Premenstrual syndrome and premenstrual dysphoric disorder in adolescents

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Abstract: Premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) represent two premenstrual disorders characterized by physical and psychological symptoms that occur in the luteal phase of the menstrual cycle, prior to the onset of menses, and have a negative impact on the psychosocial functioning of affected individuals. PMS, more common than PMDD, affects 20-40% of menstruating women, with common symptoms including fatigue, irritability, mood swings, depression, abdominal bloating, breast tenderness, acne, changes in appetite and food cravings. PMDD, affecting a smaller percentage of women, is characterized by more severe symptoms and is listed as a depressive disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). While the pathophysiology of these premenstrual disorders remains unclear, it has been hypothesized that sensitivity to hormonal fluctuations during the luteal phase of the menstrual cycle, abnormal serotonergic activity, and aberrations in progesterone and the neurotransmitter gamma aminobutyric acid (GABA) may all play a role in these disorders. Treatment of PMS and PMDD is focused on alleviation of symptoms and improvement of functioning and quality of life for affected individuals. The treatment of severe PMS and PMDD typically requires pharmacologic therapy with selective serotonin reuptake inhibitors (SSRIs), oral contraceptive pills (OCPs), gonadotropin-releasing hormone (GnRH) agonists, and non-contraceptive estrogen formulations. Non-pharmacologic treatment with diet, exercise, cognitive behavioral therapy (CBT), certain vitamin and herbal supplements, and acupuncture may additionally be effective for some individuals.

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Introduction

Premenstrual disorders (PMDs), including premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD), are characterized by a constellation of mood/affective symptoms and physical symptoms, occurring predictably in the luteal phase of the menstrual cycle and resolving after the onset of menses, with a symptom-free period during the follicular phase. The identification and treatment of premenstrual disorders are vital to improving the quality of life and psychosocial functioning of affected patients. This chapter will provide an overview of the epidemiology, pathophysiology, diagnosis, and treatment options for patients with PMS and PMDD.

Premenstrual disorders (PMDs), including premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD), are characterized by a constellation of mood/affective symptoms and physical symptoms, occurring predictably in the luteal phase of the menstrual cycle and resolving after the onset of menses, with a symptom-free period during the follicular phase.

Epidemiology

While the exact prevalence of PMS and PMDD are not known, it is estimated that up to 80% of women experience some physical and emotional changes prior to the onset of menses, with 20 to 40% experiencing some degree of functional impairment, and 2.5 to 5% experiencing a significant impact on functioning.[1] The prevalence of PMS among menstruating women is estimated to be between 20 to 30%, while PMDD is estimated to affect 1.2 to 6.4% of women.[2] Other cited data on prevalence suggest that 80 to 95% of women experience physiologic premenstrual symptoms, 30 to 40% have PMS, and 3 to 8%

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have PMDD.[3] The data on prevalence rates of PMS and PMDD in adolescents demonstrates similar findings.[4,5]

Historically, the lack of precise data on the prevalence of premenstrual disorders was due to the absence of strict diagnostic criteria, particularly for PMS. Recognition of the need for further research on the topic of premenstrual disorders resulted in the formation of the International Society for Premenstrual Disorders (ISPMD), a multidisciplinary group comprising international experts on the topic of PMDs. The inaugural meeting of the ISPMD was held in Montreal in 2008, where the group defined premenstrual disorders and established two categories: core PMDs and variant PMDs.[3] Core PMDs were defined as premenstrual disorders where symptoms (somatic and/or psychological) occur in the luteal phase of the menstrual cycle, resolve after menstruation, and result in functional impairment, interference with work, school, or interpersonal relationships, and/or cause significant distress. Importantly, symptoms must be documented prospectively for at least two menstrual cycles, and symptoms must not be the result of a premenstrual exacerbation of another psychiatric or medical disorder. The ISPMD included PMS and PMDD in the category of core PMDs. Variant PMDs, which will not be discussed in this chapter, included four additional entities: premenstrual exacerbation of underlying medical or psychiatric conditions occurring in the luteal phase, non-ovulatory premenstrual disorders, progesterone-induced premenstrual disorders, and premenstrual disorders without menstruation.

Although PMDs can present with a varying number and severity of symptoms, they have been demonstrated to have a significant impact on the lives of affected individuals.[6,7] PMDs, including PMS and PMDD, have been shown to have both direct and indirect economic costs for women, in the form of medical bills, missed work days and decreased productivity, and to result in impairments in social functioning.[6] PMDs have additionally been shown to have a negative impact on health-related quality of life (HRQoL), defined as an individual's perceived physical and mental health over time.[7] Notably, the morbidity of PMDs has likely been under-recognized and under-reported prior to the creation of more widely utilized diagnostic criteria.

