Review
Premenstrual syndrome, a common but underrated entity: Review of the clinical literature

Dilbaz and Aksan. Premenstrual syndrome, A common entity

Berna Dilbaz¹, Alperen Aksan²

¹Department of Obstetrics and Gynecology, University of Health Sciences Turkey, Ankara Etlik Zübeyde Hanım Women’s Health and Research Center, Ankara, Turkey
²Department of Obstetrics and Gynecology, University of Health Sciences Turkey, Ankara Etlik Zübeyde Hanım Women’s Health and Research Center, Ankara, Turkey

Address for Correspondence: Berna Dilbaz
e.mail: sdilbaz@hotmail.com ORCID: orcid.org/0000-0003-1137-8650


Received: 28 July, 2020 Accepted: 06 January, 2021

Abstract
Premenstrual syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD) are characterized by somatic and psychologic symptoms that arise at the luteal phase of the menstrual cycle and subside with menstruation. For definitive diagnosis prospectively self-reported symptoms should demonstrate a cyclic pattern and other psychological pathologies and thyroid dysfunction that may present themselves with similar symptoms should be excluded. Both entities effect millions of women at reproductive age as the prevalence of PMS is given as 10-98% while PMDD effects 2-8%. Sex steroids and neurotransmitters have a huge role in the etiology. The role of vitamins, minerals in etiology and treatment of PMS and PMDD is open to discussion. Drugs that suppress ovarian sex steroid production such as combined oral contraceptives or selective serotonin re-uptake inhibitors (SSRIs) enhancing central serotonin delivery are used for treatment. Life style changes, regular exercise also have a positive effect in mild cases. Tricyclic antidepressants and GnRH analogues can be used in selected cases.

Keywords: Premenstrual syndrome, premenstrual dysphoric disorder, etiology, treatment

Introduction
Premenstrual Syndrome (PMS) is an entity characterized with the presence of psychiatric symptoms such as mood swings, depression, loss of confidence, anxiety and irritability without any underlying psychiatric disorder accompanied by physical symptoms. The typical complaints are bloatedness and mastalgia encountered at the luteal phase of the menstrual cycle (LPMC), that deteriorates the well-being of the women and then subsides or disappears with menstruation (1). Premenstrual Syndrome affect a huge amount of women at reproductive age. It is typically characterized with the cyclic recurrance of the symptoms shown in Table-1(82) during the LPMC. (2-4). The symptoms occur mostly in women of 25-35 years old although it may be observed at any age between adolescence to menopause.
Premenstrual dysphoric disorder (PMDD) is a more grave entity of premenstrual syndrome (PMS) that is described as the cyclic recurrence of psychological (irritability, nervousness, agitation, anger, insomnia, difficulty in concentrating, severe fatigue, depression, anxiety, confusion), neurologic and vascular (headache, dizziness, numbness, heightened sensitivity of arms and/or legs, palpitation), gastrointestinal, ocular symptoms that disrupt the daily life and functioning of the women. The mood disorder symptoms that are experienced both in PMS and PMDD disappear within the first days of the menstruation. Diagnostic and Statistical Manual of Mental Disorders (DSM-5) established seven criteria (A through G) for the diagnosis of PMDD. For the diagnosis of PMDD of at least five of these symptoms should be present, while one of the symptoms should be from numbers 1-4. (5) Both PMS and PMDD show a cyclic pattern with affective, behavioral and somatic symptoms beginning at the LPMC and disappearing within a few days after the onset of menstruation. These cyclic symptoms can also be observed in amenorrheic reproductive aged women who had a hysterectomy but have functioning ovaries.

**Epidemiology and prevalence**

During the LPMC at least one physical or psychiatric symptom is observed in 80% of the women however most of them do not report any change in their daily life and activities. (6). In a study on 2800 French women 12% demonstrated the diagnostic symptoms of PMS while only 4% had more severe symptoms. (7). Although most women experience one or a few of these symptoms during the LPMC, only 3-8% demonstrate clinically significant PMS symptoms (8).

Three prospective population-based studies that utilized the strict criteria for diagnosis of Premenstrual Disphoric Disorder (PMDD) reported a prevalence of approximately 2% among the study population (8-9).

