

Premenstrual Syndrome and Premenstrual Dysphoric Disorder: Symptoms and Cluster Influences

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Abstract: Many women in their reproductive years experience some mood, behavioral, or physical symptoms in the week prior to menses. Women experiencing mild symptoms may have a wide variability in the level of symptom burden, whereas a minority suffers severe and debilitating symptoms. Severe premenstrual syndrome (PMS) affects 3% to 5% of women of reproductive age and has been classified under the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) as premenstrual dysphoric disorder (PMDD). Both disorders are characterized mainly by symptoms confined to the premenstrual period, which reduce not only patients' quality of life, but also their working activities. Women suffering PMDD experience severe dysphoric mood, and a greater desire and actual intake of certain foods, demonstrating impaired cognitive performance during the luteal phase. Several theories have been proposed to explain the underlying mechanisms of PMS and PMDD with complex bio-psycho-social factors involved. Although precise causes are unknown, the late luteal phase could be associated with diverse psychosomatic and behavioral symptoms appearing premenstrually which should be appropriately treated. Notwithstanding this high prevalence, no specific symptoms or signs appear, nor have any recognizable anatomical factors been identified in women suffering PMS or PMDD, and hence, no universal treatment yet exists. Despite this, therapeutic progress has been reached, although the ideal treatment has not yet been obtained due to the many clusters involved.

Keywords: Premenstrual syndrome, Premenstrual dysphoric disorder, Psychosomatic gynecology, Drospirenone, Selective serotonin reuptake inhibitors, GABA.

INTRODUCTION

The *premenstrual syndrome* (PMS) and *premenstrual dysphoric disorder* (PMDD) constitute psychosomatic gynaecological paradigms. They share some endocrine and nervous system causes, nutritional influences and psychosocial factors. All complaints are associated to increased costs –more indirect than direct- due to loss of work days and reduced productivity. Furthermore, they cause interpersonal problems that erode health, social and family relationships [1-6]. Although physical discomfort and mood changes related to menstruation have been known since Hippocrates times, it has taken quite long to reach a PMS definition. In 1931, Frank described 15 women with severe premenstrual symptoms proposing the concept of *premenstrual tension*. In 1953, Greene and Dalton introduced the term *premenstrual syndrome*, proposing an imbalance between estrogens and progesterone during the luteal phase as the biological cause, and used progesterone as a therapeutical option. The syndrome is a complex condition that includes up to 200 symptoms, but the most frequent are irritability, breast tenderness and dysphoria, among others.

Its basic clinical hallmark is the temporary presence of symptoms which appear in the luteal phase, and are reduced during menstruation and disappear in the follicular phase. In 1987, the American Psychiatric Association introduced in the Diagnostic and Statistical Manual of Mental Disorders (DSM) III-R, the concept of *late luteal phase dysphoric disorder* to conjunctly group all temporary changes in behavior [7]. In the fourth DSM edition (DSM-IV), nomenclature changed to *premenstrual dysphoric disorder* (PMDD) maintaining almost the same criteria [8]. PMDD defines a narrow group of women with the most severe emotional symptoms and functional impairment which are exacerbated premenstrually.

Emotional symptoms are frequent in moderate to severe PMS, but it also includes physical symptoms (Table 1). Contrarily, emotional symptoms predominate in PMDD. In the DSM-IV list, 10 of 11 are emotional and behavioral in nature, while one includes multiple common physical symptoms (Table 2). The diagnosis of PMDD requires 5 of the 11 specific symptoms that define its dysphoric nature. Symptoms must also meet the following requirements: 1) be present during most of the time of the week previous to menstruation, reduce on menstruation, disappear during the week following menstruation and affect the majority of cycles of a year; 2) symptoms must interfere with personal and social relationships; 3) the alteration is not an

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exacerbation of an emotional or physical symptom; and 4) the criteria must be confirmed by a diary over at least two consecutive menstrual cycles [3]. However, there is a significant intra-patient variability in terms of PMDD symptom duration and time-to-onset and offset [9]. Findings during physical examination are usually unremarkable. Mild edema of the ankles, feet, and fingers may occur secondarily to fluid retention. Breast tenderness may also be present. Women with PMDD express dysphoric mood and a greater desire and actual intake of certain foods and have an impaired cognitive performance during the luteal phase.