While the precise pathophysiology underlying premenstrual disorders has not been fully elucidated, several plausible etiologies have been studied and identified, including: an increased sensitivity to ovarian hormone fluctuations during the luteal phase of the normal menstrual cycle, abnormal serotonergic activity, and aberrations in progesterone and the neurotransmitter gamma aminobutyric acid (GABA).

Pathophysiology

While the precise pathophysiology underlying premenstrual disorders has not been fully elucidated, several plausible etiologies have been studied and identified, including: an increased sensitivity to ovarian hormone fluctuations during the luteal phase of the normal menstrual cycle, abnormal serotonergic activity, and aberrations in progesterone and the neurotransmitter gamma aminobutyric acid (GABA).

The theory that increased sensitivity to the cyclic fluctuations of estrogen and progesterone may contribute to the symptoms of PMS and PMDD in some individuals is supported by several findings. These include: twin studies suggesting a possible genetic predisposition to the development of PMDs; the absence of abnormal levels of estrogen, progesterone, testosterone, cortisol, or prolactin in patients with PMDs; the fact that gonadotropin-releasing hormone (GnRH) agonists and oophorectomy can alleviate symptoms in affected individuals; and that re-exposure to physiologic doses of exogenous estradiol or progesterone results in recurrence of symptoms in women previously treated successfully with GnRH agonists.[8-10] Interestingly, it appears that it is the change in ovarian hormone levels (for example, from low to high) that triggers the symptoms of PMDD, rather than exposure to a steady state of hormones, as patients in one study exposed to exogenous estradiol and progesterone experienced symptoms in the first month of add back therapy, but not during the following two months when plasma levels stabilized.[10] The finding supports the theory that it is sensitivity to the fluctuations in hormones during the luteal phase of

the menstrual cycle that triggers symptoms in women with PMDs, rather than the presence of the hormones themselves.

Abnormal serotonergic activity has also been implicated in the pathophysiology of PMDD, as evidenced by the efficacy of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) in the treatment of the disorder.[11] The correlation between decreasing estrogen levels in the late luteal phase with depressed mood is consistent with the finding that estrogen increases serotonergic activity and serotonin levels in the body by a number of mechanisms. These include: increasing the production of tryptophan hydroxylase, the enzyme responsible for the conversion of tryptophan to serotonin; antagonizing the serotonin reuptake transporter (SERT), thereby allowing serotonin to remain in the synaptic cleft for a longer period of time; and increasing the number of serotonergic receptors.[12,13]

The effect of progesterone on GABA, the main inhibitory neurotransmitter in the brain responsible for the regulation of anxiety, alertness, and stress, has also been studied. Progesterone is metabolized to form the neurosteroids allopregnanolone and pregnanolone, which are modulators of the GABA neurotransmitter system in the brain. It has been suggested that reduced allopregnanolone levels or neurosteroid sensitivity in the luteal phase in patients with PMS may contribute to symptoms, and may explain why benzodiazepine medications can be effective in treating some symptoms of PMS.[8,14] Additionally, in women with PMDD, GABA levels have been shown to decrease in the late luteal phase, compared to healthy controls who demonstrated an increase in GABA levels during the late luteal phase.[15] Low levels of GABA have additionally been demonstrated in some patients with anxiety and depression, suggesting an overlap in pathophysiology.[11]

The neuroendocrine processes that underlie PMDs help to explain why these disorders are not seen prior to menarche, during pregnancy, after bilateral oophorectomy, or after the onset of menopause. Additionally, they help to elucidate how targeted pharmacotherapy with agents such as SSRIs, combined oral contraceptive pills, and GnRH agonists can be effective, and why suppression of the hypothalamic-pituitary-ovarian (HPO) axis and induction of anovulation alleviates symptoms in some women.

Diagnosis

PMS and PMDD are defined as core PMDs by the ISPMD Montreal consensus, and differ from PME (premenstrual exacerbation) of an existing medical or mental health condition, such as seizures, migraines, or depression, which is considered a variant PMD.[3] The key difference between the core PMDs and other mental health or medical disorders is that symptoms must occur during the luteal phase of the menstrual cycle, with remittance after the onset of menses and during the follicular phase. Additionally, because the majority of women experience some degree of physical and psychological premenstrual symptoms, it must be demonstrated that symptoms affect an individual's psychosocial functioning and cause distress to be considered PMS or PMDD.

