximum sensation of pain is established. This indicates that the pain is caused not so much by the muscle contractions themselves as by the ische-mia with these contractions (spasmogenic dysmenorrhea), that is the pain is anoxic. The architecture of muscle fibers is disturbed, spastic contractions of the myometrium and uterine vessels are observed. This leads to oversaturation of myofibrils and muscle cells with calcium ions and biologically active substances, which causes persistent spasm of the myometrium. There is an increase in intrauterine pressure, amplitude and frequency of uterine contractions (2–
2.5 times compared with healthy women). In parallel, there is ischemia of other organs and tissues, which causes symptoms such as headache, nausea, diarrhea, tachycardia [4]. In the pathogenesis of PD consider a representative of eicosanoids — thromboxane A2 with a pronounced vasoconstrictor effect. A significant contribution to the contractile activity of the myometrium and the development of pain can make lipoygenase, which is a source of leukotrienes — substances with potent constrictive properties [4]. There are hypotheses about the role of psychological factors in the pathogenesis of PD. Patients with dysmenorrhea often have psychological features, including depression [5]. The threshold of pain sensitivity (essential dysmenorrhea) is important [6]. It should be noted and the hereditary factor, which is allocated up to 30 %. The authors believe that a prerequisite for the development of PD is the functional failure of the protease endometrium and impaired fragmentation of the falling uterine mucosa [7]. To date, the main principles of PD therapy include hormonal drugs (progestogens, combined oral contraceptives), non-hormonal drugs (nonsteroidal anti-inflammatory drugs, symptomatic drugs), physiotherapy procedures (acupuncture, respiratory gymnastics, transdermal electrical stimulation therapy), therapeutic exercise, psychotherapy, diet therapy. The most effective in the treatment of PD are combined estrogen-progestogen drugs [8]. Given the number of contraindications to hormone therapy, young age of patients, ineffectiveness of some symptoms of dysmenorrhea and negative contraceptive effect, the search for a more acceptable therapeutic agent continues.

The purpose of the study is to develop and evaluate the effectiveness of treatment of primary dysmenorrhea, taking into account the multicomponent pathogenesis of the disease.

Materials and methods

There were 60 women observation, randomly divided into two groups: 30 women with PD (main group) and 30 healthy women (control group). Group of patients are comparable with age, social status, absence of extragenital pathology and mass-growth indicators.

PD was diagnosed on the basis of patients’ complaints of painful menstruation and related symptoms, excluding organic gynecological pathology and diseases of the internal organs in consultation with a physician and endocrinologist. The intensity of pain was assessed using a verbal-analog scale (VAS): 0 — no pain, 2 — mild pain, 4 — moderate pain, 6 — severe pain, 8 — very severe pain, 10 — excruciating pain. The examined patients of both groups were intact, 4–6 days lasting 27–30 days of menstrual cycle in patients of both groups is intact, 4–6 days lasting 27–30 days.

All patients 100 % of the main group complained of fear of excessive bleeding, 50 % of them had pain 1 year after menstruation. The pain occurred on day 1–2 of the MC, was highly intense, localized in the hypogastrum. In 33 % of patients the pain radiated to the lumbar region, in 43 % — to the inner surface of the thighs, in 23 % — to the lumbar and inner surface of the thighs. 23 % of patients with PD had emotional and mental symptoms (irritability, depression, insomnia, bulimia, drowsiness), 10 % — had autonomic disorders (most often nausea, hiccups, diarrhea, sweating, chills, dry mouth, hot flashes, frequent urination, bloating), 17 % — vegetative-vascular symptoms (most often dizziness, loss of consciousness, headache, tachycardia, numbness of the extremities), 13 % — symptoms of metabolic and endocrine nature (severe weakness, vomiting, itchy skin, swelling of the eyelids, face, polyuria, joint pain, most often in the hip and shoulder). 37 % of patients with PD had a combination of different groups of symptoms.

All patients in the main group indicated the fear of experiencing pain during menstruation, reduced efficiency and social activity during this period. The menstrual cycle in patients of both groups is intact, 4–6 days lasting 27–30 days with moderate bloody discharge.

