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Premenstrual syndrome: management and pathophysiology

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Summary

Premenstrual syndrome (PMS) is triggered by hormonal events ensuing after ovulation. The symptoms can begin in the early, mid, or late luteal phase and are not associated with defined concentrations of any specific gonadal or non-gonadal hormone. Women with PMS experience affective or somatic symptoms that cause severe dysfunction in social or occupational realms. Although evidence for a hormonal abnormality has not been established, the symptoms of the premenopausal disorders are related to the production of progesterone by the ovary. The progesterone metabolites may bind to a neurosteroid-binding site on the membrane of the neurotransmitters. Thus, ovulation suppression is an area of focus for diagnostic and treatment options. Many treatment studies have focused on suppression of ovulation with gonadotropin-releasing hormone analogs (GnRHa), high doses of transdermal estrogen, and bilateral oophorectomy all have positive evidence as treatment options for prevention of PMS. However, because of these limitations and their substantial intensive care, these do not appear to be appropriate methods for conventional treatment of PMS. Serotonergic antidepressants, selective serotonin reuptake inhibitors, are well-established, highly effective, and first-line pharmacologic therapy.

Key words: Premenstrual syndrome; Selective serotonin reuptake inhibitor; Gonadotropin-releasing analogue; Premenstrual dysphoric disorders.

Introduction

Premenstrual syndrome (PMS) is defined as recurrent moderate psychological and physical symptoms that occur during the luteal phase of menses and resolve with menstruation [1-5]. Symptoms must be linked to the luteal phase, beginning sometimes after ovulation, and ending by the conclusion of the menstrual flow, with a symptom-free interval before the next subsequent ovulation [1-5]. Physical symptoms of this disorder include headaches, breast tenderness, abdominal bloating, peripheral edema, and general fatigue, while psychological or behavioral disorders include irritability, mood swings, food cravings, social withdrawal, anxiety, and depression. While definitive diagnosis of these disorders remains debatable, a prospective record of cycle related symptoms is the gold standard for diagnosis by establishing a relationship between the symptoms and the late luteal phase of the menstrual cycle. Retrospective, self-reporting of symptoms is found to be reasonably sensitive [6, 7]. Up to 80 percent of women report one or more physical, psychological or behavioral symptoms during the luteal phase of their menstrual cycle without experiencing substantial disruption to their daily functioning [1, 8]. PMS, in which mild to moderate symptoms affect some facet of the woman's life, occurs in 20 to 30 percent of premenopausal women; the more severe symptoms of premenstrual dysphoric disorder (PMDD) affect up to eight percent of premenopausal women [1, 8]. PMS and PMDD have been shown to negatively affect relationships, work attendance, productivity, and health care costs and utilization. [1, 9] This article aims to review the current understanding of the pathophysiological mechanisms underlying the premenstrual disorders. The role of serotonin is addressed in some detail because serotonergic antidepressants have well-established efficacy.

Etiology

The etiologies of PMS/PMDD are not definitive, but several candidate factors responsible for provoking symptoms of PMS are postulated (Table 1).

Progesterone

Women with PMS/PMDD appear to have more symptoms with normal cyclic levels of sex steroids [10]. In women whose normal cycles were blocked with administration of a gonadotropin-releasing hormone analog (GnRHa) and who were then given exogenous hormones, those with PMS experienced more symptoms of sadness, anxiety, irritability, bloating, and impaired function than those without PMS [10]. During anovulatory cycles, when a corpus luteum fails to form, the symptoms of PMS are not observed. Those who have undergone bilateral oophorectomy also do not experience PMS [2, 9].

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Table 1. — *Proposed pathophysiological mechanisms underlying premenstrual disorders.*

Factor	Considerations	Ref.
(Allo) pregnanolone	A metabolite of progesterone may contribute to the generation of the affective and physical symptoms of PMDDs through a different receptor other than classical progesterone receptor.	[2, 15, 16]
γ Amino butyric acid (GABA)	GABAergic acyivity likely contributes to the negative mood symptoms associated with PMS.	[2, 29]
Serotonin	Serotonergic function is decreased during the luteal phase of menstrual cycle in women with PMS.	[2, 5, 12, 13, 30-35]

There is a number of studies suggesting oral contraceptive pills, regardless of the elimination of ovulation, can be associated with PMS-like negative affective and physical symptoms such as irritability, depression, anxiety, bloating, fatigue, and breast tenderness in a subset of women [11]. Taken together, the factor responsible for provoking PMS symptoms has been attributed to the exogenous progestogen and endogenous progesterone.

