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Premenstrual syndrome: pathogenesis, prevention and treatment

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The objective: **to improve the efficiency of diagnosis and treatment of premenstrual syndrome (PMS) based on the establishment of new aspects of pathogenesis (forming the concept of genetic predisposition) and development of differentiated approach to treatment and prevention of various forms of pathology by studying hormonal, psychological markers.**
***Patients and methods*. Research included 200 women of reproductive age with PMS. We studied the importance of social factors, levels of female sex hormones, as well as the role of polymorphisms of estrogen receptor gene ESR1, progesterone receptor gene PROGINS, angiotensin converting enzyme gene ACE and glutathione-S-transferasegenes (GSTT1 and GSTM1), cytogenetic markers, and psychological aspects, quality of life in these patients. The scheme of correction of clinical manifestations and above data, taking into account the clinical form and severity of the syndrome was developed.**
***Results*. It was determined that social factors, as well as level of progesterone, prolactin, folliclestimulatingand luteinizing hormones, A-351G polymorphism of ESR1estrogen receptor gene, T1T1 genotype of gene PROGINS, DD genotype of geneACE and deletion of GSTT1 gene, specific cytogenetic indiceshave meaning in development of syndrome. In addition, individuals with PMS have certain psychological characteristics and reduced quality of life. Use of differentiated treatment which takes into account the various forms and severity of syndrome has led to decrease of clinical symptoms of the disease, normalization of hormonal, psychological markers and increase quality of life of patients.**
***Conclusion*. Differentiated treatment of PMS, which takes into account the form of pathology has allowed to achieve greater frequency of disappearance of clinical symptoms and improve the quality of life of patients.**
Key words: *premenstrual syndrome, hormones, gene polymorphism, psychological dysadaptation, quality of life, differentiated treatment.*

Premenstrual syndrome (PMS) is a functional disorder of central nervous system under the influence of adverse exogenous or endogenous factors on the background of acquired or congenital liability of hypothalamic-pituitary-ovarian system [6]. Prevalence of pathology according to different authors ranges from 25% to 90% of women in reproductive age [13] and with age of person number of such patients increases [9]. The disease has not only medical aspect but also the social one. Behavior changes lead to decline of quality of life, reduce of daily activity, worse of relations with other people and so on [12].

Changes of female hormones, increased activity of the renin-angiotensin-aldosterone syste, impact of prostaglandins, dysregulation of neurotransmitters, the presence of psychological or psychogenic effect, nutrient deficiency and so on are important factors in development of PMS [1]. Classical hypothesis is a theory hyperestrogeny. However, some scientists point to significant growth not only of estradiol in luteal phase of menstrual cycle (MC), but also of progesterone [5]. Researches of I.B. Ventskivska indicate on hypoestrogeny and hypoprogesteronemy in the second phase MC and activation of adrenal system that allows to consider this pathology as stress-induced one [2]. The role of progesterone and its metabolites, including allopregnanolone, is a determining influential factor on gamma-aminobutyric acid system in central nervous system that lead to behavioral manifestations and changes of mood by PMS [10]. Hyperprolactinemy is also one of main mechanisms of PMS development [7], but these data are not confirmed by other researchers [5]. Thus, studies of hormonal changes do not allow to understand clearly and analyze all aspects of the disease.

There are researches about role of neurotransmitters – serotonin, tryptophan, dopamine, monoaminotransferases [4]. Problem of psycho-emotional reactions of patients with PMS, due to their wide prevalence and impact of inadequate studies of mental health on the reproductive system, and vice versa are of great interests now [15].

There are scientific articles about the genetic nature of PMS. However, they are based on insufficient number of studies and concern mainly family history [14]. Information of importance of functional variants of genes in development of syndrome is not enough both in foreign and domestic literature, and it devoted mainly about serotonin transporter gene [11].

Polypahogenetic and multifactor aspects of diseases lead to the development of new treatment schemes of PMS. Today, there is a substantial list of medications to correct the manifestations of disease [6]. Each group of drugs acts on specific pathogenetic mechanism of the disease and may lead to leveling of certain symptoms. Taking into attention of presence of different types of symptoms in one person risk of polypharmacy can increase.

