Diagnosis, pathophysiology and management of premenstrual syndrome

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Key content
• An overview of current information available on premenstrual syndrome (PMS), which is in accordance with the new RCOG Green-top Guideline.
• Definition of PMS and explanation about the different types of premenstrual disorders.
• How to accurately diagnose PMS.
• Discussion about various treatment options available in accordance with the current literature.

Learning objectives
• Develop an understanding of the pathophysiology behind PMS.
• How to diagnose PMS accurately and understand the different classifications of PMS.
• How to treat PMS, including the different treatment options available and discussion about side effects and benefits.

Ethical issues
• Discussion about the long-term risks of GnRH analogue use, and the impact of long-term estrogen deficiency following a bilateral salpingoophorectomy.
• Misdiagnosed PMS in patients with underlying psychiatric and medical conditions.

Keywords: epidemiology / gynaecology / HRT regimens / menopause / pathology / psychiatry

Introduction
Premenstrual syndrome (PMS) is defined as a condition with emotional, physical and behavioural symptoms that increase in severity during the luteal phase of the menstrual cycle, and resolve by the end of menstruation. By definition, there must be a symptom-free interval after menstruation and before ovulation.1,2

Symptoms are usually up to 14 days before the start of menses, causing impairment of life, with anger and irritability being the most severe and longer lasting symptoms.3,4

Studies have shown that 3–8% of menstruating women are affected by PMS, and that 15–20% of women meet the criteria for subclinical PMS.5

Classification
The International Society for Premenstrual Disorders (ISPMD) defined precise criteria for diagnosing premenstrual disorders (PMD), and divided PMS into core and variant. In all PMD, symptoms should cause impairment of daily activities at work, social activities and interpersonal relationships.

Core (or typical) PMD is associated with spontaneous ovulatory menstrual cycles and may be subdivided into predominantly physical symptoms, predominantly psychological or mixed.1,6,7

Women whose symptoms are predominantly psychological or mixed may also fulfil the criteria for premenstrual dysphoric disorder.

Variants of PMD encompass more complex features, divided into the four following categories: premenstrual exacerbation of an underlying condition; PMS in the absence of menstruation; progestogen-induced PMS; and PMS with anovulatory ovarian activity.6,7

For an accurate diagnosis of PMS, symptoms must occur regularly in ovulating women during the luteal phase of the cycle, with resolution by the end of menstruation (Box 1).6
Box 1. Criteria for diagnosing core premenstrual disorder

- It is precipitated by ovulation
- Symptoms are not defined, although typical symptoms exist
- Any number of symptoms can be present
- Physical and psychological symptoms are important
- Symptoms recur in the luteal phase
- Symptoms disappear by the end of menstruation
- A symptom-free week occurs between menstruation and ovulation
- Symptoms must be prospectively rated
- Symptoms are not an exacerbation of an underlying psychological or physical disorder
- Symptoms cause significant distress and impairment of daily activities, such as work commitments, social interactions and family activities.

Pathology

Research is yet to find a conclusive pathophysiological explanation for PMS. Early theories thought there were abnormalities in ovarian sex steroid levels, however this has been disproved, as no differences have been demonstrated between symptomatic and asymptomatic women, and no study has demonstrated differences in progesterone levels. It has now been recognised that aetiology is centred around the ovarian cycle, and this theory is supported by the lack of symptoms before puberty, during pregnancy, after menopause, and during treatment with gonadotropin-releasing hormone (GnRH) analogues.

Sex steroids easily pass the blood–brain barrier, and their receptors are abundant in many areas of the brain including the amygdala and hypothalamus. It has now been hypothesised that progesterone is metabolised in the brain to allopregnanolone and pregnanolone, which stimulates the gamma-aminobutyric acid (GABA) inhibitory neurotransmitter system. GABA receptors are associated with alterations in mood, cognition, and affect.

In high concentrations pregnanolone and allopregnanolone produce anxiolytic, sedative and anaesthetic effects, however at lower levels allopregnanolone can cause anxiety, negative mood and aggression. The GABA receptors become less sensitive to allopregnanolone after exposure to high concentrations, and hence the worsened symptoms experienced during the luteal phase.