While the diagnosis of PMS does not require the presence of any specific number of symptoms, the diagnosis of PMDD has defined criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[16] PMS and PMDD are both clinical diagnoses based on a patient's reported symptoms and their relationship to menses. There is no single laboratory or imaging study that is used in making the diagnosis of a premenstrual disorder. In addition to patient history, validated symptom rating scales are available to establish a diagnosis, particularly for PMDD. The American College of Obstetricians and Gynecologists (ACOG) divides the common symptoms of PMS into two categories: psychological and physical.[1] The most common psychological symptoms include fatigue, irritability, mood swings, and depression. The most common physical symptoms include abdominal bloating, breast tenderness, acne, and changes in appetite/food cravings. Although there is no minimum required number of symptoms for diagnosis, the symptoms must occur cyclically in the luteal phase of the menstrual cycle and resolve after onset of menses.

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PMDD, formerly considered a "severe form of premenstrual syndrome" and previously known as late luteal phase dysphoric disorder, is now one of the depressive disorders identified in the DSM-5.[16] The DSM-5 diagnostic criteria for PMDD requires the presence of at least five symptoms in the week prior to menses, with improvement during menses, and resolution in the week following menses (follicular phase of the menstrual cycle). The symptoms should additionally have been present for the majority of menstrual cycles in the preceding year and resulted in functional impairment. At least one of the five symptoms must be mood-related, including labile affect or mood swings, irritability or anger, depressed mood or hopelessness, and/or anxiety. Additional symptoms should include one or more of the following: decreased interest in activities, difficulty concentrating, fatigue/low energy, change in appetite or overeating, insomnia or hypersomnia, feeling overwhelmed or out of control, and/or physical symptoms such as breast tenderness, joint pain, and bloating.

Notably, symptoms should be documented using daily rating scales prospectively over the course of at least two menstrual cycles to confirm the diagnosis of PMDD, although it is acceptable to make a provisional diagnosis in the interim. The use of prospective rating scales is particularly helpful to distinguish PMS/PMDD from other medical or mental health conditions that may demonstrate premenstrual worsening of symptoms. For example, the presence of depressive symptoms unrelated to the menstrual cycle would be more suggestive of major depressive disorder rather than PMDD. Importantly, the presence of comorbid major depression and anxiety disorders, among other psychiatric disorders, is common in patients with severe PMS and PMDD and must be considered during evaluation.[17]

Several symptom rating scales have been validated for the diagnosis of PMDD, including the Daily Rating of Severity of Problems (DRSP), the Premenstrual Tension Syndrome Rating Scale, and the Visual Analogue Scales for Premenstrual Mood Symptoms.[16] A retrospective screening tool, the Premenstrual Symptoms Screening Tool (PSST), can be helpful during initial assessment, and has been modified for use in adolescents.[5]

Treatment

Treatment of premenstrual disorders should be individualized, with consideration of the following factors: the severity of symptoms, the need for contraception, and previous treatment trials.[18] The goals of treatment in PMDs include alleviation of symptoms and improvement in the functioning and quality of life of affected individuals. The approach to mild symptoms involves providing validation and education, recommendations for lifestyle modification and non-pharmacologic treatment. Severe PMS/PMDD typically requires pharmacologic treatment with medications that either modify serotonin transmission or suppress ovulation. The most commonly used psychotropic medications are selective serotonin reuptake inhibitors (SSRIs), while hormonal treatments to suppress ovulation typically include combined oral contraceptive pills (combined OCPs), gonadotropin-releasing hormone (GnRH) agonists, and non-contraceptive estrogen formulations.

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Pharmacologic treatment

Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are considered the first-line therapy for severe PMS/PMDD in adults; data in adolescents, however, is limited.[17,19] SSRIs block the reuptake of serotonin in the neural synapse, thereby increasing levels of serotonin in the synaptic cleft. Currently, fluoxetine, sertraline, and paroxetine are Food and Drug Administration (FDA)-approved for the treatment of PMDD. Escitalopram, citalopram, and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine have also been used off-label and have demonstrated efficacy in the treatment of PMDD.[20-22] SSRIs are efficacious in the treatment of severe PMS/PMDD, both when used continuously and when used in the luteal phase only, beginning on day 14 and taken until the onset of menses or several days thereafter.[18] In contrast to patients using SSRIs for the management of depression, where maximum benefit may not be seen for four to six weeks, patients using SSRIs for

PMDD experience improvement in symptoms within several days of medication initiation, and the medications can be efficacious at lower doses.[11,18,19] A 2013 Cochrane review evaluating the use of SSRIs in women with PMS or PMDD identified thirty-one randomized controlled trials comparing fluoxetine, paroxetine, sertraline, escitalopram, and citalopram to placebo.[23] The authors concluded that the SSRIs reduced symptoms significantly more than placebo. Reported SSRI side effects included nausea, decreased energy, somnolence, fatigue, decreased libido, and sweating; these side effects were found to be dose-related.