The role of progesterone in triggering adverse symptomatology is not straightforward. Compelling evidence points to the role of progestogen in the pathophysiology of PMDD. For example, PMS symptoms are absent during pregnancy, in spite of high sex steroid concentrations. In multiple studies, measurement of serum progesterone in women with PMS compared with controls failed to show any significant differences [1, 2, 12-14]. The most plausible explanation is that the classical progesterone receptor is not involved in this process. This proposal may be supported by lack of reduction in physical or behavioral manifestation of PMS with administration of the progesterone receptor antagonist, mifepristone [15].

γ Amino butyric acid (GABA)

Neurotransmitters, particularly serotonin and GABA, appear to be involved in PMS manifestations. The main inhibitory neurotransmitter in the brain, GABA, is a widely distributed neurotransmitter in the central nervous system and evidently is an important regulator of stress, anxiety, vigilance, alertness, and seizures [16, 17]. GABA is derived from glutamate by glutamic acid decarboxylase exclusively found in GABAergic neurons. Three subtypes of GABA postsynaptic receptors have been identified: GABA-A, GABA-B, and GABA-C. However, it is the GABA-A receptor that is the site of action of endogenous agents such as neuroactive steroids derived from progesterone or synthesized *de novo* in the central nervous system, as well as exogenous agents such as progestogens after metabolism to reduced steroids), benzodiazepines, barbiturates, alcohol, and anticonvulsants [18, 19].

In the ovary and the brain, progesterone is metabolized to form the potent neuroactive steroids, 3-α-hydroxy-5-α-pregnane-20-one (allopregnanolone) and 3-α-hydroxy-5-β-pregnane-20-one (pregnanolone) [16] These metabolites act as positive allosteric modulators of GABA transmitter system in the brain [2, 16]. There is strong evidence that acute effects of the neurosteroids are not related to interactions with classical steroid hormone receptor that regulate gene transcription. However, chronic effects of neurosteroids are due to genomic (classical intracellular steroid receptors) and non-genomic rapid actions (ion channels and membrane receptors) in the brain. Furthermore, the genomic effects of neurosteoids are mainly due to their metabolic interconversion to traditional steroids. Overall, neurosteroids are not themselves active at intracellular steroid receptors. They modulate brain excitability primarily by interaction with neuronal membrane receptors and ion channels [16]. Finally, neurosteroids have been demonstrated to directly modulate the activity of ligand-gated ion channels, most notably GABA-A receptor [20].

Progesterone-derived neurosteroids may be important for the clinical manifestations of PMS [21, 22]. In normal women, allopregnanolone varies very similar to progesterone throughout the menstrual cycle with greater levels in the luteal phase than in the follicle phase [23]. Thus, allopregnanolone could play an important role in the pathophysiology of PMS. Serum concentrations of progesterone metabolite allopregnanolone during the luteal phase are lower in women with PMS [24, 25] and withdrawal from progesterone (allopregnanolone) increases anxiety in animal models [26]. Both at baseline and after stress, an enhanced ration of allopregnanolone/cortisol has been reported [25]. There is a marked insensitivity to benzodiazepine therapy in patients wit PMS [27], which might be due to the development of cross-tolerance between benzodiazepines and neurosteroids. Although neurosteroids represent promising approach for PMS, natural progesterone supplementation in women with PMS has no clear beneficial affect [28]. This could be due to several reasons, such as hormone side effects, disruption of ovarian rhythms or conversion of progesterone to other neurosteroids with negative properties [16].

The alterations in GABA-A subunit configuration and GABAergic activity likely contribute to the negative mood symptoms associated with PMS [29].

Serotonin

Amines (e.g. serotonin (5-hydroxytryptamine), histamine (1H-imidazole-4-ethanamine) and melatonin (*N*-acetyl-5-methoxytryptamine)) within the brain have been implicated in the modulation of mood, eating, arousal, and circadian rhythms. In particular, changes in serotonin level overlap symptoms associated with reduction in serotonin transmission. Biochemically derived from tryptophan, serotonin is primarily found in the gastrointestinal tract, platelets, and in the central nervous system of animals and humans. It is popularly thought to be a contributor to feelings of well-being and happiness. Serotonergic function has been shown to be altered during the luteal phase of menstrual cycle in women with PMS [2, 5, 12, 13, 30-35]. Serotonin depletion leads to anxiety and depressive-like symptoms. Serotonin turnover is also modulated in part by ovarian sex steroids. Ovarian sex steroids have also been implicated in serotonin uptake, turnover, binding, and transport [36, 37].