On general examination, asthenic body structure was found in 63 % of patients, low body weight — in 23 %, overweight — in 7 % of patients with PD, which did not differ from control group (p > 0.05). At gynecological examination and according to ultrasonography pathology was not detected in the examined patients, gynecological and somatic anamnesis were not burdened in patients of both groups. The social status of patients with PD is represented by female students — 63 %, IT workers — 30 % and business workers — 7 % without differences from the control group: 57, 33 and 10 %, respectively.

Statistical processing of the obtained data was performed using standard methods of descriptive and categorical statistics and a package of certified programs Statistica for Windows 13.0 (Statsoft Inc., USA).

Results

All patients 100 % of the main group complained of painful menstruation, 50 % of them had pain 1 year after menstruation. The pain occurred on day 1–2 of the MC, was highly intense, localized in the hypogastrum. In 33 % of patients the pain radiated to the lumbar region, in 43 % — to the inner surface of the thighs, in 23 % — to the lumbar and inner surface of the thighs. 23 % of patients with PD had emotional and mental symptoms (irritability, depression, insomnia, bulimia, drowsiness), 10 % — had autonomic disorders (most often nausea, hiccups, diarrhea, sweating, chills, dry mouth, hot flashes, frequent urination, bloating), 17 % — vegetative-vascular symptoms (most often dizziness, loss of consciousness, headache, tachycardia, numbness of the extremities), 13 % — symptoms of metabolic and endocrine nature (severe weakness, vomiting, itchy skin, swelling of the eyelids, face, polyuria, joint pain, most often in the hip and shoulder). 37 % of patients with PD had a combination of different groups of symptoms.

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Statistical processing of the obtained data was performed using standard methods of descriptive and categorical statistics and a package of certified programs Statistica for Windows 13.0 (Statsoft Inc., USA).
The results of the hormonal balance of healthy women indicate a decrease in Pg, E2, Prl on the 2nd day of MC compared to the 22nd, a stable content of Adr and a slight increase in K, which does not exceed the reference values. In women with PD before treatment compared with healthy in the second phase of MC revealed a decrease in Pg, increase in E2, Prl, K. On the 2nd day of MC revealed a significant decrease in Pg, E2 and increase in Prl, K, Ts, Adr compared with healthy women and compared with the second phase of MC (table 1).

During treatment with the drug containing Vitex agnus castus there is a dynamics of hormonal parameters in patients with PD, namely: after 1 month decreased the amount of Adr, after 2 month decreased the amount of Adr and Prl, after 3 month increased the content of E2, Prl, K, Ts, Adr and increased vPgs content on the 2nd day of MC (table 2).

### Discussion

Taking into account the obtained hormonal results of the examination and the accompanying symptoms for therapeutic purposes, the combined drug brestagyn (SERIS S.R.L., Italy) is pathogenetically justified, due to the components that are part of it. The main active ingredient of the drug is Vitex agnus castus L. extract. Vitex agnus castus L. extract binds to opioid beta-estrogen receptors, dopamine D2 receptors, and inhibits the secretion of Prl from pituitary cells [9]. The extract normalizes the ratio of gonadotropic hormones, increases the secretion of luteinizing hormone, resulting in increased Pg synthesis and normalizes the estrogen-progestogen ratio, eliminating the state of relative hyperestrogenism. Elimination of hyperprolactinemia also leads to the elimination of a number of neuropsychiatric symptoms. 3,3-diindolylmethane is involved in E2 metabolism, prevents the formation of the carcinogenic metabolite 16-alpha-hydroxyestrone [10]. Indole-3-carbinol promotes normalization of estrogen metabolism by induction of active cytochrome CYP1A1, responsible for the formation of 2-hydroxyestrone, inhibition of pathological cell proliferation, induction of apoptosis [11]. The components of passionflower extract inhibit the transmission of nerve impulses in the brain and spinal cord, reduce the excitability of the central nervous system, causing a sedative effect. Passionflower improves mood in depressive states, reduces anxiety and mental stress, has a mild hypnotic effect without feeling depressed during awakening, eliminates a number of autonomic symptoms (palpitations, hot flashes, sweating), which is equally important for patients with PD [12]. California alkaloids of the California protopine group increase