In a study conducted at Switzerland in 2007, a total of 3,913 women aged 15 to 54 responded to the questionnaire inquiring PMS symptoms and 3,522 (90%) reported that PMS intervened their daily life. While 90% had at least one symptom, 10.3% had PMS, and 3.1% met PMDD criteria. (10)

Also in a meta-analysis covering 18,803 women, the overall prevalence of PMS was 47.8% (95% CI: 32.6-62.9). The lowest and highest prevalence were reported as 12% (95% CI: 11-13) in France and 98% (95% CI: 97-100) in Iran, respectively. The authors emphasized that the prevalence of PMS was studied more in Asia than other continents. (11)

A global study involving 7226 women from South America, Europe and Asia, the frequency of PMS symptoms was found to be parallel between the countries and the regions, but in some countries, such as Pakistan, women were found to be less familiar with the term PMS compared to the European women (12).

**Risk factors for PMS and PMDD**

The part of genetic factors in the predisposition to PMS and PMDD has been an active and interesting area for many researchers yet definitive results were not obtained. Some studies suggest a possible association with the estrogen receptor alpha (ESR1) gene (13-15). In one report, cells from women with and without PMDD appeared to show different response patterns to the components of the ESC / E (Z) complex containing the ESR1 gene. (16). Other risk factors for PMDD development include lack of education and smoking (17), history of traumatic events or anxiety disorder, and higher daily difficulty scores (18).

**Etiology and patogenesis**

Although various hypotheses have been put forward, the etiology of PMS and PMDD is not still fully known. (19) The most known hypothesis is the presumed part of circulating gonadal
steroids in development of PMS symptoms as the suppression of ovulation has a beneficial effect on PMS (20-22). However, cyclic changes in ovarian steroids do not appear to be the only cause of PMS symptoms, as daily serum progesterone and estrogen concentrations are shown to be parallel in women with and without PMS. An early study by Andersch demonstrated that apart from the prolactin level that was lesser in the follicular phase of the PMS group all the sex steroids were similar in the groups of control and the PMS, in the LPMC (23). In two studies no correlation was found between the serum progesterone levels and the affective and/or somatic symptoms (24,25). Deficiencies in progesterone, progesterone metabolites (some of them which have anxiolytic specialties) and progesterone receptor have also been blamed to be a possible cause of PMS / PMDD. However, as mentioned, serum progesterone concentrations are normal in women who have PMS. In addition, serum concentrations of progesterone metabolites allopregnanolone and pregnenolone are similar in women with PMS and without PMS (25). It has been shown in previous studies that blocking the effect of progesterone in the LPMC with a progesterone receptor antagonist (mifepristone) does not alleviate PMS symptoms. (26). Women with PMS may have an abnormal response to normal ovarian hormonal changes, even though serum progesterone and estrogen concentrations are within normal limits (21).

Current evidence suggests that PMS is a disorder triggered by changes in gonadal steroids during the LPMC in susceptible women. This is thought to be due to the interaction between cyclic changes in ovarian steroids and the functioning of central neurotransmitters. One of the most frequently mentioned neurotransmitters in PMS pathogenesis is serotonin, but beta-endorphine, gamma-aminobutyric acid (GABA) and autonomic nervous system are also part of the pathogenesis of PMS. Based on in vitro data and animal studies, there is evidence that cyclic variation in circulating estrogen and progesterone result in marked changes in the opioids (27), GABA (28) and serotonin (29) systems.

The potential role of the GABAergic system in PMS has not been extensively investigated previously. The main effect of GABA is to reduce cellular excitability through chloride system. The hypothesis that asserts the modulatory role of progesterone in GABAergic system is supported by the improvement observed in PMS symptoms when agents such as benzodiazepine and alprazolam that increase GABAergic activity are used (30). Additionally, GABA-A enhances receptor function and has anxiolytic effects. Low levels of the progesterone metabolite allopregnanolone are shown to produce a similar anxiolytic effect [31]

Current studies highlight the pivotal role of serotonin in the etiology of PMS. In a number of studies, patients with PMS have been shown to have lower intake of whole blood serotonin and platelet serotonin, and imipramine binding and serotonin metabolite in the LPMC.[32-36]. In cerebrospinal fluid, 5-hydroxyindoleacetic acid has been shown to have higher levels compared to the dopamine metabolite homovanillic acid. [37]. In a study by Menkes and Brezenski, improvement in PMS symptoms is achieved with serotonin agonist fenfluramine use [38] and aggravated with acute reduction of the serotonin precursor tryptophan [39]. In addition, serotonin reuptake inhibitors that increase the serotonin level in brain- such as fluoxetine—are one of the most effective drugs for treatment of PMS.

