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Current issues of the premenstrual disorders development

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Premenstrual disorders remain one of the most prevalent pathologies in women all over the world. The core disorders – premenstrual syndrome (PMS) and premenstrual dysphoric disorder – predominate in women of reproductive age. Also, there are four variants of premenstrual disorders – premenstrual exacerbation, premenstrual disorders due to nonovulatory ovarian activity, progestogen-induced premenstrual disorders, premenstrual disorders with absent menstruation. Recently, the prevalence of any premenstrual disorder is up to 87% in female population.

In this article some mechanisms that are involved in the pathogenesis of PMS are presented. The fluctuations of different hormones (namely, estradiol, progesterone, testosterone, etc.) and not normal response of the central nervous system to such variations can lead to psychological changes. Serotonin, serotonin transporter, gamma amonibutyric acid are involved in the mechanisms of mood disorders. Genetic factor is studied in different woman's reproductive diseases. Gene polymorphism of *SERT*, *COMT*, *MAOA*, *BDNF*, *ESR1* and *ESR2* genes were studied most often in PMS development. One of the subtypes of premenstrual disorders is premenstrual exacerbation, when clinical manifestations of underlying diseases are expressed more before menstruation. Special attention is paid to the association of metabolic syndrome, overweight, obesity with premenstrual syndrome. There is a negative impact of these diseases of the regulation of menstrual cycle processes – early menarche onset, abnormal uterine bleeding (irregular periods, heavy menstrual bleeding or amenorrhea), hyperandrogenism, low concentration of sex steroid-binding globulin. It was found that the frequency of PMS in overweight and obese women is almost twice higher than in normal weight women. Women with metabolic syndrome who suffer from PMS have poor sleep quality, they are more depressive and anxiety. The most common association of gene between obesity, diabetes mellitus and PMS is related to angiotensin converting enzyme gene and its I/D polymorphism, however, the results of such relationship are controversial. It is very important the for different medical professionals to understand the manifestations of premenstrual disorders and prescribe to the patients not only medicament treatment, but also perform for them psychological support and give recommendations about lifestyle changes.

Keywords: *premenstrual syndrome, etiology, pathogenesis, hormones, genes, quality of life, metabolic syndrome, obesity, diabetes mellitus, microbiota.*

Актуальні питання механізмів розвитку передменструальних розладів

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Передменструальні розлади залишаються однією з найпоширеніших патологій у жінок у всьому світі. Основні передменструальні розлади – передменструальний синдром (ПМС) і передменструальний дисфоричний розлад – переважають у жінок репродуктивного віку. Також розрізняють чотири підтипи передменструальних розладів: передменструальне загострення фонового захворювання, неовуляторний передменструальний розлад, прогестерон-індукований передменструальний розлад та передменструальні розлади з відсутністю менструації. Останнім часом поширеність будь-якого передменструального розладу становить до 87% серед жіночої популяції.

У цій статті описано механізми, які беруть участь у патогенезі ПМС. Коливання різних гормонів (зокрема естрадіолу, прогестерону, тестостерону та ін.) і ненормальна реакція центральної нервової системи на такі коливання можуть призвести до психологічних змін. Серотонін, транспортер серотоніну, гамма-амонімасляна кислота беруть участь у механізмах розладів настрою. Генетичний фактор вивчено при різних захворюваннях репродуктивної системи жінки. Найчастіше досліджували поліморфізм генів *SERT*, *COMT*, *MAOA*, *BDNF*, *ESR1* та *ESR2* при розвитку ПМС. Одним із підтипів передменструальних розладів є передменструальне загострення фонового захворювання, коли перед менструацією відзначаються більш виражені клінічні прояви основного захворювання. Особливу увагу приділено асоціації метаболічного синдрому, надмірної ваги, ожиріння з передменструальним синдромом. Встановлено негативний вплив цих захворювань на регуляцію процесів менструального циклу – раннє настання менархе, аномальні маткові кровотечі (нерегулярні менструації, рясні менструальні кровотечі або аменорея), гіперандрогенія, низька концентрація глобуліну, що зв'язує статеві стероїди. Виявлено, що частота ПМС у жінок із зайвою вагою та ожирінням майже вдвічі вища, ніж у жінок із нормальною вагою. Жінки з метаболічним синдромом, які страждають на ПМС, мають незадовільну якість сну, вони більш депресивні та тривожні. Найпоширенішою асоціацією між ожирінням, цукровим діабетом і ПМС є ген ангіотензинперетворювального ферменту та його поліморфізмом I/D, проте результати вивчення такого зв'язку є суперечливими. Медичним працівникам різних спеціальностей дуже важливо розуміти прояви передменструальних розладів і призначати пацієнткам не тільки медикаментозне лікування, а й здійснювати психологічний супровід та надавати рекомендації щодо зміни способу життя.