Serotonergic activity in the brain is also affected by estrogen and progesterone. Progesterone increases monoamine oxidase (MAO), which decreases the availability of 5-hydroxytryptamine (5-HT), resulting in a depressed mood. Whereas estrogen increases the degradation of MAO, thus increasing the availability of free tryptophan in the brain, which enhances serotonin transport, and therefore stimulates 5-HT binding sites in the brain, resulting in an antidepressant effect.

Diagnosis

For an accurate diagnosis of PMS, prospective charting of symptoms over two menstrual cycles is required. The Daily Record of Severity of Problems (DRSP) is a well-validated scale used in the diagnosis of PMS (Box 2). Prospective documentation should demonstrate a presence of symptoms during the luteal phase and resolution of symptoms during menstruation. If there is a discrepancy over the symptom pattern, then a third cycle of rating should be carried out.

The ISPMD first consensus reviewed the diagnostic criteria for PMS. It highlighted the importance of an accurate history of symptoms, which should be recorded for a minimum of 2 months, as stated above. The symptoms should be present during the premenstrual phase and absent during the follicular phase, as well accurately recording symptoms on a symptom chart.

Many patients find conscientious completion of charts difficult. A new App, PreMentricS is now available (currently iPhones only [Feb 2015]) which graphically documents symptoms, provides a diagnosis, and monitors therapy (Figure 1). It differs from previous charts but has yet to be scientifically validated.

Patient perspective

One woman had been under the care of psychiatrists, with regular psychiatric admissions premenstrually. Her diagnoses included bipolar disorder and borderline personality disorder but PMS was diagnosed through prospective charting. The woman’s symptoms were so persistent (including progesterone-induced PMS when on estrogen treatment) that she requested a hysterectomy with bilateral salpingoophorectomy (BSO) at the age of 28 despite not having children. After much debate she underwent surgery. Post-surgery and estrogen replacement, the woman commenced a university degree and remained symptom-free.

A quotation from another woman highlighted how debilitating PMS can be to social and family life: “GnRH followed by estrogen and Mirena saved my marriage”.

Treatment

Management of PMS is usually performed in a step-wise manner from non-pharmacological strategies, antidepressant medications, hormonal strategies, with surgical options being a last resort.

Women should have their symptoms confirmed by prospective charting, and only when other underlying medical and psychiatric conditions have been addressed should treatment be commenced.
Women with presumed PMS should initially be investigated for other conditions such as depression, anxiety disorders, and hypothyroidism, with referral to the appropriate medical specialty, and adequate communication with their general practitioner. There are links between PMS and sexual abuse, as well as with post-traumatic stress disorder, and therefore a full history to assess these aspects should be obtained.14

**Non-pharmacological treatment**

A course of cognitive behavioural therapy (CBT) to address relaxation, stress management, and assertiveness training, has been reported to be effective in mild PMS, with success being comparable to treatment with fluoxetine.10 Successful CBT could avoid the need for pharmacotherapy; studies have shown a more sustained but less rapid improvement with the use of selective serotonin reuptake inhibitors (SSRIs).

**Complementary therapies**

Rigorous research on complementary therapies for the treatment of PMS is limited, with few well designed randomised controlled trials. One study on the extract of the Agnus cactus fruit (*Vitex agnus castus*) showed improvement in PMS symptoms in up to 52% of patients,14 however the trial numbers were small. Alternative therapies such as exercise, dietary changes and relaxation may help reduce PMS symptoms, and can improve general health, but have not been scientifically proven.15,16

**Antidepressants**

The use of selective SSRIs, particularly fluoxetine 20–60 mg, paroxetine 20–30 mg, citalopram 20–40 mg and sertraline 50–150 mg, has shown a substantial reduction in the emotional, behavioural and physical symptoms in the treatment of core PMD. The short onset of action of SSRIs in women with PMS, means that SSRIs can be taken 14 days

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**Box 2. Item content of the Daily Record of Severity of Problems (DRSP)**