Serotonergic activity in the brain is affected by estrogen and progesterone; specifically sex steroids can modify serotonin availability at the neuronal synapses. For example, estrogen has been shown to increase degradation of monoamine oxidase (MAO), enzyme responsible for oxidation of monoamines [38]. Estrogen's role in increasing degradation of MAO and COMT results in augmenting action of serotonin in regulating the availability of free tryptophan in the CNS and improving clinical effect of selective serotonin re-uptake inhibitors (SSRIs). In contrast, progesterone and its metabolites increases MAO activity, therefore decreases 5-HT availability, which may result in depressed mood (Figure 1) [39-42].

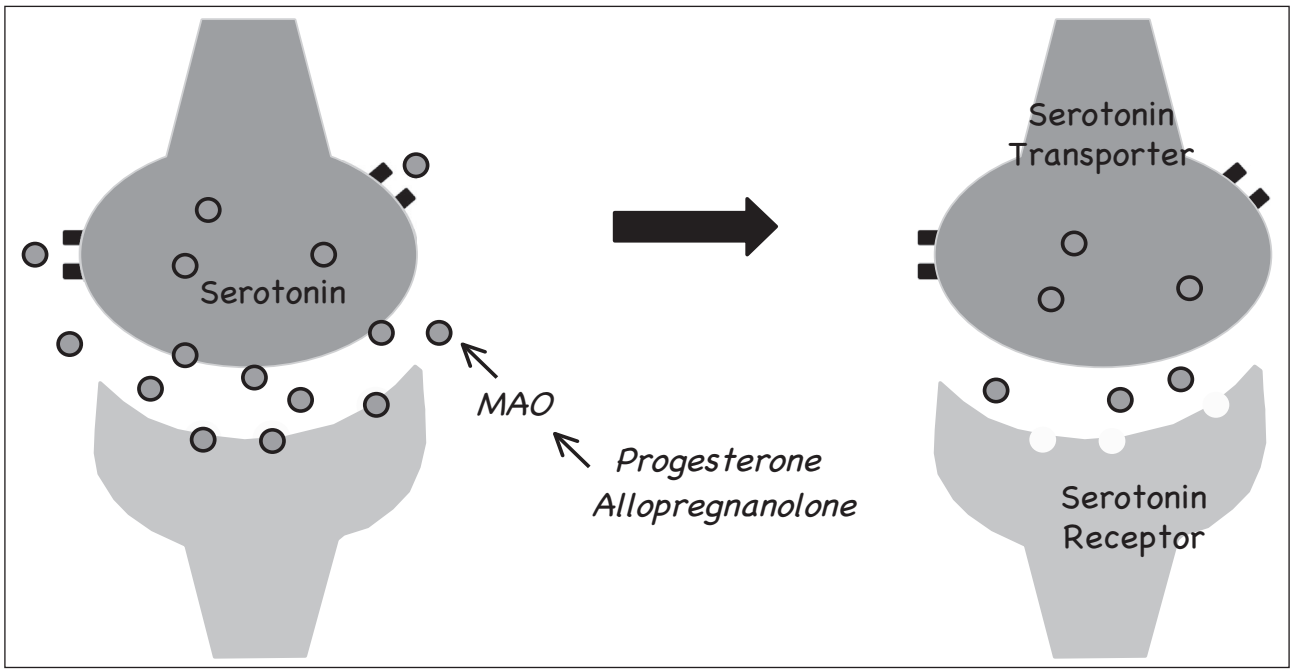

Figure 1. — Decreased serotonin turnover by progesterone. Progesterone metabolite allopregnanolone increases monoamine (MAO) oxidase activity, therefore decreases serotonin availability, leading to a depressive mood.

Treatment

As noted above, PMS does no occur during anovulatory cycles or in women who have undergone bilateral oophorectomy. Thus, ovulation suppression is an area of focus for diagnostic and treatment options. Many treatment studies have focused on suppression of ovulation with oral contraceptives, GnRHa, high doses of transdermal estrogen and bilateral oophorectomy all have positive evidence as treatment options for prevention of PMS and PMDD. Table 2 lists current evidence-based treatment for PMS.