Notably, other anti-depressant medications (eg. – tricyclic antidepressants and bupropion) and anxiolytics have not demonstrated consistent efficacy in the treatment of PMDs; therefore, their routine use is not recommended.[18]

Hormonal treatment

Historically, studies of various formulations of combined OCPs, which induce anovulation via suppression of the HPO axis, have shown mixed results, demonstrating some improvement in the physical symptoms of PMS but with inconsistent results with regards to mood symptoms.[24] Notably, OCPs are known to worsen mood symptoms in some women. Studies of continuous therapy with OCPs (with elimination of the hormone-free interval) have also shown mixed results, despite the hypothesis that elimination of the hormone withdrawal period would be beneficial in women with PMS/PMDD.[25]

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In 2006, the United States FDA approved the use of a combined OCP containing drospirenone 3 mg with 20 μg ethinyl estradiol in a 24/4 formulation for the treatment of PMDD after multiple studies demonstrated symptom improvement in patients with PMDD.[26-28] Drospirenone, a newer progestin, is a spironolactone analogue with antiandrogenic and antimineralocorticoid properties, binding to aldosterone receptors and blocking aldosterone action in the kidneys, leading to increased sodium and water excretion.[29] The efficacy of this specific OCP formulation has been attributed to several factors, including: the spironolactone-like activity of drospirenone, the lower dose of ethinyl estradiol, and the shorter hormone-free interval (4 days compared to the traditional 7 days), resulting in more follicular suppression and a more stable hormonal status.[30] It remains the only OCP approved by the FDA for treatment of PMDD, and can additionally be used for women who desire contraception. Notably, in adolescents, OCPs provide the additional benefits of cycle regulation, improvement in anemia, dysmenorrhea and acne, and reduction in functional ovarian cysts.[17]

Other hormonal treatments that have been studied for the treatment of PMS/PMDD include GnRH agonists, non-contraceptive estradiol, and progesterone.

Gonadotropin-releasing hormone (GnRH) agonists are considered third line therapy for severe PMS/PMDD behind SSRIs and combined OCPs, as they have been found to effectively treat the physical and psychological symptoms of PMS, but can have adverse effects on bone density and cause undesirable "menopausal" side effects due to the creation of a hypoestrogenic state, requiring "add back" therapy with estrogen; they are also typically costly medications.[2,31] Non-contraceptive estradiol preparations have also been used in the treatment of PMS, although robust evidence for their use is lacking. A Cochrane review of five randomized controlled trials that included 305 women evaluating the safety and efficacy of non-contraceptive estradiol in the treatment of PMS found very low-quality evidence to support the effectiveness of transdermal estradiol or subcutaneous implants plus progestin in the management of PMS.[32] The authors additionally found that oral unopposed estrogen given in the luteal phase may actually make PMS symptoms worse. Finally, a systemic review of 10 trials of progesterone therapy and four trials of progestogen therapy, including a total of 909 women, found no clinically significant difference between women taking progesterone versus placebo for PMS and concluded that the evidence did not support the use of progesterone or progestogens in the treatment of PMS.[33]

Symptomatic treatment

Other therapeutic agents utilized to manage premenstrual symptoms include nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, for management of dysmenorrhea, and spironolactone, for management of breast tenderness and bloating/fluid retention. NSAIDs inhibit cyclooxygenase, thereby reducing the synthesis of prostaglandins, the compounds responsible for the premenstrual symptoms of dysmenorrhea, nausea, vomiting, diarrhea, and fatigue.[19]

Spironolactone is an aldosterone receptor antagonist diuretic with anti-androgenic properties that has demonstrated effectiveness in improving negative mood symptoms, as well as physical symptoms, in women with PMS.[34] It is helpful for fluid excretion due to its antimineralocorticoid activity, and can specifically improve the PMS symptoms of breast tenderness and bloating/fluid retention. The studied dose is 100 mg daily from day 12 of the menstrual cycle until the onset of menses.

