Premenstrual Syndrome

& PREMENSTRUAL DYSPHORIC DISORDER –

Diagnosis, Pathophysiology and Evidence-Based Treatment

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Introduction

Premenstrual syndrome (PMS) represents a spectrum of disorders related to hormonal fluctuations in the normal menstrual cycle. Nearly 50% - 80% of women of reproductive age experience PMS like symptoms ranging from mild to severe. However, only 5-8% of women experience the symptoms at the extreme end of the spectrum known as Premenstrual Dysphoric Disorder (PMDD).[1] Non-specific symptoms and overlapping presentations with other medical and mental illnesses cause a significant delay in diagnosis and treatment, contributing to substantial morbidity and social burden due to the disease.(Table 1)

Table 1: **Differences between PMS and PMDD**

	PMS	PMDD
Prevalence	50-80%	3 – 8%
Severity of symptoms	Mild to severe	Severe
Presenting symptoms	Physical or emotional or both	Predominantly emotional
Diagnostic criteria	Subjective	DSM-V
Affective symptoms	May or may not be present	Always present
Who can manage	Usually managed in Primary Care	Mostly need a referral to secondary care/ Multidisciplinary care
Treatment	Can be managed on lifestyle modifications	Mostly need pharmacological treatment. May also need surgery

Pathophysiology

PMS/PMDD symptoms do not occur before puberty, during pregnancy and after menopause, highlighting that cyclical fluctuations in ovarian hormonal levels are obligatory for the manifestation of alteration in mood, cognition and affect.[2] Research indicates that women with PMDD have altered sensitivity to normal hormonal fluctuations, particularly estrogen and progesterone, that influence CNS function through alterations in neuroactive steroids. Modulation of neurotransmitters leads to higher activity in the brain's amygdala region, responsible for regulating emotions and behaviour. Recent work also suggests that progesterone metabolite (allopregnanolone) levels have a paradoxical effect on GABA receptors which mediates inhibitory neurotransmission in the brain and hence explains the predominant mood symptoms of PMDD.[3]

Diagnosis

Women with PMS/PMDD can present with a range of physical and emotional symptoms, commonly headache, breast tenderness, bloating, abdominal pain, greasy hair, changes in appetite and sex drive, mood swings, tiredness, disturbed sleep and anxiety. Essential diagnostic criteria are:

1) Temporal relation of symptoms to the luteal phase of the ovarian cycle
2) Relief of symptoms with menstruation
3) Symptom-free period before next ovulation
4) Symptoms cause significant distress and impairment of daily personal, professional or social commitments during the luteal phase.

Table 2: **Symptoms of PMDD**

Core Symptoms	Additional Symptoms
1. Marked affective lability (e.g., mood swings; feeling suddenly sad or tearful, or increased sensitivity to rejection)	1. Decreased interest in usual activities (e.g., work, school, friends, hobbies)
2. Marked irritability or anger or increased interpersonal conflicts	2. Difficulty in concentrating
3. Marked depressed mood, feelings of hopelessness, or self-deprecating thoughts	3. Lack of energy, easy fatigability
4. Marked anxiety, tension, and/or feelings of being keyed up or on edge	4. Marked change in appetite, food cravings
	5. Feeling overwhelmed "out of control."
	6. Changes in sleep (hypersomnia, insomnia)
	7. Physical discomforts such as breast tenderness, joint/muscle pains, headaches, bloating, weight gain

The American Psychiatric Association (APA) has included PMDD as a category under Section II (Depressive disorders) of the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V), 2013.[4] The World Health Organization (WHO) included Premenstrual Dysphoric Disorder (PMDD) to the International Statistical Classification of Diseases, Eleventh Revision (ICD-11) in May 2019. PMDD is now a legitimate medical diagnosis with its ICD code (GA34.41). PMDD is primarily listed in diseases of the genitourinary system as well as cross-listed in depressive disorders. DSM-V has clearly defined the diagnostic criteria for PMDD. (Box 1)

Investigation

Prospective recording of symptoms over two cycles using symptom diary charts is the most crucial investigation for the diagnosis of PMS/PMDD. Many PMDD specific charts are available for recording symptom. Daily Record of Severity of Problems (DRSP), Prospective Record of the Impact

Box 1. DSM-V Diagnostic Criteria[4] for PMDD

A. **Definite temporal relation** to menstrual cycle - Symptoms must be present in the last week of menstrual cycle before the onset of menses, start to improve within few days of start of menses and become minimum or absent in the week post-menses.

B&C. Minimum 5 out of 11 symptoms with at least 1 core symptom, should be present for most cycles over the past 12 months. (Table 2)

D. Symptoms to **interfere markedly** with usual activities (work, school, social, relationships).

E. Symptoms are **NOT** a mere exacerbation of an underlying condition (e.g., depression, anxiety).

F. **NOT** attributable to the physiological effects of a substance (drug abuse, medication, other treatment) or other medical condition (eg. Thyroid disorders)

G. PMDD should be confirmed by prospective daily symptom diary for two consecutive cycles.

and Severity of Menstrual Syndrome Diary (PRISM) are few commonly used charts. PreMentricS App for iPhone developed by Dr O'Brien, Consultant Obstetrics and Gynaecologist at University Hospital North Staffordshire, helps women track symptoms and record menses and treatment received[1]. Important points to consider while diagnosing PMS/PMDD are (Box 2):

Box 2. Diagnostic Approach

1) Prospective recording of symptoms over 2 cycles using DRSP7 or similar charts to document severity of symptoms, cyclical relation to menses and symptom free period before next ovulation.

