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RATIONAL APPROACH IN THE TREATMENT OF WOMEN OF REPRODUCTIVE AGE WITH MASTALGIA AND MASTODYNIA

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More than 82 % of women of reproductive age note pain in the mammary gland. Every fifth woman feels severe pain (mastalgia) and swelling (mastodynia) in the mammary gland. Cyclic mastalgia is combined with hyperprolactinemia. Hyperprolactinemia occurs when dopamine does not suppress pituitary function enough to reduce prolactin release. Agni casti fructus, known for its dopaminergic activity, relieves pain and discomfort in the mammary glands. 50 patients were under observation. Only 10 % of patients felt mild pain, 32 % experienced moderate pain, 50 % assessed it as severe, and 8 % experienced extreme pain. After the treatment, the complete absence of pain was noted by 76 % of patients. The results of the conducted studies indicate a high efficiency of 76 % and the safety of using Agni casti fructus in treating mastalgia and mastodynia. The high efficiency in the treatment of mastalgia and mastodynia with the herbal medicine Agni casti fructus without the additional use of hormonal drugs can be explained by the fact that this drug normalizes the hormonal balance of a woman.

Key words: pain, mastalgia, mastodynia, Agni casti fructus, treatment.

Л.Б. Маркін, Т.В. Фартушок, Н.В. Фартушок, І.С. Пилипчук, В.В. Флуд, Е.А. Джалілова РАЦІОНАЛЬНИЙ ПІДХІД У ВЕДЕННІ ЖІНОК РЕПРОДУКТИВНОГО ВІКУ З МАСТАЛГІЄЮ ТА МАСТОДИНІЄЮ

Наявність болю в молочній залозі відмічають більше 82 % жінок репродуктивного віку, кожна п'ята жінка відчуває сильний біль (масталгію) і нагрубання (мастодинію) у молочній залозі. Циклічна масталгія поєднується на з гіперпролактинемією. Гіперпролактинемія спостерігається коли дофамін недостатньо пригнічує функцію гіпофізу, щоб зменшити вивільнення пролактину. Agni casti fructus відомий своєю дофамінергічною активністю, полегшує біль та дискомфорт в молочних залозах. Під спостереженням знаходилося 50 пацієнток. Слабкий біль відчували тільки 10 % пацієнток, у 32 % пацієнток помірний, 50 % пацієнток оцінювали як сильний і надсильний – 8 %. Після проведеного лікування повну відсутність болю відмічали 76 % пацієнток. Результати проведених досліджень свідчать про високу ефективність 76 % і безпечність застосування Agni casti fructus у лікуванні масталгії і мастодинії. Високу ефективність у лікуванні масталгії і мастодинії фітопрепаратом Agni casti fructus без додаткового використання гормональних препаратів можна пояснити тим, що цей препарат нормалізує гормональний баланс жінки.

Ключові слова: біль, масталгія, мастодинія, Agni casti fructus, лікування.

The study is a fragment of the research project "Improving the prevention of intranatal fetal damage in labor abnormalities", state registration No. 0122U000166.

Mastalgia and mastodynia are the most common disorders in women of reproductive age. Stressful factors in modern conditions cause increased secretion of prolactin by the pituitary gland, which is the cause of mastalgia and mastodynia. About 82 % of women of reproductive age complain of cyclic mastalgia of varying degrees of severity [1]. Pain and swelling in the mammary gland are the leading complaints that women consult their doctor [2].

Acyclic pain in the mammary gland most often occurs in the presence of a pathological process: tumour, trauma, inflammatory process (mastitis, thrombophlebitis), or diffuse benign changes (mastopathy, dysplasia) [3]. The cause of acyclic pain in the mammary gland is the use of high- and low-dose combined oral contraceptives (COCs) [4].

As of today, the etiology and pathogenesis of mastalgia and mastodynia have not been definitively studied. The ratio of estradiol and progesterone concentrations in breast tissues determines its functioning. Violating the ratio of estradiol and progesterone causes functional (mastalgia, mastodynia) and morphological (fibrocystic mastopathy) changes.