Table 1. Diagnostic Criteria for Premenstrual Syndrome (ICD-10) According to the World Health Organization

Mild psychological symptoms
<i>Sensation of bloating and weight gain</i>
<i>Breast tenderness</i>
Swelling on the hands and feet
Muscular and joint pain
Poor concentration, anxiety and emotional lability
Sleep disturbance
Appetite change and craving for certain foods

Limits between PMS and PMDD are not precisely defined and may possibly constitute a "continuous" pathophysiological process. The diagnosis of both PMS and PMDD is established by exclusion of other diseases. However, it seems that PMDD is a distinct clinical disorder than the PMS. The key criterion for PMDD diagnosis is the interference with social and occupational functioning, to distinguish it from the less severe PMS. PMDD has also been considered a variant of depressive disorders in which premenstrual psycho-biological changes would exacerbate mild or atypical depressive symptoms [10]. Nevertheless, considerable controversy exists in relation to the PMS and the PMDD status, its pathophysiology, diagnostic characteristics and therapeutical standards, as well as their social, industrial, ideological and political consequences. Moreover important to mention is the fact that many taboos have been linked to menses. Some investigators suggest that PMDD has been marketed by pharmaceutical companies to increase the therapeutical demand [11,12]. In 2003, fluoxetine manufacturer was required by The European

Agency for the Evaluation of Medicinal Products to remove PMDD from the list of indications for fluoxetine sold in Europe [13]. In Australia, although PMDD is officially recognized, SSRIs are not subject to reimbursement under the Pharmaceutical Benefits Scheme [14].

PREVALENCE

PMS prevalence during life span may vary from 75 to 85% of women if an isolated symptom is considered, between 10 and 15% when cases request medical assistance, and from 2% and 8% if interruption of social activity is referred [15,16]. In the United Kingdom, current estimates are that approximately 800,000 severe PMS cases exist, many of which are PMDD [17]. In addition, PMS may take a long time to be properly diagnosed and treated. Kraemer and Kraemer [2] have reported that 220 out of 492 women have doctor shopped, seeing an average 3.75 physicians over an average interval of 5.33 years before being diagnosed with PMS and/or effectively treated to alleviate their symptoms. The syndrome affects women with normal ovulatory functions; its greatest incidence is among women aged 25 and 40, sometimes having a background of depressive or mood disorders, often with at least one previous birth, and in some cases with postpartum depression. In women with severe (six symptoms) or moderate PMS (one to five symptoms), there is a high level of intraindividual variation over time. Thus, 72% of women demonstrate fluctuation in their PMS status [18].

Reported PMDD prevalence may in fact be overestimated due to overdiagnosis [19] which may create psychological and social problems and also lead to unnecessary prolonged pharmacologic therapy [20]. The low specificity of symptoms frequently contributes to this misinterpretation; thus, other disorders should carefully be excluded. On the other hand, some studies show that the premenstrual period is phase that increased the risk for the exacerbation of psychiatric disorders such as obsessive-compulsive behavior, increased alcohol consumption, higher suicide rate or admission of symptomatic schizophrenics. PMDD is associated with low educational level, a history of major depression and current addiction to smoking, and its prevalence increases in the premenopausal phase [15, 21].

Premenstrual mood symptoms did not exhibit familial aggregation in families with bipolar or major depressive

Table 2. Symptoms Required PMDD Diagnosis

Major Criteria	Minor Criteria
1. Depressed mood, feelings of hopelessness, or self-deprecating thoughts 2. Anxiety, tension 3. <i>Mood changes, emotional instability (feeling suddenly sad or tearful or increased sensitivity to rejection)</i> 4. Irritability, anger or increased interpersonal conflicts	5. Lack of interest in 6. Difficulty everyday activities, anhedonia in concentrating 7. Lethargy, easy fatigability, or marked lack of energy 8. Change in appetite, overeating, or specific food cravings 9. Insomnia, hypersomnia 10. Subjective sense of being out of control or overwhelmed 11. Physical symptoms: headaches, arthralgia, myalgia, weight gain, edema, breast tenderness, sensation of bloating

In most menstrual cycles during the past year, five (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week post-menses. At least one of the symptoms being either 1, 2, 3 or 4 (major criteria).

disorders [22]. PMDD women have more stressful events and their daily life stressors have a greater impact on their lives than non-PMDD women [23,24]. PMDD women also report more traumatic life stress, including sexual and physical abuse [21,25]. Due to stressful or traumatic events, women may have an impaired stress response, being PMDD women more vulnerable [24,26,27].

Obesity is strongly associated with PMS. Thus, obese women (BMI ≥ 30) have nearly a three-fold increased risk for PMS than non-obese ones. In addition, PMS is more prevalent among Caucasian, younger and smoking women [28].

