

Review article

The management of Premenstrual syndrome: A review

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Abstract

Premenstrual Syndrome is a set of physical, emotional and behavioural symptoms that start during the week preceding menstruation and are alleviated when the menstrual flow begins. Epidemiological surveys have estimated that the frequency of PMS symptoms is about 80-90% with impairment of functioning.

Women with severe PMS should be managed by a multi disciplinary team, which might comprise a hospital or community gynaecologist, psychiatrist or psychologist, dietician and counselor. Where there is multidisciplinary provision of care, this is of benefit both from the diagnostic and therapeutic point of view, giving the ability to offer a broad range of interventions from lifestyle interventions and cognitive behavioural therapy (CBT) to gynaecological interventions.

Keywords: Premenstrual Syndrome; Cognitive behavioural therapy; Psychotherapy; Herbal therapy.

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Introduction

Cyclic premenstrual pain and discomfort (CPDD) which causes symptoms that recur in the premenstrual or luteal phase of the premenstrual cycle is called premenstrual syndrome (PMS)¹. It has emerged as a twentieth century phenomenon²; many women are punctuated with distressing premenstrual symptoms that can disrupt their quality of life and relationships. It has been calculated that affected women experience almost 3000 days of severe symptoms during the reproductive years. The symptoms can be psychological symptoms (irritability, mood swings, depressed mood, crying spells, low self-esteem, anxiety, sleep disturbance, increased appetite, lethargy or fatigue), cognitive symptoms (forgetfulness, decreased concentration) and physical symptoms (breast tenderness, bloating, fluid retention, weight gain, constipation, hot flushes, headaches, musculoskeletal discomfort, acne, rhinitis, palpitation³).

In the late luteal phase when estrogen levels have declined women with PMS exhibit specific serotonin (5-HT) abnormalities. These include a deficiency in whole blood 5-HT, blunted 5-HT production in

response to L-tryptophan challenge, and aggravated premenstrual symptoms during tryptophan depletion⁴ and γ -aminobutyric acid (GABA) also appear to contribute to the pathogenesis of PMS.⁵

Severity of symptoms varies, about 80% of women report mild symptoms; 20%-50% report moderate symptoms and about 5% report severe symptoms for several days with impairment of functioning⁶. PMS is prevalent in women of all ages causing substantial morbidity with obvious detriment to interpersonal relationships, social interactions, lifestyle, work performance, emotional well-being and overall health-related quality of life⁷.

Despite the magnitude of this problem, a lot of confusion exists in medical communities like about what is effective and not effective for treatment of PMS. A range of treatments currently available reflect this theoretical diversity.

Management

1) Nonpharmacologic Treatments^{8,9,10,11,}

2) Life style changes

- Dietary modification
- Exercise
- Sleep hygiene

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- Stress reduction
- 3) **Psychotherapy and group support**
 - Supportive therapy and patient education
 - Cognitive behavioral therapy (CBT)

4) **Nutritional supplements**

- Vitamin B6
- Vitamin E
- Calcium
- Magnesium
- Tryptophan

5) **Herbal products**

- Chaste berry (*Vitex Agnus-castus*)
- St. John's wort (*Hypericum perforatum*)
- Black Cohosh (*Cimicifuga racemosa*)
- Evening primrose oil

II. **Pharmacological Treatment**^{10, 12, 13,}

- 1) Selective serotonin reuptake inhibitors (SSRIs)
- 2) Other Serotonergic antidepressants
- 3) Anxiolytics
- 4) Hormonal therapy
- 5) Miscellaneous pharmacologic interventions

III. **Surgical Treatment**¹⁴

- 1) Hysterectomy

I. **Nonpharmacologic Treatments**

1) **Lifestyle changes:** The ACOG and AAFP recommend lifestyle change as the first line of treatment option for PMS¹⁵. It may be valuable in patients with mild to moderate symptoms and benefit their overall health¹³.

- **Diet:** Dietary changes often reduce premenstrual symptoms. Decreasing caffeine, sugar, alcohol intake can abate anxiety and irritability; and reducing sodium decreases edema and bloating. Increased consumption of fruits, vegetables, legumes, whole grain and water is also beneficial¹³.
- **Exercise:** Aerobic exercise for 20-30 minutes, 3-4 times per week also reduces the symptoms. Reduction of body weight to within 20% of ideal is an appropriate goal^{9, 12, 15}.
- **Sleep hygiene:** PMS is associated with sleep irregularities; to alleviate the associated distress and discomfort, adoption of a regular sleep-wake pattern may be helpful¹⁵.
- **Stress reduction:** Encouraging women to avoid planning stressful activities for the premenstrual period whenever possible can be helpful. Light therapy with 10,000 Lx, cool-white fluorescent light is also beneficial in reducing stress and can be beneficial for PMS¹⁵.

2) **Psychotherapy and group support**

- **Supportive therapy and patient education:** Group support can be effective in managing PMS. Assertiveness training and anger management can reduce symptoms and interpersonal conflicts. Educating patients and their families about the disorder can promote understanding of it¹².