It is not absolute, but a relative hyperestrogenic state is essential. Relative hyperestrogenism occurs in the second phase of the menstrual cycle due to insufficient function of the corpus luteum. Local hyperestrogenism plays a leading role in the pathogenesis of mastalgia and mastodynia. Comparing the concentrations of estradiol and progesterone in the blood plasma and the connective tissue of the mammary gland, an increase in the level of estradiol in the connective tissue of the mammary gland by 10–20 times and progesterone by 5–10 times is noted [5]. Estrogens cause edema and hypertrophy of the connective tissue of the breast. DNA synthesis and the mitotic activity of ductal epithelium increase with long-term hyperestrogenism, alveoli enlarge, and cystic cavities form [6].

Under the influence of progesterone, the development of the mammary gland's ducts and alveoli is stimulated, differentiation into lobes occurs, and the mitotic activity of the epithelial cells of the mammary

ducts is inhibited [7]. Mitotic activity is replaced by apoptosis. In addition, progesterone reduces the effect of estrogens on breast tissue [8].

Prolactin plays an equally important role in the pathogenesis of cyclic mastodynia. Being in chronic stressful situations (industrial, family, socio-political and other problems) of a modern woman causes a pathologically increased secretion of prolactin.

Chronic stress causes hypothalamic dopamine neurons to reduce their secretion into the portal vascular system. A condition develops that is explained by a lack of dopaminergic inhibition. This condition is confirmed by the fact that the introduction of synthetic dopamine agonists reduces the level of prolactin [9].

Increased prolactin activates aldosterone, which retains sodium, and vasopressin, which retains fluid and electrolytes in the mammary gland, leading to breast tenderness and swelling [10].

About 30 % of women with mastalgia and mastodynia need therapy aimed at reducing pain. Using bromocriptine, tamoxifen, and danazol is pathogenetically justified [11]. However, the development of side effects limits the use of these drugs. When choosing treatment tactics, women prefer herbal medicine [11].

Because of this, the role of *Vitex agnus-castus*, known for its dopaminergic activity, in alleviating the pain and discomfort characteristic of mastalgia and mastodynia has been widely investigated [12].

The mechanism of action of *Agni casti fructus* consists of binding to type 2 dopamine receptors in the brain, which decreases the activity of cells (lactotropic cells) that produce prolactin in the anterior lobe of the pituitary gland [13].

A German expert commission recommends extracts from the Abraham tree to treat premenstrual mastodynia disorders.

When hyperprolactinemia and cyclical pain (mastalgia) occur, drugs based on *Agni casti fructus* are used.

So, because *Agni casti fructus* normalizes a woman's hormonal balance and has an analgesic, anti-edematous, antioxidant, and immunomodulating effect, it is used in the treatment of fibrocystic mastopathy and mastalgia.

The purpose of the study was to study the effectiveness of *Agni casti fructus* for the treatment of women of reproductive age who suffer from cyclical mastalgia and mastodynia.

Materials and methods. Fifty women with cyclical mastalgia and mastodynia were observed, who underwent an outpatient examination before and after treatment with *Agni casti fructus*. All patients were prescribed one tablet of *Agni casti fructus* at 20 mg daily for three months. The effectiveness of the treatment was determined based on the complaints of the patients according to the data of the visual-analogue scale in combination with the verbal ranking scale and the ultrasound scanning results (US).

The examination included collecting medical history data, general clinical and gynecological examination, and ultrasound of the pelvis and mammary glands. When collecting anamnesis, attention was paid to the time of the first menstruation, the number of deliveries, the duration of breastfeeding, and previous pelvic inflammatory diseases. When examining the mammary glands, attention was paid to their shape, symmetry, subcutaneous fat tissue, discharge from the nipples, and the presence or absence of painful areas. Patients aged 18 to 45 with complaints of cyclical mastalgia and mastodynia participated in the study with their voluntary consent.