PATHOPHYSIOLOGY OF THE PREMENSTRUAL SYNDROME AND PREMENSTRUAL DYSPHORIC DISORDER

Symptoms related to menstruation are multidimensional and affect different physiological systems. PMS is characterized by an imbalance of complex interactions of hormones, essential nutrients and neurotransmitters, in combination with psycho-social stress. These unbalanced conditions vary from one person to another, and in the same person from one cycle to another. Homeostasis alterations and deficient adaptation constitute the nucleus of the pathophysiological mechanism [16,29]. PMDD is also a cluster of genetic, emotional, motivational, cognitive and behavioral changes which occur in regular association immediately prior to/ or during the early menstrual days.

Genetic Influences

During the last years, there has been a growing interest to determine if premenstrual mood symptoms, either PMS or PMDD, exhibit familial aggregation or some degree of heritability. Some behavioral characteristics, including personality, cognitive capacities and susceptibility to emotional and mental disorders have been postulated to be linked to genetic polymorphisms. Changes in psychiatric phenotypes due to genetic factors are seldom the result of gene polymorphisms [30,31]. Preliminary studies have reported that there is no evidence for a specific genetic contribution in the risk of suffering PMS due to the unreliability in measuring premenstrual symptoms. However, self-reported PMS symptoms are different in monozygotic twins and in dizygotic ones [32].

Kendler *et al.* [33] used a twin-measurement model that allows estimation of the causative roles of genetic and environmental factors with correction for measurement errors or short-term temporal fluctuations. In 1,312 menstruating female twins followed-up over 6 years, retrospectively reported that premenstrual-related depressive and anxiety symptoms are moderately stable over time and are substantially heritable. The relative contribution of genes to premenstrual symptoms and the extent of genetic and environmental co-variation with the personality trait neuroticism and lifetime major depression have been studied in an Australian monozygotic and dizygotic twin cohort [34]. Although there were genetic correlations between reported PMS and neuroticism, and with lifetime major depression,

there was a 39% PMS genetic variance that was not explained by these factors.

Preliminary results have demonstrated that women with prospectively diagnosed PMDD were associated with estrogen receptor alpha gene (ESR1) genetic variation [35]. Women with PMDD differ from symptom-free subjects in terms of serotonin-related biological markers. However, women with prospectively diagnosed PMDD, as compared to healthy controls, did not display associations between the disease and polymorphisms that encode the 5-hydroxytryptamine transporter, tryptophan hydroxylase 1, and monoamine oxidase A. These results do not support a significant role for studied marker polymorphisms [36].

Polymorphism of the serotonin receptor 1A C(-1019)G was studied in women with PMDD and healthy control subjects. Despite the postulated high risk G/G, there was a marked overrepresentation of the C/C genotype in women suffering PMDD, being the C allele a contributing risk for PMDD [37]. The transcription factor AP-2 family, which is involved in the regulation of the monoaminergic system, has been postulated as a risk factor for PMDD. However, genotype frequencies did not differ between women with PMDD and controls [30,31].

Steroid Hormone Influences

Attempts have even been made to relate PMS symptoms with estrogen/progesterone levels and the estrogen/progesterone ratio. It is considered that progesterone presence at the beginning of the luteal phase is essential for PMS to occur. In the case of PMDD, the results failed to find any correlation between anxiety and depression when compared to estrogen/progesterone levels [4,38,39].

Estrogen might influence the serotonin system, producing a positive mood and wellbeing, whereas progesterone decline, characteristic of the late luteal phase had been linked to changes in the central nervous system in terms of gamma-aminobutyric acid (GABA) and progesterone metabolites that interact with the GABA_A receptor complex [40-43]. Bilateral ovariectomy or treatment with gonadotrophin releasing hormone (GnRH) agonists followed by progesterone treatment can induce premenstrual symptoms, while progesterone treatment during the luteal phase is devoid of benefits over premenstrual symptoms [44,45].

Estrogens and progesterone also interact with the renin-angiotensin-aldosterone system (RAAS) which controls hydromineral balance. Estrogens could stimulate the RAAS, increasing angiotensinogen synthesis in the liver, this being responsible for bloating and weight gain [46]. Aldosterone competes with progesterone at the receptor level causing an antimineralocorticoid effect manifested as a dominant natriuresis during days of increased progesterone secretion [47]. The majority of synthetic progestagens do not have the antimineralocorticoid effect of progesterone; nevertheless drospirenone, a recently developed progestagen, has the same antimineralocorticoid effects as progesterone and is effective in the treatment of symptoms associated with premenstrual bloating [48]. The combined anovulatory drug

which includes this progestagen is specially useful in cases of PMS and cyclic liquid retention [49].

Allopregnanolone, a metabolite of progesterone, serves in homeostatic mechanisms restoring normal GABAergic and hypothalamic-pituitary-adrenal functions following stress. Animal models indicate that this neuroactive steroid may be related to PMS/PMDD pathophysiology. It is a neuroactive steroid with contradictory effects. Thus, anesthetic, sedative and anxiolytic as well as aggressive and anxiogenic properties have been reported [42,43,50].