Ключові слова: *передменструальний синдром, етіологія, патогенез, гормони, гени, якість життя, метаболічний синдром, ожиріння, цукровий діабет, мікробіота.*

Premenstrual disorders are characterised by somatic and psychological symptoms of varying severity that occur during the luteal phase of the menstrual cycle and dissapear during menstruation [1]. The core types of premenstrual disorders are premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) [2]. Besides PMS and PMDD, there are some other variants of premenstrual disorders – premenstrual exacerbation, premenstrual disorders due to nonovulatory ovarian activity, progestogen-induced premenstrual disorders, premenstrual disorders with absent menstruation [2].

PMS is characterized by physical, behavior and psychological manifestations that occur not due to the organic diseases or underlying psychiatric pathologies. Symptoms recur regularly during the luteal phase of each menstrual cycle and dissolve or significantly regress by the end of menstruation. The main PMS psychological manifestations include mood changes, filling of anxiety, depression, emotional lability, changes in appetite, etc. Among physical symptoms are breast tenderness, fluid retention, oedema, headache, changes in skin, hair, etc. Some studies indicate that PMS symptoms have almost 80% of women [3]. According to the literature search which was performed by P. Das and S. Jungari, in Google Scholar, PubMed, JSTOR, Scopus and Sci Direct databases for the period 2000–2022, the prevalence of any menstrual disorders in female population account from 3 to 87% [4]. There is a significant widespread of PMS, which increases from 1990 till 2019 year and estimates from 652.5 million till 956.0 million persons, respectively, that is the rise by 46.5% [5]. The premenstrual symptoms rate (40–71% of women) is on the second place after dysmenorrhea incidence (46–76% of females). While the results of D. Dwivedi et al. notify the first rank for PMS prevalence (41.63%) compared to dysmenorrhea (28.29%) [6]. As to the distribution between physical and psycho-emotional symptoms frequency, according to C. Franco-Antonio et al. study, which was performed in women 19–23 years old, the physical manifestations (92.7%) prevailed over the emotional signs (55.6%) [7]. Regarding the age period, it was found the most frequency of PMS among females 20–29 years old (46.7%), less rate was established in women 30–39 years old (38.3%) and 40–49 years (15.0%) [8]. In women aged 20–29 years and 40–49 years psychological signs of anxiety/tension predominated, in 30–39 years old females the most spread psychological symptoms were irritability and anger. Commonly, PMS is positively related to stress, sleep disorders, depression, eating problems, and in the contrary, sleep disturbance, strength of menstrual pain influence on intensity of PMS manifestations [9]. The kind of working activity also impact on the presence and intensity of premenstrual symptoms. The rate of PMS is more in working women who have higher educational qualification, work position, career occupation and sexual activity compared to women with lower quality of life [10].

There is also a great social and economic impact of PMS on woman's life [3, 11]. Premenstrual disorders worth the daily activity of women ($p = 0.039$), relationship with family ($p = 0.001$) and other persons ($p = 0.002$) [12]. According to the results of the standardized World Health Organization Quality of Life (WHOQOL-BREF) questionnaire in young women with PMS the lowest quality of life score was assessed to mental health ($p = 0.006$), the highest score – to social relationship ($p = 0.002$) [13]. The evidences suggest the PMS and PMDD role in the perinatal depression development, as during pregnancy, as well in postpartum period [14–16]. The main diagnosis tool for PMS is the using of different daily questionnaires for fixations of symptoms.