Pain complaints were recorded according to the visual-analogue scale (VAS) and the verbal rating scale (VRS) proposed by V.V. Kuzmenko (1986). The combined scale is a straight line 10 cm long with centimeter divisions applied, which correspond to the intensity of pain from 0 to 10 points. 2 cm corresponds to the descriptor "mild", 4 cm – "moderate", 6 cm – "severe", 8 cm – "extremely severe", 10 cm – "unbearable" pain. The patients themselves determined the intensity of pain before the start of treatment and at the end of the third month of treatment. The patients were tested during the premenstrual phase on the 24th-30th day of the menstrual cycle.

When performing the work, measures are provided to ensure the safety of human health, human dignity and moral and ethical standards by the principles of the Helsinki Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine and the relevant laws of Ukraine (conclusion of the Commission on Bioethics of the Danylo Halytsky Lviv National Medical University).

Statistical processing of the obtained results was done using the Statistica 6.0 program using the Student's t-test.

Results of the study and their discussion. The mean age of the patients was 31.4 ± 5.8 years. The mean age at which the first menstrual period began was 12.4 ± 1.2 , the duration of menstruation was 4.6 ± 2.1 days, and the cycle duration was 28.3 ± 4.8 days. Analyzing the obtained results, it can be asserted that the patients had no deviations in the establishment and course of menstruation. 35 (70 %) women were married,

32 (64 %) women noted regular (2 times a week) sex life. Analyzing the obstetric anamnesis, 33 (66 %) women were pregnant, 26 of them had single births, and 7 had artificial abortions. Infertility was found in 15 (30 %) patients.

The examined patients noted mastalgia and mastodynia for 1 to 10 years. All patients complained of pain, swelling, and heaviness in the mammary glands, which occurred a few days before menstruation or from the middle of the menstrual cycle, and an increase in the volume and density of the mammary gland tissues.

We examined 50 patients, divided into three groups commensurate with age and obstetric, gynecological, and somatic anamnesis data. The first group consisted of 17 women with mastalgia and mastodynia combined with diffuse mastopathy. The 2nd group included 17 patients with mastopathy and the appearance of small-filled cysts. The 3rd group consisted of 16 women with mastalgia and mastodynia without detected changes in the mammary glands.

Features of the gynecological history and data on childbirth and breastfeeding are given in Table 1.

Table 1

Features of obstetric and gynecological history in the examined patients

Pathology	Group 1, n=17 abs. number %	Group 2, n=17 abs. number %	Group 3, n=16 abs. number %
Violation of the cycle	9 (52.9 %)	5 (29.4 %)	6 (37.5 %)
Insufficiency of the luteal phase	7 (41.2 %)	6 (35.3 %)	3 (18.8 %)
Dysmenorrhea	8 (47.1 %)	5 (29.4 %)	3 (18.8 %)
Infertility	6 (35.3 %)	7 (41.2 %)	2 (12.5 %)
Miscarriage	10 (58.8 %)	8 (47.1 %)	4 (25.0 %)
Inflammatory diseases	9 (52.9 %)	8 (47.1 %)	6 (37.5 %)
Uterine leiomyoma	8 (47.1 %)	7 (41.2 %)	6 (37.5 %)
Single birth	11 (64.7 %)	10 (58.8 %)	9 (56.3 %)
Childbirth after 25 years	8 (47.1 %)	9 (52.9 %)	10 (62.5 %)
Breastfeeding for a year	3 (17.6 %)	3 (17.6 %)	4 (25.0 %)
Low milk supply	6 (35.3 %)	7 (41.2 %)	5 (31.3 %)

Analysis of the gynecological history shows the predominance of inflammatory diseases of the female genital organs and neuroendocrine pathology in patients of the 1st and 2nd groups: menstrual cycle disorders, luteal phase deficiency (LPD), dysmenorrhea, infertility, miscarriage, uterine leiomyomas.

Analyzing the obstetric anamnesis data of the examined patients, it can be stated that only half of them gave birth, and these were the only births. Childbirth after the age of 25 occurred from 47.1 % to 62.5 % of women.

In women of group 3, uterine leiomyomas and inflammatory diseases of the genital organs were the most common gynaecological diseases. Only 17.6 % of women in group 1 and 17.6 % of women in group 2 were breastfeeding, and low milk supply was registered in 35.3 % of the patients in group 1 and 41.2 % in group 2, respectively. Among women of group 3, low milk supply was observed in 31.3 % of cases, and 25 % of women breastfed during the year.