In women, allopregnanolone fluctuates during the menstrual cycle [51]. Luteal phase serum allopregnanolone levels are lower in PMS patients as compared to controls. Serum progesterone levels are lower in PMS women in both the follicular and luteal phase while serum estradiol levels are in the normal range in both groups [52]. The relative low levels of both allopregnanolone and progesterone may be associated with inadequate neuroactive steroid production which impairs response to stressful conditions. As compared to controls, women with PMDD had greater luteal phase serum allopregnanolone and lower cortisol levels during both basal condition and under mental stress. In addition, PMDD women had a greater allopregnanolone/progesterone ratio than control subjects [53]. In fertile women, progesterone induces adverse mood, related to allopregnanolone serum concentrations, equivalent to an inverted U-shaped curve. This effect may be similar when progesterone is added to postmenopausal women hormone treatment. In this model, negative mood symptoms occur when serum allopregnanolone concentrations are similar to endogenous luteal phase levels, while low and high concentrations have less effect on mood. The maximal effective allopregnanolone concentration capable of producing negative mood is in the range serum luteal phase concentrations [54].

Serum allopregnanolone levels are reduced in the luteal phase of women with PMS causing an inability to increase GABA levels in the CNS required during states of excitability as occurs during ovulation and physical and psychological stress [51]. Low levels of this progesterone metabolite favour disorders such as anxiety, tension and depression. The reduced basal levels of progesterone and allopregnanolone in the luteal phase are accompanied by high dehydroepiandrosterone (DHEA) and free testosterone levels which contribute to cyclic bouts of anxiety, aggressiveness and irritability that occur in patients with PMS [54]. However, not all studies agree regarding blood allopregnanolone levels [55].

Symptomatic women would have an inadequate allopregnanolone response to stress due to reduced functional sensitivity of the GABA_A receptor [24]. Additionally, rodent stress studies that involve social isolation find irregularities in GABA activity [56]. Severe life stress may result in alterations in the GABA_A receptor function in women with PMDD [57,58].

Neurotransmitters and the Nervous System Function

One of the most controversial aspects of PMS refers to the effects of ovarian hormones on the central nervous

system. In PMS there is a relationship between low estradiol levels during the luteal phase and lower brain noradrenergic activity during ovulation and the luteal phase. The low levels of norepinephrine in women with PMS correlate negatively with sudden changes of mood, impatience, nervousness, tiredness, weakness, apathy and headache [59]. Platelet *alpha-2* adrenergic receptor is involved in anxiety and depressive disorders. In PMDD women, there were no differences in platelet binding parameters between phases of the menstrual cycle; although receptor density correlated positively with symptom severity during the luteal phase [60].

Serotonin plays a central role in the aetiopathogenesis of PMS and PMDD; specially as an expression of irritability and anger, symptoms of depression, and the craving for specific foods found in PMDD sufferers. Estrogens increase cerebral serotonin receptor density and the sensitivity toward serotonin agonists. PMDD women had higher serotonergic function in the follicular phase but lower in the luteal phase, compared to women with PMS without PMDD and normal controls, suggesting a relevant role for serotonin function alterations in women with PMDD [61]. The role of this neurotransmitter is reinforced by the clinical effectiveness of selective serotonin re-uptake inhibitors (SSRIs) in the treatment of PMDD [62,63].

During the menstrual cycle, gonadal steroids are also involved in GABA neuronal function modulation. In animals, estradiol enhances excitatory neurotransmission while progesterone-derived neurosteroids produce GABAergic inhibition. Brain GABA content fluctuates along the menstrual cycle in both healthy and PMDD women [64]. PMDD women display increased cortical GABA from the follicular phase until half way through or the end of the luteal phase [65]. These results suggest that the GABAergic system is modulated by ovarian steroids and these changes could be important in the pathogenesis of PMDD.

Glutamate fluctuations across the menstrual cycle in the medial prefrontal cortex of PMDD women and healthy controls have been demonstrated with proton magnetic resonance spectroscopy. PMDD women may display an increased sensitivity to phase-related alterations of the menstrual cycle [66]. Alterations in pain threshold have also been associated with the severity of symptoms [67].

Grey matter regional variation over the menstrual cycle has been studied by magnetic resonance imaging. In the postmenstrual period, grey matter is relatively increased in the right anterior hippocampus and relatively decreased in the right dorsal basal ganglia [68]. These results show human brain plasticity associated with endogenous hormone fluctuations and clinical symptoms.