However, analyzing literature, dedicated to pathogenesis, diagnosis and treatment of PMS, it can be concluded that pathogenesis is not still clear enough as well as those about individual approach to its treatment based on neuroendocrine, psychological changes and genetic predisposition.

Aim of research: to increase the effectiveness of diagnosis and treatment of PMS through the establishment of new aspects of pathogenesis (development of the concept of genetic predisposition) and development of differentiated approach to prevention and treatment of various forms of pathology by studying hormonal, psychological formation markers.

Tasks of research:

1. To assess the nature, structure, frequency, intensity of symptoms and the main factors of development of PMS.

2. To determine deletion polymorphism of estrogen receptor gene ESR 1 polymorphisms (polymorphisms of A-351G, T-397C variants) and progesterone receptor gene (PRO-

GINS), angiotensin-converting enzyme gene (ACE) and glutathione-S-transferase genes (GSTT1 and GSTM1) and their associations with risk of development and severity of disease.

3. To examine the immunogenetic status of PMS patients based on cytogenetic markers.

4. To research the features of hormonal changes and psychosomatic aspects in patients with this syndrome.

5. To establish the relationship between the clinical course, hormonal status, psychological changes, genetic predisposition in women with PMS.

6. To develop and implement the algorithm of differential diagnosis, criteria of medicamental therapy and prevention of various forms of PMS by examining the features of hormonal, psychological markers of formation and genetic predisposition based on therapy, depending on the form of pathology.

PATIENTS AND METHODS

The research included 200 women in reproductive age with diagnosis of PMS who formed basic group. Control group consisted of 50 women without diagnosis of PMS. Verification of diagnosis was performed in accordance with Order № 676 of Ministry of Health of Ukraine [6]. Form of PMS (edematous, neuropsychical, cephalgic, crisis) was determined according to V.P. Smetnik's classification [8]. 72 persons in basic group had neuropsychical form of PMS, 70 – edematous, 33 – cephalgic, 25 – crisis one.

Level of hormones (estradiol, progesterone, folliclestimulating hormone (FSH), lutenizing hormone (LH)), prolactin, testosterone) was determined in blood serum at 5–7th and 18–22^{d} days of MC by immunofermental method. Polymorphism of A-351G, T-397C variants of estrogen receptor gene ESR1, T1T2 polymorphism of progesterone receptor gene PROGINS, polymorphism of angiotensionconvertating enzyme gene ACE and glutathione-S-transferases genes (GSTT1, GSTM1) were studied in research laboratory (Department of Medical Genetics, Shupyk National Medical Academy of Postgraduate Education). Cultivation of lymphocytes and making chromosomes preparations were carried under guidelines approved by Ministry of Health of Ukraine out [3] in Department of Medical Biology and Medical Genetics, Ivano-Frankivsk National Medical University. Kind of temperament and level of neurotism were defined by H. Eysenck's test, level of anxiety and depression – by Zung Anxiety Rating Scale and Zung Self-Rating Depression Scale, level of social adaptation and stress – using T. Holmes and R. Rahe' test. Quality of life was studied by questionnaire SF-36.

All patients with PMS had non-medical and pharmacological correction of diseases with duration of 6 months according to Order № 676 of Ministry of Health of Ukraine. Primarily we proposed lifestyle modifications: recommendations of regime of work and rest, moderate exercises, sleep up to 8 hours a day, to keep fractional specific diet. According to type of therapy patients of basic group were divided into two groups – I and II. Women of I group received differentiated therapy: women with mild neuropsychical form of PMS received herbal extract of Vitex agnus castus with dose of 40 drops per day (20 persons); women with severe neuropsychical form took combined estrogen-progestagen medicines containing 20 mcg ethinylestradiol (EE) and 3 mg drospirenone in regime 24+4 (15 persons); patients with edematous form of PMS (34 women) – estrogen-progestagen medicines containing 30 mcg EE and 3 mg drospirenone in regime 21+7 ; women with cefalgic form (18 patients) and women with crisis form of PMS (13 patients) received selective serotonin reuptake inhibitor fluoxetine 20 mg daily for two days from ovulation and in seven days after the first dose for two days. Women of II group received traditional therapy in the second phase of MC – vitamin E 200 mg 1 time per day, vitamins B (Neurovitan 1 table 1 per day), spironolactone 25 mg two times a day, suppositorium indomethacin 0,05 g rectally once a day.