Therefore, the results of the gynecological and obstetrical anamnesis indicate the leading importance in the etiology and pathogenesis of mastalgia, mastodynia and mastopathy of gynecological neuroendocrine and inflammatory pathology, as well as the absence or a small number of births, births after 25 years, low milk supply and rare cases of breastfeeding up to a year.

When examining the mammary glands of patients of group 1 with mastopathy (fibrocystic disease), we palpated diffuse thickenings in the form of cords in the upper outer quadrants of the mammary glands. Among the patients of group 2, palpation of the mammary glands revealed a small cyst. During palpation, mammary gland formations in groups 1 and 2 patients were painful. We observed colostrum discharge when pressing on the nipples in a third of the women of the 1st and 2nd groups.

The results of the treatment are presented in Table 2.

The analysis of the results shows that the patients we examined experienced significant pain in the mammary glands. Pain intensity was assessed as mild pain in only 5 (10 %) patients; 16 (32 %) patients rated pain as moderate, 25 women (50 %) severe and super – severe (8 %) patients.

After the treatment, 38 (76 %) of 50 patients noted a complete absence of pain. Two (4 %) patients noted mild pain. However, they indicated that pain intensity decreased compared to before treatment.

The complete absence of pain was indicated by all patients of Group 3, in whom mastalgia and mastodynia were not combined with destructive changes in the mammary glands. When mastalgia was combined with cystic changes in the mammary glands, 70.6 % of patients indicated complete absence of pain. Among the patients in this group, only 1 (5.8 %) experienced mild pain, which was considered a positive result of the treatment.

Efficacy of treating patients of the examined groups by pain intensity

Examined groups n=50	Terms of examination	Characteristics of pain				
		Mild n %	Moderate n %	Severe n %	Excessive n %	Unbearable n %
Group 1, n=17	Before treatment	2 (11.7 %)	3 (17.6 %)	10 (58.8 %)	2 (11.7 %)	0
	After treatment	1 (5.8 %)	1 (5.8 %)	0	0	0
Group 2, n=17	Before treatment	2 (11.7 %)	10 (58.8 %)	5 (29.4 %)	0	0
	After treatment	1 (5.8 %)	3 (17.6 %)	0	0	0
Group 3 n=16	Before treatment	1 (6.3 %)	3 (18.8 %)	10 (62.5 %)	2 (12.5 %)	0
	After treatment	0	0	0	0	0

In the patients of group 1, the pain disappeared in 12 (70.6 %) patients and 1 (5.8 %) patients experienced significant relief, but mild pain remained in 1 (5.8 %) patients.

So, we observed the complete disappearance of mastalgia after 3 months of treatment with Agni casti fructus in 76 % of cases. It should be noted that the highest efficiency (100.0 %) was observed in patients in whom cyclic mastalgia is not combined with dystrophic changes in the mammary glands.

While conducting a clinical examination, we noted the disappearance of swelling, density of the mammary glands, and reduction or even disappearance when pressing on the mammary glands of colostrum secretions from the nipples.

Analyzing the results of the use of Agni casti fructus in ultrasound of the mammary glands, 3 months after the start of treatment, a decrease in fibrocystic formations was noted in 14 (82.4 %) patients of group 1. Among the patients of group 2, a reduction of cysts by 1.5-2 times was found during ultrasound of the mammary glands. In 3 (17.6 %) patients of group 2, no changes in the size of cysts were detected, in connection with which they were recommended to continue using the herbal preparation Agni casti fructus for a total duration of 6 months with further consultation of a gynecologist.