Behavior changes in women with PMS can be related to the fluctuations of hormonal levels, genetic predisposition [3]. Hypothalamic-pituitary-ovarian (HPO) axis is considered one of the main pathogenetic factors in the disorders of female reproductive organs. The changes in the HPO axis function are related to the mood disturbances in female organism. Not normal response of the central nervous system on the variations of neuroactive steroids hormones that occur during the menstrual cycle usually leads to mood problems [17, 18]. Ovarian steroids hormones, estrogen and progesterone vary in different periods of woman's life, as well there are fluctuations of their concentration in different phases of the menstrual cycle. These changes of the hormonal levels influence throw the limbic system on the brans functioning. Numerous researches found the influence of sex steroids hormones on brain activity, including the mood system [19]. The more considerable elevation of serum blood estradiol concentration was determined in women with severe PMS in the luteal phase of the menstrual cycle compared to the follicle phase. There is more expressed estradiol increasing in such patients than in healthy individuals [20]. As to the progesterone, its increasing in the luteal phase compared to the follicle phase of the menstrual cycle was less than in healthy women [21, 22]. The results of S. Hashemi et al. indicate higher prolactin, triglyceride amount in PMS women compared to controls, while levels of testosterone, high density lipoprotein and 17-hydroxyprogesterone are decreased [23]. On another side, it was determined that, women with PMDD – the severe form of premenstrual syndrome – commonly have lower estrogen concentration in the luteal phase of menstrual cycle and women with depression seem to be related to lower testosterone and dehydroepiandrosterone sulfate concentrations [24].

The influence of genetic factors for in premenstrual disorders development is not fully studied [17, 25]. Gene polymorphism of *SERT*, *COMT*, *MAOA*, *BDNF*, *ESR1* and *ESR2* genes were studied most often. The results demonstrated not very convinced evidence [25]. The methodology using machine learning algorithms on the rat models was developed [26]. This model helps to determine the pathogenetic mechanisms for the mood changes (anxiety and depression) in rats using ribonucleic acid sequencing and subsequent quantitative polymerase chain reaction. 17 main genes were established for such changes. Different pathologies of female reproductive organs are related to genetic predisposition. The researches demonstrated the role of *ESR1* polymorphism (PP + Pp genotype) in the dysmenorrhea development in Korean adolescents, while there was no significant difference in the glutathione S-transferase mu 1 (*GSTM1*), glutathione S-transferase theta 1 (*GSTT1*), glutathione S-transferase pi 1 (*GSTP1*) gens in persons with and

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without dysmenorrhea [27]. Also, an association of *ESR1* gene polymorphism was determined with polycystic ovary syndrome. G allele careers for polycystic ovary syndrome development odds ratio (OR) = 1.92 (95%), confidence interval (CI) = (1.300–2.859), relative risk = 1.38 (1.130–1.691) p-value < 0.001 [28]. At the same time PvuII-rs2234693 C > T gene polymorphism of *ESR1* gene has no connection with an increased risk of polycystic ovary syndrome [28]. The results of other research indicate the role of rs2234693 *ESR1* gene not only in hormonal changes in the polycystic ovary syndrome, but more significant in the metabolic disorders, that occur in women with polycystic ovary syndrome [29]. The evidences suggest that some variants of single nucleotide polymorphisms of *ESR1* and *ESR2* genes can be diagnosis prediction the biomarkers of the polycystic ovary syndrome [30]. The association of different female reproductive pathologies and *PROGINS* gene polymorphism was revealed. The studies inform about the improved predisposition of *PROGINS* in women with polycystic ovary syndrome [31]. The results of meta-analysis of 25,405 controls and 19,253 female reproductive cancer cases demonstrated that progesterone receptor gene *Alu* insertion and the *V660L* polymorphism contained in the *PROGINS* polymorphism can be assessor reason for female reproductive cancer [32]. There is a relation of *PROGINS* gene polymorphism in breast cancer [33, 34], fibromyalgia syndrome [35], and no association with uterine fibroids [36, 37].