For statistical analysis we used parametric and non-parametric methods. We calculated arithmetic mean value, standard error of the mean, Chi-square (ч^2), Odds Ratio (OR), Relative risk (RelR), Confidence Interval (CI), probability of differences results of research (p). To compare two independent groups on one feature we used nonparametric Mann-Whitney test, to compare two dependent groups – Wilcoxon test. All calculations were performed with reliable probability (1-P) 0,95.The difference between the values comparing considered reliable at p?0,05.

RESULTS AND THEIR INTERPRETATION

The article presents new data and new solving of scientific problem of modern endocrine gynecology – to increase the effectiveness of diagnosis and treatment of PMS through the establishment of new aspects of pathogenesis (development of the concept of genetic predisposition) and development of differentiated approach to prevention and treatment of various forms of pathology by studying hormonal, psychological formation markers.

Literature data demonstrated that problem of PMS is not fully resolved. This is confirmed by significant spread of pathology among women of reproductive age and low efficiency of preventive and treatment measures.

Research results identified the main social (higher education (χ^2=8,57; p=0,003, OR=2,67, 95%CI=1,41–5,03, p=0,003), intellectual employment (χ^2=4,29; p=0,04, OR=2,03, 95%CI=1,08–3,80, p=0,03), lack of physical activity (χ^2=20,90; p<0,001, OR=2,36, 95%CI=1,23–4,51, p=0,01), irrationality of work and rest (χ^2=4,39; p=0,04, OR=2,11, 95%CI=1,10–4,05, p=0,02), constant systematic stress conditions (χ^2=10,92; p<0,001, OR=3,88, 95%CI=1,73–8,69, p=0,001), irregular diet (χ^2=12,75; p<0,001, OR=3,30, 95%CI=1,73–6,30, p<0,001)) and medical (chronic inflammatory diseases of uterine appendages (χ^2=5,15; p=0,02, OR=2,38, 95% CI 1,18–4,80, p=0,02), vegetative dystonia (χ^2=4,29; p=0,04, OR=3,80, 95%CI=1,12–12,83, p=0,03)) factors of pathology.

Psycho-emotional manifestations are dominated in structure of clinical symptoms of PMS, especially common ones are emotional liability (60,00±3,46%), irritability (38,50±3,44b%), excitation (37,00±3,41%), sense of tension and anxiety (24,00±3,02%). Among the most common physical manifestations are mastalgia (50,00±3,54%), peripheral edema (45,00±3,52%), abdominal distension (27,00±3,14%), weight gain (24,00±3,02%), headache (17,00±2,66%). The frequency of symptoms increases with the severity of the syndrome and depends on its clinical form.

The interrelation between A-351G polymorphism of and estrogen receptor gene ESR1, T1T2 polymorphism of progesterone receptor gene PROGINS and severity of PMS was determined. High risk of development of severe PMS was defined in the presence of pathological GG genotype of A-351G variant of gene ESR1 (χ^2=4,88; p=0,03, OR=11,29, 95% CI=1,29–98,89, p=0,03, RelR=8,00, 95%CI=1,08-59,33, p=0,04), and presence of T1T1 genotype marked tendency to its occurrence (χ^2=3,21; p=0,07, OR=3,69, 95%CI=1,05–12,96, p=0,04). Individuals with DD genotype of ACE gene and deletion polymorphism of GSTT1 gene also have tendency to develop severe course of disease (respectively χ^2=3,06; p=0,08, OR=3,43, 95% CI=1,02–11,47, p=0,04, RelR=2,17, 95%CI=0,98-4,79, p=0,05 and χ^2=2,74; p=0,09, OR=4,13, 95% CI=0,97–17,70, p =0,057). There is no clear link between above

genes polymorphisms of clinical form of the syndrome except edematous form of PMS. It is associated with T1T1 genotype of gene PROGINS (χ^2=4,50; p=0,03, OR=4,85, 95% CI=1,29–18,26, p=0,02), and women with pathological GG genotype of A-351G variant gene ESR1have tendency to its formation (χ^2=3,72; p=0,054, OR=9,33, 95% CI=1,05–82,78, p=0,045, RelR=7,00, 95% CI=0,93–52,80, p=0,06).