The autonomic nervous system may also play a crucial role in controlling body response to external and internal stimuli, maintaining nearly every important body homeostatic process. Some classical studies demonstrated that parasympathetic nerve activity in PMS women was lower in the late luteal phase than in the follicular phase [69]. Venous oxygenation index, as expression of autonomous nervous system alteration, is significantly decreased in PMS women [70]. PMDD women

had elevated norepinephrine and total peripheral resistance at rest and during mental stressors compared with control subjects; and these phenomena were present in both follicular and luteal phases [71]. In addition, PMDD women have reduced vagal tone compared to controls, this difference being more apparent in the non-symptomatic follicular phase [72]. Therefore, instability or slight disequilibrium of the autonomic system may induce reiterative premenstrual symptomatology. The cluster of symptoms, thus, may differ among women and even within each but may also fluctuate between their menstrual cycles.

In the luteal phase, women with severe PMS have decreased parasympathetic activity during sleep in association with their premenstrual symptoms as compared to the follicular phase when they have less or no symptoms [73]. Although women with severe PMS report poor subjective sleep quality during the luteal phase, polysomnograms did not detect specific sleep composition alterations. However, PMS women displayed decreased delta incidence and increased theta incidence and amplitude during the electroencephalographic study [74].

Leptin and the Growth Hormone Axis

Leptin also participates in the pathophysiology of PMS through hypothalamic receptors that control general emotional behavior. This hormone is increased during the luteal phase in comparison to the follicular phase in women with and without PMS, but those who suffer premenstrual symptoms only have a significantly increased level in the follicular phase [75]. However, GnRH analogues do not influence leptin levels in both normal and PMS, suggesting that changes of leptin levels would not be important in the pathophysiology of PMS [76].

The growth hormone axis has also been studied in women with PMS or PMDD. Patients with major depression have somatotrophic hormone alterations. Women with PMS had insulin-growth-like factor 1 (IGF-1), IGF-binding protein 3, estradiol and progesterone levels that did not differ between women with prospectively documented PMS and control subjects [77]. As compared to controls, women with PMDD have lower IGF-1, which was significantly lower throughout all phases of the menstrual cycle [78].

Nutrition and Micro-Nutrients

There is an intense interest concerning the effects of nutrients, psychological state, mental performance and well-being in PMS women. Energy consumption varies during human and animal reproductive cycles, with a nadir in the peri-ovular phase and a zenith in the luteal phase [79]. The pattern for the selection of certain foods has little consistency depending on gonadal hormones; nevertheless, changes in appetite, food cravings and calorie intake during the menstrual cycle have a certain parallelism with the serotonin rhythm. In the premenstrual phase, with low serotonin activity, there is a predisposition for the excessive consumption of food, cravings and depression. PMS has been linked with dysfunctional serotonin metabolism, and experimental evidence suggests that hormonal fluctuations do affect central serotonin levels [80,81].

A vegetarian diet reduces pain, fluid retention, weight gain and premenstrual symptoms, while at the same time increasing the globulin that transports sex hormones [82]. Analysing specific vegetable consumption reveals that neither soybeans nor isoflavones produce changes in premenstrual symptoms; on the other hand, a diet rich in carbohydrates increases premenstrual symptoms [83].

PMS among overweight women may condition the type of nutrients and calories consumed in different phases of the menstrual cycle [84]. After making appropriate adjustments, during the premenstrual phase PMS women increase their consumption of fats, carbohydrates and simple sugars. This could explain the fact of increased weight at certain moments of the menstrual cycle, as referred by some PMS women.

Estrogens regulate calcium metabolism, its intestinal absorption, and parathormone secretion, causing fluctuations throughout the cycle [85]. On the other hand, hypo- and hypercalcemia are associated with emotional disorders. PMS and hypocalcemia symptoms are similar. Calcium supplements may improve mood and physical symptoms among PMS women. Compared to controls, PMDD women displayed lower ionised calcium during menses, and lower urine calcium excretion during the late follicular, mid-cycle and early luteal phases. In addition, 1,25-dihydroxyvitamin D was significantly lower in the luteal phase of cases as compared to controls [86]. Further studies are needed since vitamin D is involved in many basic biological processes [87-90], including endocrine, cell and immune functions. Furthermore, low serum vitamin D levels have been found in mood disorders affecting women [91].

Serum calcium and vitamin D levels are lower in PMS women, and calcium supplementation may reduce symptom severity. In a nested case-control study within the prospective Nurses' Health Study II cohort, women aged 27 to 44, PMS free at baseline in 1991, were studied for the presentation of premenstrual symptoms and calcium and vitamin D intake. After adjusting for confounding factors, women in the highest quintile of total vitamin D intake had a significant lower relative risk for PMS compared with those in the lowest quintile. Calcium intake from food sources was also inversely related to PMS. Participants with the highest calcium intake had a lower relative risk [92].