The role of minerals and vitamins is still controversial issues in the etiology of PMS. In previous studies, vitamin E, vitamin A or vitamin B6 levels were not different in women who have PMS (40, 41). Several vitamins and dietary supplements have been studied as therapeutic agents for PMS, including vitamin E, B, vitex agnus castus, calcium, zinc, and magnesium.; however, there the evidence showing any of these are more effective than placebo is scarce. The Cochrane review that described a protocol for vitex agnus castus use for PMS was withdrawn (Cochrane Database of Systematic Reviews 2018, Issue 3. Art. No.: CD004632.). Also, although several studies related to iron, magnesium, zinc, zinc to
potassium ratio calcium are present in the literature, their role in the treatment and etiology of PMS/PMDD is still debatable (41, 42).

**Diagnostic criteria for PMS and PMDD**
Many groups have published diagnostic criteria for premenstrual diseases, including the World Health Organization (WHO), American College of Obstetricians and Gynecologists (ACOG), Royal College of Obstetricians and Gynecologists (RCOG), International Society for Premenstrual Disorders (ISPMD) and the American Psychiatric Association (APA; DSM-5). (1) ACOG describes symptoms consistent with PMS; as: 1- The symptoms should be restricted to the lPMC; 2- The symptom pattern should be confirmed by prospective evaluation.; 3- symptoms should cause functional impairment; and 4- other diagnoses that could better explain the symptoms should be excluded. (43). ACOG definition involves presence of at least one of the 6 affective (angry outbursts, depression, anxiety, confusion, irritability and social withdrawal) and one of the 4 somatic symptoms (abdominal bloating, headache, breast tenderness, and swelling of extremities) reported five days prior to the onset of menses in the three prior menstrual cycles and ceased within 4 days of onset of menses (43). ACOG added more symptoms in the patient resources; emotional symptoms being depression, irritability, angry outbursts, crying spells, social withdrawal, anxiety, confusion, poor concentration insomnia, increased nap taking, changes in sexual desire while physical symptoms were presented as thirst and appetite changes (food cravings), weight gain, breast tenderness, bloating and headache, swelling of the hands or feet, aches and pains, abdominal pain, fatigue, skin problems, gastrointestinal symptoms (https://www.acog.org/patient-resources/faqs).
RCOG recommends keeping a self-reported a symptom diary by the women for recording the symptoms for diagnosis of PMS and that the symptoms should be observed prospectively over two cycles. (44). ISPMD published a consensus article on the management of PMD and cited the classification published by O’Brien in 2011 (45). According to this classification (46) two entities: 1- Core Premenstrual Disorder 2-Variant Premenstrual Disorders are described. The symptom characteristics of “Core Premenstrual Disorder” (CPD) that can be somatic and/or psychological were stated as occurring in ovulatory cycles, being absent after menstruation, and before ovulation, recurring in the luteal phase and be prospectively rated for at least two cycles) and causing significant impairment (work, school, social activities, hobbies, interpersonal relationships, distress). PMDD was defined as a sub-group of CPD. The variants of PMD were a) Menstrual exacerbation of symptoms of an underlying somatic, psychological or medical disorder that significantly worsens premenstrually b) PMD due to non-ovulatory ovarian activity c) Progestogen-induced PMD related to exogenous progestogen administration d) PMD with absence of menstruation due to ongoing ovarian activity.
PMS is currently being diagnosed when any one of the four symptoms that may be physical, behavioral, or emotional / psychological (at least 1 is an emotional symptom) or physical or behavioral 5 or more symptoms are present. However, if a woman has five or more symptoms and one of them is an "emotional symptom" (Table-1[82]), it would be better to diagnose PMDD instead of PMS. (Table-1[82])
PMDD, classified by APA, should include five of the 11 symptoms required to meet the diagnostic criteria, the mood of The Diagnostic and Statistical Manual of Mental Disorders (DSM-V). And at least one of these should involve mood swings.(5).
Currently APA DSM-5 system, that provides PMDD criteria is used for diagnosis (5). These criteria require [5]:

**Table-1:**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The symptoms should be restricted to the lPMC.</td>
</tr>
<tr>
<td>2</td>
<td>The symptom pattern should be confirmed by prospective evaluation.</td>
</tr>
<tr>
<td>3</td>
<td>Symptoms should cause functional impairment.</td>
</tr>
<tr>
<td>4</td>
<td>Other diagnoses that could better explain the symptoms should be excluded.</td>
</tr>
</tbody>
</table>

**ISPMD Classification:**

1. **Core Premenstrual Disorder (CPD):**
   - Symptoms occur in ovulatory cycles.
   - Absent after menstruation.
   - Recurring in the luteal phase.
   - Prospectively rated for at least two cycles.
   - Cause significant impairment.

2. **Variant Premenstrual Disorders:**
   - Additional symptoms or variations.
   - May include somatic, psychological, or medical conditions.

PMDD is defined as a sub-group of CPD with specific criteria for menstrual exacerbation and absence of menstruation.
a) Prospective documentation of behavioral and physical symptoms (using diaries) for most of
the previous year, b) Accompanied by five or more symptoms that occur in the week before
the onset of menstruation and disappear within a few days of the onset of menstruation.
These criteria also indicate that PMDD can overlap other psychiatric disorders but in these
patients the symptoms do not exacerbate in the luteal phase.
According to DSM 5 criteria, one or more of the following must be present for the diagnosis
of PMDD: a) anger, irritability b) sudden sadness, increased sensitivity, mood swings to
rejection c) tension and anxiety d) depressed mood, feeling hopeless, self-criticizing thoughts.
To achieve a total of five symptoms, one or more of the following symptoms must also be
present:

- Premenstrual irritability
- Concentration difficulty
- Appetite change, overeating, food cravings
- Decreased interest in ordinary activities
- Easily fatigued, having reduced energy
- Feeling overwhelmed or out of control
- Bloating, breast tenderness, weight gain, or joint / muscle pain
- Sleeping too much or not getting enough sleep

These symptoms should occur in the luteal phase and must be severe enough to deteriorate
daily functions (work, school, social life)

**Symptoms**

Women with PMS experience a wide range of cyclic and recurrent emotional, physical,
behavioral and cognitive symptoms that begin in the LPMC and resolve shortly after the onset
of the menstrual period (follicular phase). The number of symptoms seen in the majority of
patients is much more limited (47). However, core symptoms include emotional symptoms
such as depression, irritability and anxiety, and somatic symptoms such as breast pain,
bloating and swelling and headache (Table-1). For most women, the types of symptoms are
very consistent between periods and usually last an average of six days a month.(48). Beside
affective symptoms, women with PMDD also have physical symptoms. Analysis of
prospective symptom studies in women with PMDD shows that mood and physical symptoms
are usually the most severe (and with functional impairment) within four days before
menstruation in the first two to three days [49].

The most common emotional or behavioral symptom of PMS is mood swings. Other non-
physical behavioral symptoms include irritability, anxiety / tension, sad or depressed mood,
increased appetite, sensitivity to rejection, and decreased interest in activities (47). The most
common physical symptoms of PMS are abdominal bloating and excessive fatigue followed
by breast tenderness, headache, dizziness and flushing. (47). Hot flushes similar to
menopausal hot flushes that occur before menstruation suggest PMS or PMDD in women
who are not in postpartum or menopause (50).

Many symptoms associated with PMS significantly affect quality of life as moderate to severe
PMS symptoms have been associated with decreased health-related quality of life (51,52).

**Differential diagnosis**

For differential diagnosis of PMS and PMDD the entities given in Table-2 should be ruled
out. (Table-2) (43-44,46) (83)

**Physical examination**

There is no specific finding in physical examination in women with PMS / PMDD. Physical
examination might be useful in ruling other entities such as endometriosis.
Laboratory findings
There is no specific biochemical or any other tests to diagnose PMS. Daily gonadotropin and sex steroid serum concentrations are not different from women without PMS in women with PMS (23,24). Thyroid tests might be useful in excluding hypothyroidism.