The role of serotonin transporter gene seems to be one of the first genes to be studied in premenstrual dysphoric disorder pathogenesis. Some researchers reject the influence of serotonin-transporter-linked promoter region (*5-HTTLPR*), in particular, the gene that codes for the serotonin transporter, rs25531 promoter polymorphism, in PMDD [38]. The studies found that genes from the gamma-aminobutyric acid (GABA) pathway – steroid-5-alpha-reductase, alpha polypeptide 1 (*SRD5A1*) and gamma-aminobutyric acid receptor subunit alpha-4 (*GABRA4*) – can protect against severe premenstrual symptoms [39]. In particular, the researchers determined that the cytosine/cytosine (C/C) genotype for the *SRD5A1* SNP, rs501999 can defend against the severe premenstrual symptoms. Allopregnanolone (Allo) – a metabolite of progesterone – is a positive $GABA_A$ receptor modulating steroid and has strong effects. There is a relationship between high Allo concentration and increased bad mood, disorders of memory and increased food intake in some human individuals and pathologies such as PMDD, hepatic encephalopathy and polycystic ovarian syndrome [40].

The study of different of estrogen gene receptor *ESR1* polymorphisms in women with PMS was performed. GG genotype of *A-351G* polymorphic variant of gene estrogen receptor *ESR1* is associated with severe PMS symptoms (OR 11.39, 95% CI 1.29–98.89, p = 0.03) and related to persons with mainly edematous manifestations before/during menstruation (OR 9.33, 95% CI 1.05–82.78, p = 0.04) [41, 42]. High serum blood estradiol growth in the luteal phase of menstrual cycle is more pronounced in women with severe PMS who are carriers of G allele of *ESR1* gene than in carriers of A allele [20]. At the same time T-397C polymorphic variant of estrogen receptor gene *ESR1* was not revealed as a marker for PMS course and development [43]. The frequency of TT, TC and CC alleles was statistically similar in premenstrual syndrome and healthy women. T1T1 genotype of *PROGINS* gene was related to a lower blood serum progesterone level in the luteal phase of the menstrual cycle in PMS women compared to the healthy women but no association was revealed between T1T2 genotype and reduced progesterone concentration in the luteal phase by PMS compared to healthy women [21, 22].

As it was mentioned, one of the forms of premenstrual disorders is premenstrual exacerbation. It is a condition when clinical manifestations are underlying psychological, somatic or medical pathology and significantly worsen before menstruation [2]. Such basic and underlying diseases can be diabetes mellitus, depression, epilepsy, bronchial asthma, migraine, etc. These patients experience symptoms, which are characterized their underlying disease throughout the menstrual cycle. Thus, a special attention should be paid to women with metabolic disorders, diabetes mellitus, obesity. There is a negative influence of obesity on the processes of menstrual cycle – early menarche onset, abnormal uterine bleeding (irregular periods, heavy menstrual bleeding or amenorrhea), hyperandrogenism, low concentration of sex steroid-binding globulin (SSBG) [44–47]. It was found the morphological and functional changes in different organs and systems, which are caused by diabetes mellitus [48–52]. It is known the impact of obesity, diabetes mellitus on the formation of cancer of female reproductive organs [53, 54]. Women with obesity are associated with premenstrual disorders (PMS and PMDD), polycystic ovary syndrome [55, 56]. Visceral adiposity, especially in women with central fat accumulation, can support PMS development [57]. Menstrual disorders, in particular, premenstrual syndrome, are typical for women with overweight and obesity [58]. The frequency of PMS among women with overweight (32.0%) and obesity I–II (32.5%) is significantly higher than in women with normal body weight index (BMI) (13.3%) [58]. The similar results were received by D. Dwivedi et at. [6]. The researchers found that rate of PMS in overweight (45.40%) and obese (51.28%) women is almost twice higher than in normal weight women (26.17%). This study also informs that underweight persons have the highest frequency of PMS – 82.98%. However, the results of M. Mizgier et al. demonstrate that women with normal body mass index (BMI < 25 kg/m^2) have PMS two times more than women with high BMI > 25 kg/m^2 [59].