In PMDD women calcium metabolism abnormalities may cause some affective and somatic symptoms. PMDD women displayed significantly lower ionized calcium at menses, lower urine calcium excretion (late follicular, mid-cycle and early luteal phase) and lower luteal phase serum vitamin D, as compared to non PMDD control women [86].

Magnesium intercellular differences, in the presence of normal plasma levels, have been reported in PMS women [93,94]. However, such differences are not limited to the luteal phase, which renders difficulties in interpreting the role of magnesium in the pathophysiology of PMDD [95].

Immunological Influences

There are bidirectional link communications between the nervous and the immune system. Produced and released neurotransmitters/hormones interact with immune cells to

alter immune functions, including cytokine production. At the same time, cytokines produced by immune/ nervous system cells regulate sleep. Emotional stability and modifications associated to natural killer (NK) cell activity modifications have also been studied [96]. In healthy subjects, anxiety and personality trait modulate NK response to psychological stress. Co-morbid anxiety and depression alter cellular immunity, and NK cell normalization is associated with successful pharmacotherapy [97]. Emotional changes are associated to subjective discomfort, significant catecholamines and cortisol increased concentrations, and to increased CD8+ and CD56+ cell counts. Induced stress is associated to different migration processes among these cells [98] that could be modulated by endocrine and nervous inputs. The influence of sex hormones on the immune system activity has been reported to be gender-associated and disappears after the menopause [99]. However, the precise links between cyclical premenstrual disorders and the immune system need specific research to determine if associations are causal or casual.

Psychosocial Aspects

In some women, menstrual cultural stereotypes may contribute to the development of premenstrual symptoms. Undoubtedly cultural attitudes, psychosocial experiences or expectations, and levels of stress influence the expression of symptoms. Tradition says that PMS occurs more frequently in psychically unstable women, those that may have a constitutional susceptibility characterized by an exaggerated response to various stimuli. PMS women have higher levels of anxiety, neuroticism, and negative attitudes toward their bodies, sex and masturbation [100-102]. Psychoanalytical theories have related PMS with a femininity complex, ambivalent desire for pregnancy and unresolved conflicts over sexual preferences. These approaches have been questioned from different perspectives [103,104].

So-called secondary impulses or conditioned motivation have great importance in moulding personality; if a response is consistently reinforced, this behavior tends to appear with greater frequency until it becomes one of the main traits of personality. In some cultures, attitudes toward menstruation and premenstrual experiences among adolescents are moulded according to the experiences of older female members of the family who transmit negative messages and the perception that menstruation is weakening and annoying [104,105].

PMDD women have a personal history of physical or sexual abuse. The latter present lower luteal phase basal norepinephrine levels as compared to their counterparts. Additionally they display more exaggerated reactions to stress in the luteal phase [106].

CLINICAL MANAGEMENT

When managing patients with variable symptoms presenting along the menstrual cycle which are suspicious of PMS or PMDD these should be differentiated from premenstrual exacerbation of other disorders. Specific diagnostic criteria for both PMS and PMDD should be supported by the precise identification of complaint and

symptom diaries. For the clinical diagnosis of PMS, the American College of Obstetrics and Gynecology recommends the work-up proposed by the San Diego University of California and the US National Institute of Mental Health [107]. The American Psychiatric Association criteria should be followed for diagnosis of women with suspected PMDD [8].

Specific diagnostic criteria should be supported by symptom diaries. Premenstrual symptom diaries for several consecutive months should be recorded in order to have details about cycle-to-cycle variability. The Moss Menstrual Distress Questionnaire allows to assess physical, emotional, and behavioral symptoms that accompany the menstrual cycle, and following up on the therapeutic effects of different treatments [108,109]. Identification of cyclical symptoms may be obtained by completing the PRISM (Prospective Record of the Impact and Severity of Menstrual Symptoms) calendar every night for three consecutive cycles. On the first cycle women may complete several other psychometric measures. Using the PRISM, a minimal 66% increase in physical symptoms from the late follicular to the late luteal phase assign subjects to luteal phase physical symptoms (LPPS) and non-LPPS groups. The presentation of severe physical symptoms in the late luteal phase of the female reproductive cycle is not always accompanied by a worsening of psychological symptoms [110]. The Daily Record of Severity of Problems may detect differences along the menstrual cycle in order to determine the degree of symptomatic variation of associated premenstrual symptom [111,112].