- **Cognitive behavioral therapy (CBT):** This kind of therapy can enhance self-esteem and interpersonal effectiveness, as well as reduce other symptoms^{12, 15}.

3) **Nutritional Supplements**

- **Vitamin B6:** It may improve premenstrual symptoms by its effects on serotonin. It is found that vitamin B6 in dosages of up to 100 mg per day is likely to benefit patients with premenstrual symptoms and premenstrual depression^{12, 16}.

- **Vitamin E:** Vitamin E, an antioxidant seems to reduce the affective and physical symptoms of PMS. Vitamin E 440 IU / day is a treatment option in women with PMS^{17, 18}

- **Calcium:** Calcium carbonate in a dosage of 1,200 to 1,600 mg per day is a treatment option in women with PMS. The intake of skimmed or low-fat milk is also associated with a lower risk of PMS^{19, 20}.

- **Magnesium:** It is found that magnesium 200-400 mg may decrease premenstrual pain. A possible biological rationale for the effectiveness of magnesium is the inhibition of PGF2 α and the promotion of muscle relaxation and vasodilatation^{18, 21}.

- **Tryptophan:** a substrate for serotonin may also benefit some patients²².

4) **Herbal therapies:** Herbal products have been effective in treating PMS.

- **Isoflavones (e.g. soy/red clover):** The treatment with soy isoflavones, dongquai and black cohosh extracts has shown a significant improvement in menstrual migraine²³.

- **Agnus castus:** Fruits of chaste tree (*Vitex agnus castus*) contains a mixture of iridoids and flavonoids. The mechanism of action may be related to modulation of stress-induced prolactin secretion via dopamine, without directly affecting luteinising or follicle-stimulating hormones²⁴.

- **St John's Wort:** St John's Wort (*Hypericum perforatum*) is a herbal remedy shown to alleviate mild to moderate depression. It relieves the symptoms of PMS. It has positive effects on mood and that it may moderate brain neurotransmitters^{12, 13, 18}.

- **Evening primrose oil:** Evening primrose oil, a rich source of gamma linoleic acid, is often used as a treatment for severe PMS^{12,13,18}

I. Pharmacologic Treatment

Women with severe symptoms or symptoms resistant to non-medical approaches should be considered for drug therapy. The two chief evidence-based medical treatments of moderate to severe PMS are categorised by ovulation suppression and selective serotonin reuptake inhibitors (SSRIs)²².

1) Selective Serotonin Reuptake Inhibitors (SSRIs)

The serotonergic antidepressants are the first-line treatment of choice for severe PMS/PMDD²⁵. It is effective in continuous and intermittent dosing. Intermittent administration has many advantages. It is less expensive, reduces the overall rate of side effects, limits exposure to medications, may reduce tolerance and is more acceptable to many women. The drug is started between 7 and 14 days before the next menstrual period, with the start day individualized to begin at or just before the expected onset of symptoms²².

- **Fluoxetine:** Fluoxetine is approved by U.S FDA. Its use has shown significant reduction of all symptoms. Fluoxetine 20 mg per day for continuous or luteal phase administration is recommended. Long term side effect of continuous use is decreased libido or delayed orgasm²².
- **Sertraline:** It benefits all symptoms of PMS. It is given in the dosage of 50 to 150 mg per day for full cycle. It has transient GI and sexual side effects. It is approved by FDA for this use^{10,22}.
- **Paroxetine:** It benefits all symptoms of PMS. It is given in the dosage of 10 to 30 mg per day for full cycle or luteal phase. It has transient GI and sexual side effects. It is recently approved by FDA for this use^{10,22}.
- **Citalopram:** It benefits physical, cognitive and emotional symptoms. It is given in dosage of 10 to 30 mg per day for full cycle or luteal phase only. Luteal-phase use is superior to continuous treatment. It is not approved by FDA for this use^{12,22}.

2) Other Serotonergic Antidepressants

- **Clomipramine:** It is a tricyclic antidepressant (TCA) that is potent but relatively nonselective inhibitor of serotonin reuptake. It benefits all symptoms of PMS. It is given in the dosage of 25 to 75 mg per day for full cycle or luteal phase. It has anticholinergic and sexual side effects. It is

not approved by FDA for this use^{12,22}.