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1a. Felt depressed, sad, ‘down,’ or ‘blue’</td>
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<tr>
<td>1b. Felt hopeless</td>
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<td>1c. Felt worthless, or guilty</td>
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<td>2. Felt anxious, tense, ‘keyed up’ or ‘on edge’</td>
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<td>3a. Had mood swings (e.g., suddenly felt sad or tearful)</td>
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<td>3b. Was more sensitive to rejection or my feelings were easily hurt</td>
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<td>4a. Felt angry, irritable</td>
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<td>4b. Had conflicts or problems with people</td>
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<tr>
<td>5. Had less interest in usual activities (e.g., work, school, friends, hobbies)</td>
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<td>6. Had difficulty concentrating</td>
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<td>7. Felt lethargic, tired, fatigued, or had a lack of energy</td>
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<tr>
<td>8a. Had increased appetite or over-ate</td>
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<tr>
<td>8b. Had cravings for specific foods</td>
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<tr>
<td>9a. Slept more, took naps, found it hard to get up when intended</td>
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<tr>
<td>9b. Had trouble getting to sleep or staying asleep</td>
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<tr>
<td>10a. Felt overwhelmed or that I could not cope</td>
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<tr>
<td>10b. Felt out of control</td>
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<td>11a. Had breast tenderness</td>
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<td>11b. Had breast swelling, felt ‘bloated’, or had weight gain</td>
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<tr>
<td>11c. Had headache</td>
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<tr>
<td>11d. Had joint or muscle pain</td>
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*At work, at school, at home, or in daily routine, at least one of the problems noted above caused reduction of productivity or inefficiency.*

*At least one of the problems noted above interfered with hobbies or social activities (e.g., avoid or do less).*

*At least one of the problems noted above interfered with relationships with others.*

**Figure 1.** Symptom view and diagnosis of woman with typical (core) premenstrual disorder generated by the PreMentricS App (Permission Granted by PMS O’Brien).
before menses, as well as continuously.\textsuperscript{12,14} A meta-analysis on randomised control trials which involved SSRIs in the management of PMS, showed the efficacy of SSRIs compared to placebo.\textsuperscript{18–23} Many studies suggest that intermittent SSRI use is as effective as continuous use in reducing irritability and other mood symptoms, but less effective in reducing somatic symptoms. It is important to note that the European Medicines Agency agrees that SSRIs seem to work in PMS, and certain SSRIs are approved in parts of the world (for example USA for PMDD). However neither the use of intermittent nor continuous SSRI treatments are licensed in the UK and when they are used they are off-licence.\textsuperscript{12,24–27}

Patients should be informed of side effects including nausea, fatigue, insomnia and sexual dysfunction, and that side effects are less with intermittent use.\textsuperscript{6} Unfortunately PMS symptoms recur following discontinuation of SSRIs.\textsuperscript{38} There can be significant effects if used during the course of pregnancy even if this is only the initial stages. Women who have failed two or more SSRI trials should probably try hormonal treatment.\textsuperscript{19}

The ISPMD second consensus further supports the use of SSRIs,\textsuperscript{10} and within the second consensus it was found that SSRI use as a first-line treatment was the most important recommendation in the management of PMS, as well as highlighting the importance of explaining the side effects associated with the use of SSRIs. In practice this means that a diagnosis should be accurately ascertained and a systematic approach to the management of starting with SSRIs should be utilised.

**Estrogen**

Estrogen therapy which inhibits ovulation has been proposed as a method for management in PMS.\textsuperscript{28,29} Estrogen is usually administered as a transdermal patch, or subcutaneous implant,\textsuperscript{29} and is an effective agent in the treatment of PMS symptoms.\textsuperscript{29} Transdermal patches are more readily available within the UK, and hence are a frequent choice compared to the implant. Receiving unopposed estrogen will require progestogen cover to prevent endometrial hyperplasia, unless the woman has had a hysterectomy. Progesterone itself can cause PMS like symptoms, and therefore the lowest dose possible, for the shortest time is recommended. The side effects from synthetic progestins can be minimised through the use of micronised progesterone, which is identical to that produced by the corpus luteum.\textsuperscript{30} Alternatively administration of progesterone directly to the endometrium using the levonorgestrel-containing intrauterine system may reduce recurrence of progesterone-induced PMS symptoms in the long term. A few months after insertion there are minimal systemic levels of progesterone. Although excellent endometrial protection is provided, patients should be advised that initially PMS like symptoms may occur.\textsuperscript{12,29}