The role of metabolic disorders in PMS syndrome is confirmed by other studies [47, 60]. P. Sharifan et al. determined that the excessive use of monounsaturated fatty acid and young age are more risk factor for severe PMS (p = 0.041, OR = 23.789, 95% CI for OR: 1.138 and 497.294) while riboflavin intake decrease the severity of the pathology [47]. Women with metabolic syndrome who suffer from PMS have poor sleep quality, they are more depressive and anxiety compared to PMS persons without metabolic syndrome (p < 0.001) [60]. According to the results of linear regression every one unit of PMS score increase the likelihood of metabolic syndrome growth on 12% (p = 0.033) [23].

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The studies reveled the connection of diabetes mellitus as a risk factor for PMS ($p < 0.001$) [61]. The presence of PMS may strengthen the mechanisms of menstrual cycle regulation on insulin sensitivity [62]. Other researches inform that glucose and insulin resistance concentrations are less in PMS women in two phases of menstrual cycle than in healthy subjects [63]. The most common association of gene between obesity, diabetes mellitus and PMS is related to angiotensin converting enzyme (ACE) gene and its I/D polymorphism. It is known that angiotensin-converting enzyme is involved in the processes of regulation of blood pressure, adipocyte growth, lipids homeostasis. There is a relationship of ACE gene I/D polymorphism with body mass index, overweight, obesity, waist circumference, dyslipidemia [64], diabetes mellitus [65, 66]. On the other side, there is insignificant relation of ID polymorphism in Chinese patients with diabetes mellitus type 2 [67]. Also, F. F. Pirozzi et al. did not find any association between 2 type diabetes mellitus, obesity, and angiotensin-converting enzyme gene insertion/deletion (I/D) [68], and the results of D. F. Lelis et al. demonstrated no relationship between overweight, obesity and ACE gene polymorphisms [69]. The increased risk of severe PMS has the women with DD genotype ACE gene (OR = 3.43, 95% CI 1.02–11.47, $p = 0.045$) [70].

Additionally, it is known about the association between obesity, diabetes mellitus and gut microbiota changes [71]. Also, the association of microbiota changes and some other hormonal gynecological diseases was determined [56, 72, 73]. As to the relation of microbiota features with PMS it was found a difference in beta diversity for the gut microbiota between PMS women and controls [74]. The researchers determined reduction of *Extibacter, Butyricicoccus, Megasphaera*, and *Parabacteroides* and increase in *Anaerotaenia* in women with PMS. Also, the results of other study demonstrate that the abundances of *Collinsella, Bifidobacterium*, and *Blautia* were significantly higher compared woman without PMS [75]. Namely, abundance of Collinsella increased almost 4.5 times relative to controls. The group of researchers Y. Yao et al. revealed that among 119 kinds of gut microbiota and 4 kinds of clinical phenotypes only *Escherichia/Shigella* ($p = 0.00032$, positive false discovery rate = 0.0382, OR = 1.004, 95% CI = 1.002–1.006) is associated with menstrual disorders [76]. According to some studies a positive effect on premenstrual manifestations treatment was observed using different supplements and medications which influence on gut microbiota [77, 78].

Not only gynecologists but also general physicians meet in their practice with PMS patients. Mostly, general physicians have good experience for premenstrual syndrome treatment. They give lifestyle advices, psychological care for such patients and prescribe oral contraceptives. The study of E. L. Funnell et al. demonstrated that among 339 women with PMS who visited doctor for the medical help, almost half of them (44.25%) reported that their symptoms were not taken seriously by doctors, and most patients were not recommended about lifestyle changes, receiving recommendations of non-formal sources of help; according to survey's results, better results of medical help were connected when healthcare professionals taking symptoms seriously, and give recommendations about lifestyle changes [79]. But, sometimes more training programs for better diagnosis and professional medical care for patients with PMS are necessary [80]. Additionally, the information about the PMS symptoms should be given as early as possible, even to the adolescents [11].

Thus, premenstrual syndrome remains the relevant medical and social problem. In recent years new mechanisms of its development were determined. The association of premenstrual disorders with metabolic conditions extremely impact of each other course and lead to more severe manifestations. It is very important the for different medical professionals to understand the manifestations of premenstrual disorders and prescribe to the patients not only medicament treatment, but also perform psychological support and give recommendations about lifestyle changes.

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