1. Nonpharmocologic
Lifestyle modifications

Although some physicians recommend increasing exercise of decreasing intake of caffeine, salt, and refined sugar for PMS symptom relief, no current evidence substantiates these recommendations. Improved diet and exercise should be recommended for good health, but not as evidence-based treatment for PMS/PMDD [1].

Bilateral oophorectomy and/or hysterectomy

In order to eliminate ovarian function, women may desire to proceed with bilateral oophorectomy. This approach has been shown to be effective in women with severe PMS [43-45]. If bilateral salpingo-oophorectomy is being considered as treatment modality for severe and debilitating symptoms of PMS, it may be beneficial to consider a trial of GnRHa first to establish the relative contributions of endocrine-related pathology as the etiology of symptoms versus underlying other dysfunction. After bilateral oophorectomy, it is important to replace estrogen until the age of natural menopause in order to prevent the complications of premature menopause. It may be important to perform a hysterectomy at the timing of bilateral oophorectomy in order to allow women to receive unopposed estrogen replacement and to avoid recurrent progestogen-induced premenstrual symptoms with the combined hormonal replacement.

Table 2. — *Proposed managements for the premenstrual disorders.*

Management	Considerations	Ref.
Oral contraceptives	Though the use of oral contraception has been fairly unhelpful in PMS management given cyclically or continuously as the progestogen element again gives rise to symptoms.	[1, 13]
GnRHa	These drugs are expensive and have all of consequences of hypo-estrogenic side effects.	[47, 52]
Estrogen	Unopposed estrogen may lead to endometrial hyperplasia and cancer but oral progesterone may worsen symptoms of PMS.	[2, 50]
Serotonergic antidepressants	Well-established and highly effective. First-line pharmacologic therapy.	[1, 31, 51, 53]
Bilateral oophorectomy and/or hysterectomy	Highly effective, but it is too invasive for most patients.	[43-45]

2. Pharmacologic
Oral contraceptives

While ovulation is clearly suppressed by the use of combined oral contraceptives, the progestogen content of the pill produces a new progesterone cycle for three weeks out of four and in sensitive women it may give rise to virtually continuous symptoms or certainly ones with a prolonged cyclical component. The usual approach is to swap and change pills, but this is rarely successful [1, 13].