Four studies [8, 9, 11, 13] compared pain intensity subjectively determined by patients on a linear visual analogue scale and found that Agni casti fructus therapy was more effective than placebo in reducing breast pain intensity after three months of treatment. Heskes et al. [6] showed that pain intensity decreased significantly faster during the first two months of treatment with Agni casti fructus than with placebo. Li AD et al. [7] found that using Agni casti fructus in tablets and solutions is equally effective. Better efficacy of Agni casti fructus compared to placebo was also confirmed by Rafeian-Kopaei M et al. [9], although in a small number of patients with cyclic mastalgia (n=20), as well as Ryan SA [12] in a non-randomized study. In a randomised placebo-controlled trial, Rafique N et al. [10] evaluated mastalgia symptoms in more detail. To record pain intensity daily, the participants used the Cardiff pain chart. The results, including the nominal number of days with breast pain and the average duration of breast pain, showed that treatment with Agni casti fructus was significantly more effective than placebo.

Agni casti fructus has been compared with pharmaceuticals for treating cyclic mastalgia in one open-label randomized clinical trial [10] and three non-randomized trials [12–14]. Agni casti fructus was found to be as effective as dopamine agonists in studies by Matthewman G et al. [8] (bromocriptine) and Ryan SA [12] (bromocriptine and dostinex), and non-steroidal anti-inflammatory drugs in the studies of Semenyna HB [13] (meloxicam) and Sogame M et al. [14] (flurbiprofen). In all these studies, there was no statistically significant difference in the reduction of pain intensity between the groups using Agni casti fructus and the pharmaceutical comparison drugs.

Heskes AM et al. [6] and Ryan SA. [12] demonstrated that hormone concentrations decreased significantly in patients with elevated prolactin levels after Agni casti fructus treatment. This effect was stronger than when using a placebo [8].

Conclusions

1. A sufficient evidence base supports the high efficiency of herbal preparations in treating cyclic mastalgia and mastodynia without structural changes of the mammary glands.
2. The results of our research indicate the high efficiency (76 %) and safety of using the herbal preparation Agni casti fructus in the treatment of mastalgia and mastodynia in patients with benign pathological conditions of the mammary glands.
3. The high effectiveness of herbal medicine for mastalgia and mastodynia in patients with mammary gland pathology can be explained by the fact that Agni casti fructus normalizes a woman's hormonal balance.

References

1. Armour M, Parry K, Manohar N, Holmes K, Ferfolja T. The prevalence and academic impact of dysmenorrhea in 21,573 young women: A systematic review and meta-analysis. J Women Health. 2019; 28:1161–1171. doi: 10.1089/jwh.2018.7615
2. Bajalan Z, Moafi F, MoradiBaglooei M, Alimoradi Z. Mental health and primary dysmenorrhea : A systematic review. J Psychosom Obstet Gynecol. 2018; 40:1–10. doi: 10.1080/0167482X.2018.1470619