General approach and treatment
A thorough evaluation of patients with (PMS or PMDD is required (Table-3)(84). The cyclic occurrence of the symptoms should be questioned. It might be difficult to interpret in women who have PMS or PMDD with irregular menses. The etiology of the irregular menses should be investigated. In women who are using combined oral contraceptives the timing of the initiation of the symptoms and the relation to the onset or termination of the combined pill should be asked. Various screening tools or applications can be used for self-reporting the symptoms. In cases where the self-reported diary is not conclusive RCOG recommends use of GnRH testing, PMSS can be diagnosed if the symptoms subside when the ovarian hormonal suppression is obtained with GnRh analogues.

Treatment
The main goal of treatment for women with PMS / PMDD is to alleviate, improve and enable to keep up with her daily life. Various approaches ranging from lifestyle measures (exercise and relaxation techniques), to cognitive behavioral therapy and medications (selective serotonin reuptake inhibitors (SSRIs), and/or combined estrogen-progestin contraceptives (COC), are utilized for treatment of PMS and PMDD.

Treatment of mild symptoms
Regular exercise and stress reduction techniques are efficient and cost-effective treatment options in women with mild premenstrual symptoms. Exercise is particularly useful for physical symptoms (53). Vitex agnus castus is a popular herbal remedy that is used in dry extract, tincture or liquid form for treatment of PMS symptoms. The mode of action and pharmacodynamics is not yet completely understood. In animal studies it is shown to act on the dopaminergic receptors leading to a reduction of prolactin secretion. Van Die et al reported vitex agnus castus to be more effective than placebo for PMS symptoms, while its effectiveness for PMDD is less prominent (54).
Although a range of vitamins and dietary supplements, including St.John’s Wort, evening primrose oil, Vitamin B6, Vitamin E, Vitamin D, zinc,calcium, iron and magnesium, have been studied as therapeutic agents for mild PMS; however, the evidence that demonstrates an increased effectiveness of these agents when compared to placebo is not sufficient (41,42,44,55).

Treatment of moderate and severe symptoms
A holistic approach conducted by a team of gynecologist, clinical psychologist, psychiatrist or counsellor) and a dietician is required in treating women with moderate to severe PMS and PMDD (44). The best approach for women who meet the criteria of PMS or PMDD, is to have pharmacological and/or behavioral intervention such as cognitive behavioral therapy(CBT). CBT aims to help people to identify and change destructive or disturbing negative thought patterns. However, before starting treatment, other conditions with symptoms that may overlap with PMS / PMDD, should be ruled out. The first-line pharmacotherapy of moderate to severe PMDD will aim two targets:
a) Enhancing central serotonergic delivery. Serotonin augmenting drugs alleviate PMDD symptoms, therefore selective serotonin reuptake inhibitors [SSRIs] are highly effective in treatment of PMDD
b) Suppressing the hypothalamic-pituitary-ovarian axis to eliminate physiologic cyclic changes of ovarian sex-steroids by either gonadotropin-releasing hormone [GnRH] agonists or combined estrogen-progestin oral contraceptive pills (COCs).

SSRIs should be preferred in women who do not desire to use contraceptive pills. However, if the patient needs contraception combined oral contraceptives should either be the first-choice or combined with SSRIs therapy.

SSRIs are reported to be effective in clinical trials and systematic reviews (44,56). A Cochrane Review compared the effectiveness of paroxetine, fluoxetine, escitalopram, sertraline and citalopram with placebo and concluded that SSRIs reduced overall self-rated symptoms significantly more effectively than placebo when either used continuously or during the LPMC (57). Paroxetine is also effective, but is associated with weight gain. (58).

The beneficial effect of SSRIs will occur as early as the first cycle. If the response is low, the dose may be increased before the next cycle. Although Cochrane review demonstrated SSRI’s therapeutic effect on both somatic and psychological symptoms, they appear to be more effective for mood symptoms than somatic symptoms (46).