### Table 1. The state of hormonal balance in the examined women before treatment

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Control group (n = 30)</th>
<th>PD (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22d MC</td>
<td>2d MC</td>
</tr>
<tr>
<td>Pg, ng/ml</td>
<td>21.4 ± 4.7</td>
<td>1.1 ± 0.3</td>
</tr>
<tr>
<td>E2, pg/ml</td>
<td>109.0 ± 11.1</td>
<td>21.1 ± 3.3</td>
</tr>
<tr>
<td>PRL, pg/ml</td>
<td>15.3 ± 1.1</td>
<td>5.9 ± 0.3</td>
</tr>
<tr>
<td>K, mcg/l</td>
<td>7.3 ± 0.4</td>
<td>6.7 ± 0.5</td>
</tr>
<tr>
<td>Ts, nmol/l</td>
<td>0.61 ± 0.07</td>
<td>0.53 ± 0.01</td>
</tr>
<tr>
<td>Adr, ng/l</td>
<td>19.5 ± 0.5</td>
<td>29.0 ± 8.8</td>
</tr>
</tbody>
</table>

**Note:** * — the difference is significant compared to the control group.

### Table 2. The state of hormonal balance in women with PD in the dynamics of treatment

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Before treatment</th>
<th>1 month after</th>
<th>2 month after</th>
<th>3 month after</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22d MC</td>
<td>2d MC</td>
<td>22d MC</td>
<td>2d MC</td>
</tr>
<tr>
<td>Pg, ng/ml</td>
<td>10.1 ± 0.9</td>
<td>0.3 ± 0.1</td>
<td>11.4 ± 1.0</td>
<td>0.7 ± 0.1</td>
</tr>
<tr>
<td>E2, pg/ml</td>
<td>179.3 ± 23.1</td>
<td>96.4 ± 21.4</td>
<td>166.4 ± 38.4</td>
<td>75.1 ± 5.5</td>
</tr>
<tr>
<td>PRL, pg/ml</td>
<td>27.1 ± 5.3</td>
<td>15.0 ± 4.4</td>
<td>25.0 ± 0.7</td>
<td>10.0 ± 0.5</td>
</tr>
<tr>
<td>K, mcg/ml</td>
<td>10.9 ± 0.4</td>
<td>29.1 ± 8.8</td>
<td>11.1 ± 0.9</td>
<td>22.2 ± 1.9</td>
</tr>
<tr>
<td>Ts, nmol/l</td>
<td>1.04 ± 0.05</td>
<td>1.01 ± 0.17</td>
<td>1.00 ± 0.50</td>
<td>0.91 ± 0.08</td>
</tr>
<tr>
<td>Adr, ng/l</td>
<td>18.9 ± 0.7</td>
<td>55.2 ± 6.9</td>
<td>19.8 ± 1.0</td>
<td>34.5 ± 4.4</td>
</tr>
</tbody>
</table>

**Note:** * — the difference is significant compared to the indicators before treatment.
the *in vitro* binding of gamma-oxybutyric acid to sensitive receptors in the brain, the extract has an anxiolytic effect, improves the quality and duration of sleep [13].

Cramping pains in the lower abdomen in PD are due to spastic contractions of the uterus, spasm of arteries and bleeding of muscle tissue, which cause myometrial ischemia [14]. The results of our research are a significant contribution to understanding the causes of this condition. A decrease in the content of Pg and an increase in E₂ in the second phase of MC in PD leads to relative hyperestrogenism and hyperprolactinemia. E₂ increases the synthesis and yield of actomyosin from the uterine muscle by 67.7 %, which leads to increased contractility of the myometrium [5]. Detection of elevated androgen content in PD leads to stasis and sclerotic changes in the microcirculation, increases the fragility of myometrial vessels, contributing to local hypoaxia and accumulation of lactates, which by irritating the nerve endings cause visceral pain [14]. Painful stimulus causes stress in women, and stressful stimuli trigger the secretion of catecholamines by the adrenal medulla, which causes additional clinical symptoms in PD. Adr binds to alpha₁-adrenergic receptors, triggering vasospasm and smooth muscle contraction. In addition, the effect of Adr on hydrocarbon metabolism is known, causing activation of glycogenolysis in muscles and liver. This leads to increased glycemia and accumulation of lactic acid in the muscles, to accelerated oxygen consumption [12], creating a vicious circle in the pathophysiology of PD. Pain in PD also causes increased release of K², which is associated with metabolic-endocrine symptoms. Significantly reduced Pg content does not block, as usual, the spastic properties of the above factors, does not show its anxiolytic action, which is so important in this period of MC. Thus, the menstrual period in women with PD is a stressful situation.