Frequency of acrocentric chromosomes associations in patients with this syndrome is increased in 3,12 times (p<0,001). Associations with G (p=0,01) and D+G (p=0,047) groups of chromosomes and those are composed of two chromosomes (p<0,001) are dominated. This indicates on failure of immune system.

The feature of hormonal disorders by PMS is hypoprogesteronemy in luteal phase (73,64% of controls, p<0.005), which is clearly associated with edematous form (54,58%, p<0,001), and also with crisis (73,46%, p=0.02) and neuropsychiatric forms (80,55%, p=0,03) and is absent by cephalgic form (p=0.65). This syndrome is characterized by elevated levels of FSH in both phases of MC (respectively in 1,42 times (p=0.004) and in 1,74 times (p<0,001)), particularly expressed in the follicular phase by neuropsychiatric form – in 1,55 times (p<0.001), in luteal phase – by edematous form – in 2,07 times (p<0.001). The downward trend of LH in follicular phase of MC was connected with patients of edematous form of the syndrome (p<0,05), and its increase in luteal phase (p=0,02) is moderate by all forms of the disease. Hyperprolactinemy is a typical feature of cephalgic form in follicular (p=0.06) and luteal phases of MC as well (p<0,001).

According to results of research of psychological status we found high frequency of melancholic (34,00%; χ^2=10,01, p=0.002) and choleric persons (36,50%; χ^2=4,19, p=0,04) and low frequency of sanguine women (in 3,20 times less than in control group – 17,50% (χ^2=29,44; p<0,001)), that was accompanied by high levels of anxiety and depression, emotional stress (χ^2=4,76; p=0,03), stress tolerance and social adaptation (χ^2=6,31; p=0,01), which increased with the severity of the syndrome and depends on its clinical form, as well as significant levels of neuroticism. In patients with neuropsychiatric and forms of crisis, last parameter is the highest one and amounts on 20,67% , (p=0,002) and 19,85% (p=0,008) respectively greater than the reference value. Such disorders of psychosomatic condition lead to impairment of quality of life, especially of the psychological component.

Combined evaluation of genetic susceptibility and frequency of homozygous variants with hormonal imbalance considerably affects on clinical course of PMS with significant changes in psychological component of patients and significant decline of psychological component of quality of life. This requires differentiated individual approach to the treatment.

Differentiated treatment depending on the clinical form and severity of PMS allows to disappear and reduce clinical manifestations of disease in all patients, normalize hormonal and psychological status of the vast majority of patients and improve their quality of life, especially of psychological component.

CONCLUSION

1. For establishment risk groups of PMS it should take into account type of education, occupation, physical activity, work and rest, stress load and the presence of chronic inflammation of the uterus appendages and vegetative dystonia.

2. For the purpose of effective diagnosis and further treatment of PMS it is recommended to determine the levels of estradiol, progesterone, FSH, LH and prolactin in serum in both phases of MC.

3. Patients with severe PMS and inefficiency of previous treatment are recommended to provide molecular genetic study of polymorphic of A-351G variants of estrogen receptor gene ESR1, T1T2 polymorphism of progesterone receptor gene PROGINS, ID polymorphism of ACE gene and deletion of GSTT1 gene.

4. Therapy of women with PMS depends on form of pathology and includes:

lifestyle modifications (moderate exercises, recommendations of regime of work and rest, diet).

for women with mild neuropsychical form of PMS – herbal extract of Vitex agnus castus with dose of 40 drops per day for six months;

for women with severe neuropsychical form – combined estrogen-progestagen medicines containing 20 mcg EE and 3 mg drospirenone in regime 24+4 for six months;

for patients with edematous form of PMS – estrogen-progestagen medicines containing 30 mcg EE and 3 mg drospirenone in regime 21+7 for six months;

for women with cefalgic and crisis forms of PMS – selective serotonin reuptake inhibitor fluoxetine 20 mg daily for two days from ovulation and in seven days after the first dose for two days for six months. In the presence of hyperprolactinemy – dopamine receptor agonist drugs.