Serotonin-norepinephrine reuptake inhibitor (SNRI); Venlafaxine has also been reported to be more effective for PMDD than placebo, but SSRIs are still advised as first-line therapy because venlafaxine causes more withdrawal symptoms than SSRIs. (59,60)

Tricyclic antidepressants can also be used. Clomipramine (given during the menstrual cycle or limited to the LPMC) is more effective than placebo, but its routine use is not recommended due to its side effects (sedation, dry mouth, and weight gain). (61-62)

Three protocols used for treatment of moderate to severe symptoms of PMS and PMDD by SSRIs are: continuous daily administration, luteal phase therapy, or symptom initiated therapy. The choice of regimen depends on the duration and timing of the symptoms (including their predictability) and the patient's preference.

1. Continuous Use: SSRIs are effective for premenstrual symptoms, whether taken continuously or intermittently (63). Continuous administration is recommended for women with mild symptoms occurring with long-term intervals, as the onset of symptoms cannot be predicted. In women with serious physical symptoms, continuous dose regimens are more effective than intermittent regimens (60).

2. Luteal Phase Protocols: It is recommended for women with predictable symptoms that last more than a week before the onset of menstruation. (64). The treatment is commenced on the 14th day of the cycle and usually stopped at the beginning of menstruation, but it can continue for a few more days in women with a persistent history of symptoms. This regimen is less expensive and causes less side effects. Some individual studies [65,66] and the Cochrane review (46) have reported that SSRIs are equally effective in symptom relief when taken continuously or only in the luteal phase. It has also been reported in some studies that higher doses of SSRI are required in some women receiving luteal phase therapy to adequately treat physical symptoms. (65-66)

3. Symptom Onset Treatment: Intermittent therapy has been shown to be effective from the onset of symptoms to the first days of the month. (67). In a randomized study of Yonkers et al., symptom onset therapy with SSRIs was more effective than placebo (48). Symptom onset therapy is recommended for women with symptoms for a week or less that can easily recognize the onset of symptoms. (68,69)

If intermittent treatments are ineffective or difficult for patients, continuous treatment is recommended. (69)
The doses used for PMDD are similar to those used to treat depression. Recommended SSRI doses for SSRI regimens is given in Table-4.(85) Although majority of symptomatic women respond to an SSRI, around 30 to 40 % may not show any improvement (64). The dose of the SSRI should be adjusted according to the symptoms and lack of response to treatment should not be diagnosed after observing several treatment cycles (64). The possible adverse effects of SSRIs are insomnia, nausea, somnolence, fatigue and reduction in libido (44). Changing the SSRI initiated to a newer agent or switching to luteal phase therapy should be considered in women with side-effects (69). If the patient fails to show any improvement with more than one SSRI agent, other diseases mimicking the PMS/PMDD symptoms such as PCOS whom as having a 3.39 times increased risk for depression and a 3.64 times increased risk for anxiety,(70) major depression or substance use disorder must be investigated. On order to avoid withdrawal symptoms SSRIs if used continuously should be discontinued gradually. The patients should not continue taking SSRIs prior to and during pregnancy. The optimal duration of the treatment with SSRIs is unknown. The treatment can be continued until women with recurrent symptoms become pregnant or reach to menopausal state (44).

**Treatment with combined oral contraceptives (COC)**

For women with moderate to severe symptoms seeking hormonal contraception, treatment with a COC is recommended as these medications suppress the hypothalamic-pituitary-ovarian axis and ovulation. Monophasic preparations should be preferred as multiphasic preparations can worsen mood symptoms. (44) COC’s containing drospirenone especially with a 24 4+ regimen (3 mg drospirenone (DRSP) / 20 mcg ethinyl estradiol) with a shortened drug-free interval of four days are effective and approved of by FDA for management of PMDD (71). In case of persistence of the PMS/PMDD symptoms and/or presence of intermediate bleeding that does not improve after three month of COC use the dosage of ethinyl estradiol can be increased and a 21+7 regimen with 3 mg DRSP / 30 mcg EE containing COC can be commenced. However n, 24/4 regimen is associated with better cycle control (72). The COC can be switched to an alternative formulation if Drospirenone bearing COC fails to improve the symptoms or an SSRI can be added to COC monotherapy in order to improve the treatment results. Continuous use of COC is better than the intermittent use. In two randomized studies (73,74) and in a meta-analysis (75), it was shown that COCs containing 20 mcg EE / 3 mg Drospirenone with a four-day confinement interval are more effective than placebo in reducing the PMDD symptoms.