Non-pharmacologic treatment

Non-pharmacologic treatment options with evidence for treatment of PMS and PMDD include diet modification, exercise, cognitive behavioral therapy (CBT), specific vitamins and herbal supplements, and acupuncture.

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Consumption of a high carbohydrate diet in the late luteal phase has been shown to improve mood-related symptoms of PMS, presumably by increasing serotonin levels, providing a possible explanation for carbohydrate cravings in some women in the premenstrual period.[35] Interestingly, a study showed that providing women a specially formulated high carbohydrate beverage known to increase tryptophan levels resulted in decreased depression scores and reduced carbohydrate cravings, supporting the intake of complex carbohydrates in the luteal phase for management of PMS symptoms.[36]

Exercise has been historically recommended for women experiencing PMS symptoms, although data on the benefit of exercise on PMS symptoms has been mixed.[37] A 2009 review of the literature on exercise and PMS symptoms identified four studies, all of which demonstrated an improvement in PMS symptoms after women participated in exercise interventions.[37] However, all four studies were limited by small sample sizes and were of low methodological quality (ie. – none were randomized controlled trials).

The benefits of CBT on premenstrual symptomatology and health-related quality of life have been demonstrated by several studies.[38-40] A recent study of CBT for the treatment of PMDs found that participants who received CBT reported fewer premenstrual symptoms, improved emotional reactivity/mood, and less premenstrual distress compared to controls.[41] Additionally, a 2009 meta-analysis of nine studies evaluating the efficacy of psychological interventions for PMS found that CBT significantly reduced both anxiety and depression, and improved symptoms of daily living; however it was noted that the evidence for these findings was of low quality.[42]

Many vitamins and herbal supplements have been studied for the management of premenstrual symptoms, including calcium, vitamin B6, chasteberry (vitex agnus castus), gingko biloba, and St. John's wort, among others, with varying levels of evidence to support their use.[43] A 2011 systematic review evaluated the use of herbal remedies for the treatment of premenstrual symptoms, including 10 randomized controlled trials.[44] The evidence supported use of chasteberry, gingko biloba, and saffron for PMS symptoms; however, neither St. John's wort nor evening primrose oil was found to be beneficial over placebo.[44] An earlier systematic review published in 2009 evaluating the use of herbs, vitamins, and minerals in the treatment of PMS concluded that calcium was the only dietary supplement with good quality evidence to support its use in PMS.[45] Specifically, the use of calcium carbonate 1200 mg per day was found to be effective in the treatment of PMS symptoms in a prospective, randomized, double-blind, placebo-controlled multicenter study.[46] An additional systematic review of nine studies, including 940 patients, investigated the efficacy of vitamin B6 in the treatment of PMS.[47] The study

found low quality evidence that doses of vitamin B6 up to 100 mg per day may be beneficial in treating premenstrual symptoms and premenstrual depression.[47] Finally, a recent study evaluated the use of high-dose vitamin D (50,000 international units per week for 9 weeks) in adolescents for the treatment of PMS and dysmenorrhea.[48] The researchers found that vitamin D supplementation resulted in improvement in the physical and psychological symptoms of PMS and improved dysmenorrhea.

Lastly, acupuncture has been used effectively in some studies as a treatment modality to alleviate premenstrual symptoms; evidence for the practice, however, is limited.[49] A Cochrane review of five trials that included 277 women evaluating the effectiveness and safety of acupuncture or acupressure for women with PMS or PMDD found that acupuncture and acupressure may improve both the physical and psychological symptom of PMS when compared to a sham control.[50] However, the quality of the data was low due to small study sample sizes and bias due to lack of blinding. Additionally, there was not enough evidence to determine the safety of the procedures, and there were no studies that compared treatment with acupuncture to treatment with SSRIs.

Conclusions

The physical and psychological symptoms of premenstrual disorders can result in significant morbidity for affected adolescents and young women, impacting relationships, daily functioning, and quality of life. The development of diagnostic criteria and objective rating scales have been essential for timely identification and treatment of premenstrual disorders. While women with mild symptoms can be managed with lifestyle modification, over-the-counter medications, and supplements, women with severe PMS and PMDD benefit from pharmacotherapy with serotonergic antidepressants and hormonal treatments that suppress the hypothalamic-pituitary-ovarian axis.

Declaration of Competing Interest

The authors do not have any conflicts to declare.

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