3. Burnett M, Lemyre M. Primary dysmenorrhea consensus guideline. J Obstet Gynaecol Can. 2017; 39:585–595. doi: 10.1016/j.jogc.2016.12.023
4. Escobar LK. Two new species of Passiflora (Passifloraceae) from Northern South America. Phytologia. 2019; 69:364–367. doi: 10.5962/bhl.
5. Fernandez-Martinez E, Abreu-Sanchez A, Velarde-Garcia JF, Iglesias-Lopez MT, Perez-Corrales J. Living with restrictions. The perspective of nursing students with primary dysmenorrhea. Int J Environmental Res Publ Health. 2020; 17(22):8527. doi: 10.3390/ijerph17228527
6. Heskes AM, Sundram TCM, Boughton BA, Jensen NB, Hansen NL. Biosynthesis of bioactive diterpenoids in the medicinal plant Vitex agnus castus. Plant J. 2018; 93(5):943–948. doi: 10.1111/tpj.13822
7. Li AD, Bellis EK, Girling JE, Jayasinghe YL, Grover SK. Unmet needs and experiences of adolescent girls with heavy menstrual bleeding and dysmenorrhea: A qualitative study. J Pediatr Adolesc Gynecol. 2020; 33:278–284. doi: 10.1016/j.jpog.2019.11.007
8. Matthewman G, Lee A, Kaur JG, Daley AJ. Physical activity for primary dysmenorrhea: A systematic review and meta-analysis of randomized controlled trials. Am J Obstet Gynecol. 2018; 219:e1–e255. doi: 10.1016/j.ajog.2018.04.001
9. Rafieian-Kopaei M, Movahedi M. Systematic Review of Premenstrual, Postmenstrual and Infertility Disorders of Vitex Agnus Castus. Electron Physician. 2017 Jan 25;9(1):3685–3689. doi: 10.19082/3685.
10. Rafique N, Al-Sheikh MH. Prevalence of primary dysmenorrhea and its relationship with body mass index. J Obstet Gynaecol Res. 2018; 44:1773–1778. doi: 10.1111/jog.13697
11. Ryabukha O.I. Peculiarities of thyroidal colloid hormonal activity of white rats' thyrocytes during consumption of organic and inorganic iodine in conditions of potentiated alimentary iodine deficiency. World of Medicine and Biology 2020;4 (74): 193–198. doi: 10.26724/2079-8334-2020-4-74-193-198
12. Ryan SA. The treatment of dysmenorrhea. Pediatr Clin Am. 2017; 64:331–342. doi: 10.1016/j.pcl.2016.11.004.
13. Semenyna HB, Shatylovych KL, Fartushok TV, Komissarova OS, Yurchushyn OM. A new approach to the combination therapy of polycystic ovary syndrome. World of Medicine and Biology. 2020; 2(72):125–129 doi: 10.26724/2079-8334-2020-2-72-125-129
14. Sogame M, Naraki Y, Sasaki T, Seki M, Yokota K. Quality assessment of medicinal product and dietary supplements containing Vitex agnus castus by HPLC fingerprint and quantitative analyses. Chem Pharm Bull (Tokyo). 2019; 67(6):527–533. doi: 10.1248/cpb.c18-00725

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CHANGES IN THE ORAL MUCOSA UNDER THE INFLUENCE OF LOW-FREQUENCY ELECTROMAGNETIC RADIATION

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The study was devoted to analyze the condition of the oral mucosa under the influence of low-frequency (70 kHz) industrial frequency electromagnetic radiation in the clinical setting (111 individuals – workers of the Kharkiv Tractor Plant) and in the experimental part (36 laboratory rats of the WAG-population). The results of the clinical and experimental examination confirm the negative impact of prolonged professional exposure to electromagnetic radiation both on the oral mucosa of patients and laboratory animals, which requires implementation of therapeutic and preventive measures.

Key words: oral mucosa, low-frequency electromagnetic radiation, occupational exposure, oral lichen planus, recurrent aphthous stomatitis.

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ЗМІНИ СЛИЗОВОЇ ОБОЛОНКИ ПОРОЖНИНИ РОТА ПІД ВПЛИВОМ НИЗЬКОЧАСТОТНОГО ЕЛЕКТРОМАГНІТНОГО ВИПРОМІНЮВАННЯ

Дослідження присвячене аналізу змін слизової оболонки під впливом низькочастотного електромагнітного випромінювання промислової частоти (70 Гц) в клініці (111 осіб – працівників Харківського тракторного заводу) та в експерименті (36 лабораторних щурів популяції WAG). Проведені дослідження дозволили підтвердити негативні наслідки впливу низькочастотного електромагнітного випромінювання на стан слизової оболонки порожнини рота обраного контингенту пацієнтів та лабораторних тварин, що потребує проведення лікувально-профілактичних заходів.

Ключові слова: слизова оболонка порожнини рота, низькочастотне електромагнітне випромінювання, професійний вплив, червоний плоский лишай, хронічний рецидивуючий афтозний стоматит.

The work is a fragment of the research project “Development and implementation of modern algorithms for diagnostic, treatment and prevention of dental diseases in patients of different age periods”, state registration No. 0121U110922.

The health status of the Ukrainian population, unfortunately, shows a steady trend towards deterioration [1]. In recent years, exacerbated by the prolonged COVID-19 pandemic and Russian armed aggression, the Ukrainian population has been experiencing an intensification of chronic stress in all areas of life: social, occupational, and familial. In this context, the additional effect of adverse environmental factors, including the influence of electromagnetic fields (EMF), acquires a more significant negative