**Cognitive behavioral therapy**

Cognitive behavioral therapy has been used previously in the treatment of depression and anxiety disorders in women, but data on its use for PMS / PMDB are limited. While some studies report that it is useful (76,77), others failed to show any statistically significant benefit (78). In a randomized study covering 174 women with PMDB, women in the internet-based cognitive behavioral intervention group experienced a decrease in symptom severity compared to a waiting list control group (76). The cognitive behavioral therapy course may be useful for some women, but data on this are limited and qualified health-service providers are required for delivering this treatment.

**Gonadotropin releasing hormone agonists**

In women with severe symptoms who cannot respond or tolerate SSRIs or COCs, the next step might be considering gonadotropin-releasing hormone that provides a reversible medical oophorectomy (78). Although GnRH agonist therapy is effective in PMDD (79) it can not be used for a long period due to the menopausal side-effects related to estrogen deficiency such
as bone loss and genital atrophy. Depot leuprolide acetate per month 3.75 mg is the first choice. Add-back therapy with COC is recommended if GnRH analog will be used longer than 6 months (44).

**Alternative hormonal therapies**

Percutaneous estradiol (100 mcg estradiol patches twice weekly) opposed with a cyclical 10–12 day course of oral or vaginal micronized progesterone or long-term progestogen with the LNG-IUS 52 m are recommended regimens for PMS (44) however careful monitoring is required. Danazol 200 mg twice daily is also effective in reducing the symptoms, however virilizing side-effects such as weight gain, acne, hirsutism and deepening of the voice limits its use (44). Effective contraception must be provided during Danazol treatment as Danazol may cause virilization of the female fetus.

**Surgery**

As medical treatment of PMDD is usually successful, therefore surgery (bilateral oophorectomy / bilateral salpingoophorectomy [surgical menopause]) is considered only in a very few patients who failed to respond all the medical therapies described (44). Before surgery all the pharmacological treatment modalities especially administration of GnRH analogues should be considered (80): In young women HRT must be commenced after bilateral oophorectomy (44).

**Conclusion**

PMS and PMDD symptoms deteriorate the well-being of women and have a negative impact on quality of life. Definitive diagnosis is based on prospective self-reporting of the symptoms. Most cases are unrecognized as the presence of the symptoms is not usually questioned during the gynecological exams and routine check-ups. Exercise, healthy diet rich in vitamins and minerals and cognitive behavioral treatment are the first-line treatment modalities in mild cases. SSRIs and/or combined oral contraceptives are first-line pharmacologic treatments as they are effective in majority of the women with PMSS and PMDD symptoms. Alternative hormonal therapies can be utilized when the standard therapies fail to be successful. Surgery is the last resort and should not be applied unless all the alternative medical treatment modalities are given.

**References**

45. Green LJ, O’Brien PMS, Panay N, Craig M on behalf of the Royal College of Obstetricians and Gynaecologists. Management of premenstrual syndrome. BJOG 2017;124: e73–e105
51. Casper RF, Graves GR, Reid RL. Objective measurement of hot flushes associated with the premenstrual syndrome. Fertil Steril 1987; 47:341.
64. Freeman EW, Rickels K, Sondheimer SJ, Polansky M. Differential response to antidepressants in women with premenstrual syndrome/premenstrual dysphoric disorder: a randomized controlled trial. Arch Gen Psychiatry 1999; 56:932.
65. Treatment of premenstrual syndrome and premenstrual dysphoric disorder-Up To Date Literature review current through: Jun 2020. | This topic last updated: Nov 26, 2019
73. Tekeli A, Dilbaz B, Kiykac Altinbas S, Bayoglu Tekin Y. Comparison of short-term efficacy, side effects, benefits of two drospirenone-containing combined oral contraceptives: 21/7-day-3mg/30mcg vs. 24/4-day-3mg/20 mcg. Fertil Steril 2012 98:3 Suppl S 193
Table 1. Most frequent symptoms of Premenstrual Syndrome (PMS) /2-4/