- **Venlafaxine:** It increases the central activity of both serotonin and noradrenalin. It is given in a dosage of 37.5 to 150mg per day. It is effective in mood, function, pain and physical symptoms. Side effects are nausea, insomnia and dizziness¹⁰.
 - **Buspirone:** It is a partial 5- hydroxytryptamine receptor 1A (5-HT1A) agonist. It can be administered in the symptomatic luteal phase; its effect appears to be modest^{9,14}.
- #### 3) Anxiolytics
- **Alprazolam:** It is a high-potency benzodiazepine with mood-enhancing and anxiolytic effects and has been shown to be somewhat effective in patients with PMS. Because of the potential for drug dependence, alprazolam should be considered a second-line drug and used only if SSRIs fail to achieve an optimal response. Therapy should be limited to the luteal phase and should be given in low dosages-0.375 to 1.5 mg per day^{8,22}.
- #### 4) Hormonal therapy:
- Although the underlying cause of severe PMS remains unknown, cyclical ovarian activity appears to be an important factor. A logical treatment for severe PMS, therefore, is to suppress ovulation and thus suppress the cyclical endocrine/biochemical changes that cause the distressing symptoms. A number of drugs are capable of performing this function, but they are not without their own side effects, which may influence the efficacy of the treatment or the duration for which they may be given^{9,22}.
- **Combined oral contraceptive pill:** The new combined oral contraceptive pill, Yasmin containing an anti-mineralocorticoid and anti-androgenic progestogen, drospirenone, showed considerable promise in the treatment of severe PMS as it minimized progestogenic side effects with a mild diuretic and anti-androgenic effect^{2,22}.
 - **Transdermal estradiol:** Implanted 17 β -estradiol combined with cyclical progestogen is effective for the management of physical and psychological symptoms of severe PMS. Administered as a 100 mg implant, proved to be highly effective^{2,13,22}.
 - **Danazol:** Cycle suppression may be achieved using danazol, an androgenic steroid. Studies have demonstrated benefit for several symptoms, but due to masculinising side effects, especially at higher, cycle-suppressing doses, it is not commonly used^{2,22}.
 - **Gonadotrophin-releasing hormone (GnRH) analogues:** GnRH hormone analogues have been

very successfully employed for many years to suppress ovarian steroid production. Early resort to GnRH therapy for PMS is not recommended due to the side effects and cost. Prolonged use should be retained for women with the most severe symptoms^{22, 26}.

- **Progesterone/progestogens:** A recent meta-analysis of all published studies for progestogen and progesterone treatment of PMS demonstrated no benefit for treatment. All the trials of progesterone (by both routes of administration) showed no clinically significant difference between progesterone and placebo. Natural progesterone could have some benefits as it can have an anxiolytic effect and act as a mild diuretic^{2, 22}.

5) Miscellaneous Pharmacologic Interventions

- **Spironolactone:** In a dosage of 100 mg is effective in reducing irritability, depression, somatic symptoms, feelings of swelling, breast tenderness and craving for sweets^{2, 9, 22}.
- **Bromocriptine:** In a dosage of up to 2.5 mg three times per day may be beneficial in patients with cyclic mastalgia^{2, 13, 22}.
- **Ibuprofen:** In a dosage of up to 1,000 mg per day, can reduce breast pain, headaches, back pain, and other pain symptoms, but seems to have limited effect on mood symptoms²².

III. Surgical Therapy

- 1) **Hysterectomy:** Total abdominal hysterectomy and bilateral salpingo-oophorectomy is the ultimate form of ovulation suppression and the only true cure for PMS as this removes the ovarian cycle completely. When treating women with PMS, surgery should not be contemplated without preoperative use of GnRH analogues as a test of cure and to ensure that HRT is tolerated. Such therapy should be reserved for extremely severe PMS sufferers in whom other treatments have failed. Women who have had a hysterectomy with ovarian conservation will often continue to have cyclical symptoms in the absence of menstruation²².

Management protocol of PMS³

The following steps for treating PMS are based on recommendations outlined in an ACOG Practice Bulletin:

Step 1:

- A) In case of mild and /or moderate symptoms supportive therapy with good nutrition, complex carbohydrates, aerobic exercise, calcium supplements and possibly magnesium or chaste berry fruit is recommended.
- B) If physical symptoms predominate; spironolactone or NSAIDs, or hormonal suppression with OCPs or medroxyprogesterone acetate is to be given.

Step 2: When mood symptoms predominate and are significantly impairing function; initiate SSRI therapy. An anxiolytic can be used for specific symptoms not relieved by the SSRI medication.

Step 3: If not responsive to steps 1 or 2: Try GnRH agonists; this would not be done in an adolescent without consultation with a gynecologist.

Conclusion

Serotonergic antidepressants, selective serotonin reuptake inhibitors, are well-established, highly effective, and first-line pharmacologic therapy. However due to potential side effects of some of the treatments, lifestyle change should be considered as the first line of treatment option for PMS. These changes may be valuable in patients with mild to moderate symptoms and benefit their overall health. Group support can be effective in managing PMS. Assertiveness training and anger management can reduce symptoms and interpersonal conflicts. Educating patients and their families about the disorder can promote understanding of it. Cognitive behavioral therapy (CBT), Nutritional Supplements and Herbal therapies also play an important role in the management of PMS. The two most-studied and relevant neurotransmitter systems implicated in the genesis of the symptoms are the GABAergic and the serotonergic systems. Research on modulation of these neurotransmitters across the menstrual cycle may prove fruitful. Pharmacologic and surgical therapy should be reserved for severe cases of PMS.

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