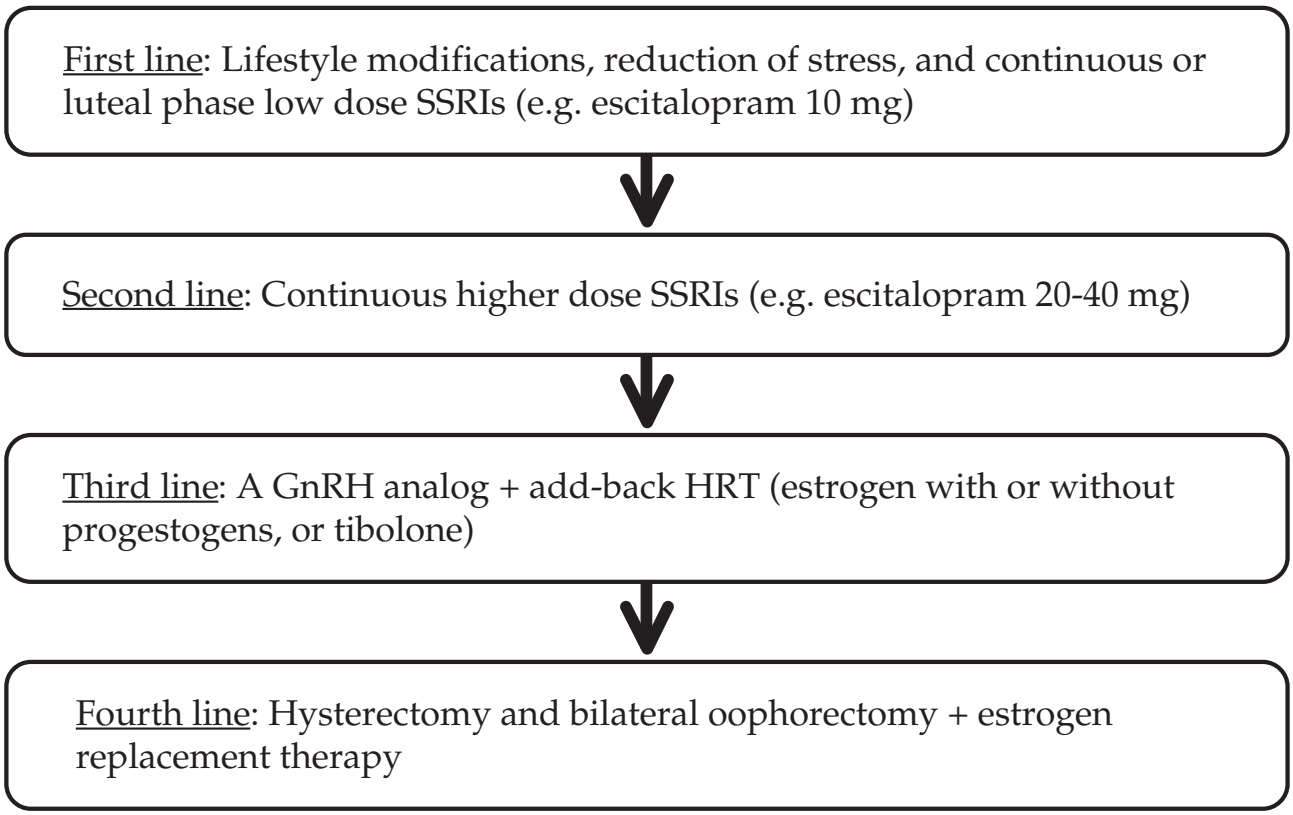

Figure 2. — Proposed algorithm for premenstrual syndrome (modified form the proposal by Panay) [14].

GnRHa

Because they suppress ovarian function, the GnRHa has been tried off-label to reduce severe physical symptoms of PMS and PMDD [46-48]. However, adverse effects, especially hot flashes and decreased bone density, limit their use to only a few months. Estrogen can be added back, but this may cause PMS and PMDD symptoms to recur [46, 49]. Because of these limitations and their substantial cost, GnRHa does not appear to be appropriate agents for the conventional treatment of PMS and PMDD.

Estradiol

The therapeutic effect of ovulation suppression by increasing plasma estradiol levels has been demonstrated in improving symptoms of PMS. Unopposed estrogen may lead to endometrial hyperplasia and cancer but oral progesterone may worsen symptoms of PMS [50].

SSRIs

Medications affecting serotonin are first-line pharmacologic treatments for severe PMS or PMDD [12, 13, 31, 32]. SSRI, taken daily or only during the luteal phase of menstruation, significantly decrease physical and psychological symptoms of PMS compared with placebo [33]. In a study of PMDD treatment with the SSRI, symptom score were reduced by at least one-half in 60 percent of participants treated with an SSRI compared with 35 percent of participants in the placebo group: 80 percent of the PMS symptom reduction with an SSRI occurred within the first month of treatment [34, 35]. SSRIs may need to be administered for three to four weeks to affect symptoms of depression: PMS symptoms, however, appear to improve more rapidly [51]. Daily use of an SSRI with an increased dose during the luteal phase, especially if PMS symptoms are comorbid with major depression or generalized anxiety, is a reasonable alternative [51].

Discussion

Premenstrual syndrome is defined as recurrent moderate psychological and physical symptoms that occur during the luteal phase of menses and resolve with menstruation. It affects 20 to 32 percent of premenopausal women. Women with premenstrual dysphoric disorder experience affective or somatic symptoms that cause severe dysfunction in social or occupational realms. The Daily Record of Severity of Problems is one tool with which women may self-report the presence and severity of premenstrual symptoms. Symptom relief is the goal for treatment of premenstrual syndrome and premenstrual dysphoric disorder. There are a number of principles that should be adhered to, when managing women with PMS. Even without an evidence basis, there is little doubt that reduction of stress, for instance is a great help in ameliorating symptoms. Also awareness of the condition and training in it management is essential.

The two chief evidence-based medical treatments of moderate to severe PMS are categorized by ovulation suppression by GnRHa and SSRIs. When treating women with

severe PMS, hysterectomy and bilateral oophorectomy has been shown to curative, but they are too invasive for most patients. A suggested treatment algorithm modified from the proposal by Panay [14] is shown in Figure 2.

Discontinuation of treatment should be considered when pregnancy is contemplated, and obviously this essential if the method is contraceptive. Treatment should be continued during the perimenopause as this is a time associated with potentially worsening of symptoms, but can be tentatively withdrawn when the patient is thought to be postmenopausal. There may be a need to resume treatment if ovarian activity persists.

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