Thus, differentiated approach to treatment of PMS, taking into account the form of pathology has allowed to achieve greater frequency of disappearance of clinical symptoms and improve quality of life of patients.

Передменструальний синдром: патогенез, профілактика та лікування

Л.В. Пахаренко

Мета дослідження: підвищення ефективності діагностики та лікування передменструального синдрому (ПМС) на основі встановлення нових аспектів патогенезу (створення концепції генетичної схильності) і розроблення диференційованого підходу до проведення лікувально-профілактичних заходів при різних формах патології шляхом вивчення особливостей гормональних, психологічних маркерів формування.

Матеріали та методи. Проведено обстеження 200 жінок репродуктивного віку з ПМС. Вивчали значення соціальних факторів, рівнів жіночих статевих гормонів, а також роль поліморфізму генів рецептора естрогену ESR1, рецептора прогестерону PROGINS, ангіотензинперетворювального ферменту ACE та глутатіон-S-трансфераз (GSTT1 і GSTM1), цитогенетичних показників, психологічних аспектів, якості життя у даної категорії пацієнток. Розроблено схему корекції клінічних проявів та порушень наведених вище показників з урахуванням форми та тяжкості синдрому.

Результати. Аналіз отриманих даних свідчить про роль соціальних чинників, а також прогестерону, пролактину, фолікулостимулювального та лютеїнізувального гормонів, А-351G-поліморфізму гена ESR1, T1T1-генотипу гена PROGINS, DD-генотипу гена ACE, делеційного поліморфізму гена GSTT1 та деяких цитогенетичних показників у формуванні патології. Крім того, особи з ПМС мають певні психологічні особливості та характеризуються зниженою якістю життя. Застосування диференційованого підходу до лікування патології з урахуванням різних форм та тяжкості синдрому привело до нівелювання клінічної симптоматики захворювання, нормалізації гормонального фону, психологічного комфорту та покращання якості життя.

Заключення. Розроблений диференційований підхід до терапії ПМС з урахуванням форми патології дозволив досягнути більшої частоти зникнення клінічних проявів та покращити якість життя хворих.

Ключові слова: *передменструальний синдром, гормони, поліморфізм генів, психологічна дезадаптація, якість життя, диференційоване лікування.*

Предменструальный синдром: патогенез, профилактика и лечение

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Цель исследования: повышение эффективности диагностики и лечения предменструального синдрома (ПМС) на основе установления новых аспектов патогенеза (создание концепции генетической предрасположенности) и разработки дифференцированного подхода к проведению лечебно-профилактических мероприятий при различных формах патологии путем изучения особенностей гормональных, психологических маркеров формирования.

Материалы и методы. Проведено обследование 200 женщин репродуктивного возраста с ПМС. Изучали значение социальных факторов, уровней женских половых гормонов, а также роль полиморфизма генов рецептора эстрогена ESR1, рецептора прогестерона PROGINS, ангиотензинпревращающего фермента ACE и глутатион-S-трансфераз (GSTT1 и GSTM1), цитогенетических показателей, психологических аспектов, качества жизни у данной категории пациенток. Разработана схема коррекции клинических проявлений и нарушений указанных выше показателей с учетом клинической формы и тяжести синдрома.

Результаты. Анализ полученных данных свидетельствует о роли социальных факторов, а также прогестерона, пролактина, фолликулостимулирующего и лютеинизирующего гормонов, A-351G-полиморфизма гена ESR1, T1T1-генотипа гена PROGINS, DD-генотипа гена ACE, делеционного полиморфизма гена GSTT1 и некоторых цитогенетических показателей в формировании патологии. Кроме того, лица с ПМС имеют определенные психологические особенности и характеризуются сниженным качеством жизни. Применение дифференцированного подхода к лечению ПМС с учетом различных форм и тяжести синдрома привело к нивелированию клинической симптоматики заболевания, нормализации гормонального фона, психологического комфорта и улучшению качества жизни.

Заключение. Разработанный дифференцированный подход к лечению ПМС с учетом формы патологии позволил достигнуть большей частоты исчезновения клинических проявлений и улучшить качество жизни больных.

Ключевые слова: *предменструальный синдром, гормоны, полиморфизм генов, психологическая дезадаптация, качество жизни, дифференцированное лечение.*

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