Women may be categorized in three groups, normal with no significant variations along the cycle, PMS, and PMDD cases, depending on the severity of premenstrual symptomatology [70,113]. Other similar scales can be used to study different aspects of menstrual cyclical disorders [114]. However, targeting women with specific premenstrual symptom scales, for specific treatment modalities, raises some concerns regarding the fact that the tools might improve response rates beyond the current ceiling of approximately 60% [115].

Many women suffering either PMS or PMDD are not diagnosed and treated. On the other hand, many others are given a label without a precise diagnosis. Those that are diagnosed are usually prescribed a medication. Placebo is significantly effective in PMS management. Thus, during PMS treatment, a significant response is commonly defined as a 50% reduction in symptom score, although this limit is empirical it seems to demonstrate the strong placebo effect of many therapeutic options [39,116,117].

TREATMENT

Treatment of PMS or PMDD women is confined to reduce symptoms and improve social and occupational function in order to increase individual quality of life. There are three therapeutical approaches for PMS and PMDD: nutritional and lifestyle, pharmacological treatment and psycho-behavioral therapy. No scientific studies have been carried out to determine which approach is most effective.

Lifestyle changes may be useful in women with mild symptoms. Aerobic exercise and a healthy diet may improve premenstrual symptoms [118-120]. Eating foods with low glycemic index along with proteins in moderate amounts through the day prevents unstable blood sugar and mood swings during PMS. Women who eat only salads and vegetables are at risk of low protein levels and are prone to experience PMS symptoms. PMS management strategies should consider factors such as high stress, caffeine intake, and stop smoking. Since obesity has been associated to high premenstrual symptom prevalence, appropriate exercise and a hypocaloric diet should be recommended in women with elevated body weight.

Recent reviews have detailed therapeutic options for both PMS and PMDD women [29,121-124]. In North America and the UK, antidepressive drugs are very popular, but this is not the case in Europe where hormone treatment, analgesics and phytotherapy are used. The U.S. Food and Drug Administration has now approved only four agents for the treatment of PMDD: fluoxetine, controlled-release paroxetine, sertraline and a 3 mg drospirenone/20- μ g ethinylestradiol oral contraceptive administered in a 24/4 regimen. In Europe and South America, there are more therapeutic agents than in North America. In Asia, different forms of traditional medicines have been used, although some methodological bias may be present in these studies.

SSRIs are most effective for irritability and anxiety symptoms than hormone therapy, whereas having lesser efficacy for 'atypical' premenstrual symptoms. An altered serotonergic system in PMDD women may be the underlying mechanism for the observed symptoms; consequently treatment with SSRIs remains to date the preferred treatment. SSRI use has demonstrated treatment efficacy for the management of PMS/PMDD complaints, having a double response rate as compared to placebo. Both mood and physical symptoms improved with SSRIs, although the greatest improvement is obtained in irritability and mood swings while fatigue had less improvement [29,121,122]. The rapid action of SSRIs on premenstrual symptoms allow their use only during the 14 days of the luteal phase. It seems that all SSRIs are effective in intermittent luteal phase dosing. Starting treatment at the time of symptom initiation and stopping after menses initiation or 3 days later is a new strategy being studied which allows even shorter term treatments.

The duration of SSRI treatment for premenstrual symptoms is unknown and the rate of relapse with different SSRIs is also not well known. It seems that women with severe symptoms at baseline are more likely to relapse as compared to women in the lower symptom severity group [125].

Although the neuroleptic malignant syndrome (NMS) does appear to be rare, and the serotonin syndrome seems more prevalent, they are both connected with antidepressants. NMS involves muscle rigidity, fever and can cause delirium. Presence seems to increase in the first few weeks of anti-depressant use and upon dose changes. Serotonin syndrome, specially in its most severe form, and

NMS are overlapping with regard to clinical features, and may not be distinguishable [126]. SSRIs, and selective serotonin/norepinephrine reuptake inhibitors (SNRIs), can cause an increase in serotonin levels. Symptoms of the serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overactive reflexes, nausea, vomiting, and diarrhea.

A very used gynecological therapeutical approach has been to produce anovulation. Thus, ovulation suppression ameliorates a broad range of behavioral as well as physical premenstrual complaints. Antigonadotropic agents (e.g., GnRH, danazol, steroid implants) and oral contraceptives that inhibit ovulation should be effective for the treatment of PMS/PMDD. However, on occasions women with severe symptoms do not achieve relief and sometimes may even become worse [4,29,49,117,125].

Low dose GnRH agonist treatment in women with severe PMS significantly decreased levels of allopregnanolone and progesterone in parallel with symptom improvement. Same women who responded to placebo during placebo phase displayed lower serum allopregnanolone concentrations than GnRH agonist responders. This was associated with improvement in symptoms compared with pre-treatment ratings. Thus, treatment response, whether induced by the GnRH agonists or placebo, appears to be associated with a decrease in allopregnanolone concentrations [127].