**Oral contraceptives**

Newer oral contraceptives containing drospirenone 3 mg and ethinyl estradiol 20 micrograms have shown a positive improvement in PMS symptoms, when hormones were administered for 24 days, followed by 4 days of inactive pills, compared to placebo.\textsuperscript{32–34} However, due to the increased risk of venous thromboembolism, this group of medication is not suitable for all women. Unfortunately although this treatment is licensed in the USA for PMS it is not in the UK.\textsuperscript{34}

No benefit has been found through the use of progesterone alone – additionally the older combined oral contraceptive pills appear to have no benefit in the treatment of PMS.\textsuperscript{35,36}

**Gonadotropin-releasing hormone (GnRH) analogues**

Long-acting GnRH analogues suppress ovarian functioning, reducing the levels of estradiol and progesterone, and subsequently inhibit the menstrual cycle. Several randomised controlled trials have demonstrated improvement of premenstrual symptoms, with a response rate to GnRH analogue treatment between 60% and 75%. A meta-analysis concluded that, compared to placebo, treatment with GnRH analogues resulted in significant symptom relief in behavioural and physical PMS symptoms.\textsuperscript{12,37}

Although GnRH analogues seem like a good long-term option for patients with severe PMS, they induce a hypoestrogenic state and eliminate ovulation.\textsuperscript{6} In the short term this results in hot flushes, night sweats, low mood and insomnia. More importantly, in the long term, risks of this estrogen deficiency include vaginal atrophy, increased cardiovascular risk and osteoporosis.\textsuperscript{6,12} Because of these long-term risks, treatment without add–back therapy should only be continued for 6 months. If women are receiving add–back therapy on a long-term basis, they should have assessment of bone mineral density. Although hormone replacement therapy can be administered to reduce the effects of estrogen deficiency, this in itself can re-stimulate PMS like symptoms.

Due to the long-term risks of GnRH analogue use, they should be reserved for women with the most severe symptoms, or where other treatments have failed. In those who fail to respond to GnRH analogues then the diagnosis of PMS should be questioned.

**Hysterectomy and bilateral salpingo-oophorectomy (BSO)**

Surgical options should be considered only as a last resort, and a trial of GnRH with positive effect is advisable before deciding to perform BSO and hysterectomy.

Hysterectomy with BSO has a beneficial effect on both mood and physical symptoms. Oophorectomy alone would stop PMS symptoms, but hysterectomy is required to ensure
estrogen replacement post-surgery can be unopposed without the risk of endometrial hyperplasia, and thus prevent the PMS side effects associated with progestogens. Success rates of hysterectomy with BSO are high and long-lasting, and now surgical intervention can usually be performed laparoscopically, it is less invasive than previously.\(^\text{38,39}\) It is important to remember that all surgical procedures carry an anaesthetic risk, as well as the risk of surgical complications. Surgery undertaken for a mood disorder is unique to PMS management.

Surgery will render the woman infertile and induces the menopause. Estrogen replacement therapy should be commenced post-surgery to prevent the effects of long-term estrogen deficiency, and should be continued until the age when menopause naturally occurs.\(^\text{12}\) Importantly of course is the absence of endometrium, the estrogen can be administered without the requirement for protective progestogen.

**Ongoing assessment**

It is important to remember that if a woman has not responded to more than one pharmacological treatment, they should be reassessed for potential underlying psychiatric or medical disorders, therefore highlighting the importance of regular patient review following initiation of treatment.

**Contribution of authorship**

SW: extensive literature search around the topic, and significant contribution to the writing of the main article, as well as referencing, and creation of several of the CPD questions. EI: creation of several of the CPD questions, appraisal of the article content and construction of the abstract. BN: contribution into the design of the article, with contribution in to the content and critical appraisal of the overall article, as well as creation of several CPD questions. SO: clinical supervisor who came up with the proposed idea for the paper, with significant input in to the formatting and content.

**Disclosure of interests**

None

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An overview of the current management of PMS