<table>
<thead>
<tr>
<th>Most frequent Symptoms of PMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral symptoms</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Insomnia Or Needing More Sleep</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Sexual Disfunction</td>
</tr>
<tr>
<td>Overeating</td>
</tr>
<tr>
<td>Psychologic Symptoms</td>
</tr>
<tr>
<td>Nervousness</td>
</tr>
<tr>
<td>Anger</td>
</tr>
<tr>
<td>Depressive Mood Changes</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Mood Changes</td>
</tr>
<tr>
<td>Difficulty In Concentrating</td>
</tr>
<tr>
<td>Confusion</td>
</tr>
<tr>
<td>Forgetfulness,</td>
</tr>
<tr>
<td>Emotional Sensitivity</td>
</tr>
<tr>
<td>Poor self-esteem</td>
</tr>
<tr>
<td>Emotional Insensitivity</td>
</tr>
<tr>
<td>Agitation</td>
</tr>
<tr>
<td>Restlessness,</td>
</tr>
<tr>
<td>Physical Symptoms</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Mastodynia and mastalgia</td>
</tr>
<tr>
<td>Backache, abdominal pain</td>
</tr>
<tr>
<td>Bloating, Weight gain</td>
</tr>
<tr>
<td>Swollen ankles, hands and feet</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Muscle and joint pain</td>
</tr>
</tbody>
</table>

Table 2. Differential Diagnosis of Premenstrual Syndrome and Premenstrual Disphoric Disorder

<table>
<thead>
<tr>
<th>Affective Disorder (Eg Depression, Anxiety, Dysthymia, Panic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Anorexia or Bulimia</td>
</tr>
<tr>
<td>Chronic Medical Conditions (Eg Diabetes Mellitus)</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
</tr>
<tr>
<td>Endometriosis</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Oral Contraceptive Pill or Progestin-only contraceptive use</td>
</tr>
<tr>
<td>Perimenopause</td>
</tr>
<tr>
<td>Personality Disorder</td>
</tr>
<tr>
<td>Substance Abuse Disorders</td>
</tr>
</tbody>
</table>
Table 3. Steps for evaluation of patients with PMS and PMDD

<table>
<thead>
<tr>
<th>Steps for evaluation</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Take a detailed history about the symptoms and their relationship with the phase of the menstrual cycle</td>
<td></td>
</tr>
<tr>
<td>Take medical history including hormonal therapy and contraceptive drug use</td>
<td></td>
</tr>
<tr>
<td>Endocrine disorders should be evaluated and investigated. (Thyroid Stimulating Hormone TSH)</td>
<td></td>
</tr>
<tr>
<td>If the symptoms are consistent with PMS / PMDD and other medical conditions are excluded, the patient should be asked to prospectively record symptoms for two months in order to confirm the diagnosis</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Recommended SSRI doses for Premenstrual Dysphoric Disorder (PMDD)

(64)

<table>
<thead>
<tr>
<th>SSRI</th>
<th>Starting Dose (per day)</th>
<th>Usual effective doses* (per day)</th>
<th>Maximum dosage ** (per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>10 mg</td>
<td>20-30 mg</td>
<td>Continous 40 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intermittent 30 mg</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>5-10 mg</td>
<td>10-20 mg</td>
<td>Continous 20 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intermittent 20 mg</td>
</tr>
<tr>
<td>Fluxetine</td>
<td>10mg</td>
<td>20 mg</td>
<td>Continous 30 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Luteal phase 30 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Symptom onset 20 mg</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10 mg</td>
<td>20-30 mg</td>
<td>Continous 40 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intermittent 30 mg</td>
</tr>
<tr>
<td>Sertraline</td>
<td>25 mg</td>
<td>50-150 mg</td>
<td>Continous 200 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intermittent 150 mg</td>
</tr>
</tbody>
</table>

*The starting dose can be increased to the usual effective dose if the initial dose is not sufficient to suppress the symptoms. **Maximum dosage required if symptom control is not achieved with the usual effective dose after a number of treatment cycles.