The hypo-estrogenic state induced by GnRH agonist treatment renders them less suitable for long-term clinical use. A meta-analysis [128] supports the feasibility of add-back therapy, although some patients report a recurrence of symptoms with add-back estrogen/progestagen treatment [129]. Segebladh *et al.* [130] evaluated three different add-back hormone replacement treatments in PMDD women who were treated with a GnRH agonist. Add-back treatments consisted of 1.5 mg estradiol and 400 mg progesterone, 1.5 mg estradiol and placebo, and 0.5 mg estradiol and 400 mg progesterone. The highest dose of estradiol associated with progesterone treatment was associated with the most pronounced symptom recurrence. As an alternative, combining a GnRH agonist with continuous treatment with tibolone may prove to be effective [128,131].

Combined oral contraceptives may produce PMS-like symptoms, including water retention and irritability. Negative symptoms are one of the major reasons for discontinuation of combined oral contraceptives. These adverse effects are related to progestogen properties. However, the prevalence of psychiatric disorders and PMDD symptoms is high in women with adverse mood changes during oral contraceptive treatments. Thus, it has been reported that women with ongoing or past self-reported adverse mood effects had an increased rate of mood disorders [132].

The new progestagen drospirenone –a spironolactone analog- has been included in contraceptive pills, profiting its ability to reduce symptoms of water retention and other side effects related to androgen excess. Drospirenone has antiminerocorticoid and antiandrogenic properties

[49,117]. The new oral contraceptive including 24 pills containing ethinylestradiol (20 µg) and drospirenone (3 mg/day), followed by 4 days of inactive pills, is associated with lower endocrine endogenous fluctuations which may reduce perimenstrual discomfort [133]. In addition, drospirenone has diuretic and antihypertensive antiandrogenic effects similar to its related compound spironolactone. Long-cycle treatment with a combined oral contraceptive has been proposed to reduce the fluctuations associated to the conventional 7-day free hormone period. Increasing the duration of active hormone intake to 24 days and shortening the hormone-free interval to 4 days, causes greater ovarian activity suppression as compared with the conventional 21/7 treatment. No difference was observed between the 24/4 and the conventional 21/7 regimen in progesterone levels. In addition as compared to the 21-day regimen, the 24-day treatment scheme produced a more consistent suppression of endogenous estradiol and reduced hormone fluctuations [134]. Continuous daily treatment with a monophasic pill (20 µg ethinylestradiol and 1 mg norethindrone acetate) produced in women a significant reduction of symptoms and improvement in behavior, compared to traditional cyclical treatment [113].

Non-steroidal anti-inflammatory drugs (NSAIDs), nutritional supplements and herbal medicines have been used to treat premenstrual symptoms associated with PMS or PMDD [29,135-137]. Taken before, or at the onset of menstruation, NSAIDs such as ibuprofen or naproxen sodium can ease cramping and breast discomfort. Consuming dietary and daily calcium supplementation may reduce PMS and PMDD physical and emotional symptoms [85,86,138]. Vitamin B-6 and magnesium also may benefit in some cases [137,139,140]. Clinical trials suggest that L-tryptophan, chasteberry (*Vitex agnus-castus*), soy isoflavones, and saffron (*Crocus sativus L.*) may reduce irritability, mood swings, anger and headaches associated with PMDD [136,141,142]. However, there are controversial results concerning the efficacy of these treatments [143-145], specially when considering severe symptoms. Other treatments, like acupuncture [146] have not been confirmed in controlled trials.

Cognitive-behavioral therapy can enhance self-esteem and social integration as well as reduce other symptoms [147]. All kinds of psychotherapy can be relevant [148], even though relaxation technique training may be particularly suitable [149].

FINAL REMARKS

Every woman has had some symptoms of PMS that present shortly before the menstruation. But when symptoms associated with the menstrual cycle become so severe that they interfere with daily activities and quality of life, the PMDD may be diagnosed. In spite of the generalization of the diagnosis criteria, PMS and PMDD remain complex and polymorphous disorders. PMS was considered for a long time as a somatic disease, but now psychiatric symptom severity most often justifies the medical care. In order to distinguish some isolated and mild complaints from the disabling disorder, standardized prospective auto-assessment

is the most relevant method to achieve a proper diagnosis. Healthy lifestyle, exercise, SSRIs and the new oral contraceptive (24/4 regimen ethinylestradiol/drospirenone) appear to be the most effective treatments. Herbal products and alternative therapies may be also used, although the level of evidence is low or controversial. However, no single intervention has proven to be effective in all PMS or PMDD patients.

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