The above-mentioned changes in homeostasis were inevitably realized in the clinical symptoms of patients with PD: they significantly reduced the intensity of pain (intolerable to treatment, strong after 1 month, moderate after 2 months, weak after 3 months on the VAS scale), and 60 % completely disappeared pain, all disappeared fear of waiting for the next menstruation, significantly reduced the manifestations of autonomic vascular (from 17 % of patients to 3 %), autonomic (from 10 % of patients to 0 %), metabolic and endocrine (with 13 % of patients up to 0 %) disorders and disorders of the emotional and mental sphere (from 23 % of patients up to 7 %), no patient had a combination of symptoms. One month after treatment, 70 % of patients with PD noted an improvement in quality of life, and 60 % — an increase in efficiency; 2 months later — 93 % and 83 %, respectively, after 3 months, all surveyed patients with PD noted an improvement in quality of life and increased efficiency. No patients had any side effects during treatment.

**Conclusions**

1. In patients with PD in the second phase of MC compared with healthy women found a decrease in the content of Pg, an increase in the content of E₂ and Prl.

2. Hormonal examinations on the second day of MC in patients with PD revealed a significant decrease in the content of Pg, a decrease in the content of E₂, a state of relative hyperestrogenism, an increase in the content of Adr, K, Prl, Tsₜₐ, compared with healthy women. The changes in homeostasis detected in patients with PD were realized in the pain syndrome of high and unbearable intensity and a number of emotional-mental, vegetative-vascular and metabolic-endocrine symptoms.

3. Therapeutic use of a combined phytopreparation with Vitex agnus castus extract for three month provided an impact on all links of pathophysiological changes in PD, showing hormonal and pronounced clinical effects in patients with PD, which led to increased efficiency and quality of life in all treated patients.

4. Given the safety, high therapeutic efficacy, satisfaction of patients with PD treatment and economic adequacy of the drug to avoid pharmacological polypragmatism, the drug based on Vitex agnus castus extract can be recommended for the treatment of young patients with PD lasting at least 3 months.

**References**


Резюме. Актуальність. Первинна дисменорея (ПД) — один з найпоширеніших видів гінекологічної патології, що спостерігається у 31–52 % молодих жінок, серед яких у 10 % інтенсивність процесу призводить до інвалідності. Патогенез ПД враховує вплив таких ейкозаноїдів, як тромбоксан А2 з вираженою судинозвужувальною дією. У статті надані результати клініко-гормонального обстеження жінок з ПД та розроблена на цій основі методика лікування.

Мета: розробити й оцінити ефективність лікування ПД з урахування багатокомпонентного патогенезу захворювання.

Матеріали та методи. Під спостереженням перебувало 60 жінок, випадковим чином розподілених на дві групи: 30 жінок із ПД (основна група) та 30 здорових жінок (контрольна група). Діагноз ПД встановлювався на підставі скарг пацієнток на болючі менструації та супутні симптоми, за винятком органічної гінекологічної патології та захворювань внутрішніх органів, на консультаціях у гінеколога й ендокринолога. Лікування хворих на ПД проводили комбінованим препаратом, до складу якого входять стандартизований екстракт Vitex agnus castus L., індол-3-карбінол, 3,3-диіндоліл-метан, екстракт пасифлори, екстракт каліфорнійської ешольці.

Результати. В результаті лікування у хворих на ПД значно зменшилася інтенсивність болю, а у 60 % біль зник повністю, у всіх зник страх очікування наступної менструації, значно зменшилися прояви вегетативно-судинної системи (з 17 до 3 % пацієнток), вегетативні (від 10 до 0 % хворих), метаболічні й ендокринні (від 13 до 0 % хворих) розлади та розлади емоційно-психічної сфери (від 23 до 7 % хворих). Через 1 місяць після лікування поліпшення якості життя відзначали 70 % (21/30) пацієнток з ПД, а підвищення працездатності — 60 % (18/30), через 2 місяці — 93 % (28/30) і 83 % (25/30) відповідно. В жодній пацієнції під час лікування не було виявлено побічних ефектів.

Висновки. З огляду на безпеку та високу терапевтичну ефективність препарат на основі екстракту Vitex agnus castus можна рекомендувати для лікування молодих хворих із ПД тривалістю не менше трьох місяців.

Ключові слова: менструальний біль; гормональний баланс; первинна дисменорея