2) Symptoms severe enough to affect quality of life.

3) Rule out other medical or mental disorders with similar presentation.

4) Use of DSM-V criteria to diagnose PMDD

5) Symptom diary to be completed before start of treatment to avoid masking of symptoms.

- It is vital to prospectively complete the symptom diary before starting treatment to avoid masking its presentation.
- The on/off nature of the symptoms in the luteal phase of the menstrual cycle distinguishes PMS/PMDD from other psychiatric disorders.
- It is a diagnosis of exclusion where other underlying medical and psychiatric disorders have been ruled out by detailed history and relevant investigations.
- When the diagnosis is in doubt, or comorbid conditions cloud the precise impact of the menstrual cycle on the overall clinical picture, a trial of medical ovarian suppression with a Gonadotropic Releasing Hormones (GnRH) agonist can provide useful information by temporarily eliminating ovarian hormone secretion.
- If symptoms occur after exogenous hormones, it might be worth reviewing symptoms after discontinuing hormones to exclude medication-induced mood disorders.

Management

The aim of the treatment is to achieve the greatest functional improvement possible for women with PMS/PMDD. Based on the pathophysiology of PMDD, management options help by either 1) reducing hormonal fluctuations related to the ovarian cycle or 2) reduce the effect of these fluctuations on neurotransmitters (serotonin) and GABAA receptors. (Box 3)

Discussion

It is recommended that primary care physicians involved in the care of women with PMDD build collaborative, multidisciplinary teams including mental health specialists and gynaecologists with interest in PMDD, to provide comprehensive care for these patients. In June 2019, The International Association of Premenstrual Disorders (IAPMD) highlighted the importance of building multidisciplinary treatment teams for PMDD patients and the crucial role of mental health providers with knowledge of PMDD in closely tracking patients with severe impairment or suicidal risk.

Box 3. Evidence-based Treatment Approach

1) **FIRST LINE:** (Reduce effect of hormone fluctuation on neurotransmitters)
   a. Life style modification –
      i. Complex carbohydrate diet during luteal phase
      ii. Aerobic exercise, yoga, meditation
      iii. Exposure to sunlight
      iv. Stop smoking/ alcohol
   b. Cognitive Behavioural Therapy (CBT)
   c. Neuromodulators [Selective Serotonin Reuptake Inhibitor (SSRI)/ Selective Nor-epinephrine Reuptake Inhibitor (SNRI)][5] – (BOX 4)
      i. Continuous, or
      ii. Luteal phase

2) **SECOND LINE**:
   a. Combined Oral Contraceptive Pills (COCP) – (Reduce fluctuations in hormone level)
   For women not planning pregnancy
      i. Combined oral contraceptive pills in continuous/ tricyclic pattern Levonorgestrol (LNG)90mcg/ Ethinyl estradiol 20mcg continuously for 3-4 months without a break
      ii. Short hormone free interval 24/4 regimen of drospirenone 3mg and ethinyl estradiol 20 mcg.[6] (Note: increased risk of venous thromboembolism (VTE) with drosperinone containing COCPs)
   b. Combination therapy with SSRIs and COCPs

3) **THIRD LINE:** (Reduce fluctuations in hormone level)
   a. GnRH analogues +/- add-back Hormone replacement therapy (HRT)[7] – GnRH agonists (monthly or 3 monthly injections) +/- add-back HRT (estrogen patches in the dose of 50-75 micrograms with micronized progesterone tablets 100 mg daily; or tibolone 2.5mg daily).

4) **FOURTH LINE:** (Reduce fluctuations in hormone level)
Total hysterectomy + Bilateral Salpingo-Oophorectomy +/- HRT – in refractory cases not responding to medical management.

NOVEL THERAPIES (Currently under research)

5-α reductase inhibitor (Dutasteride)- dose 2.5mg daily (Reduce luteal phase increase in allopregnanolone)[8]

Iso-allepregnanolone (UC1010) – Sepranolone (GABAA modulating steroid antagonist inhibits allopregnanolone action)[9]

Vitex Agnus Castus (VAC) (Balances female sex hormones through its phytochemicals)[10]

Future

Extensive research over two decades led to the inclusion of PMDD as a diagnostic entity in DSM-V and in ICD-11. To maintain uniformity of diagnosis, DSM-V has laid down strict diagnostic criteria, promoting accurate data collection for future research studies on the treatment needs and delivery of services for women with premenstrual dysphoric disorder. The benefits of including premenstrual dysphoric disorder in DSM-V will be significant. It will boost not only research and medical care but also the integrity of women who experience considerable suffering every month.[11] A clear and concise description will ensure that clinicians, patients, families, and researchers have a common language to communicate about the diagnosis and increase its legitimacy. It is high time we refrain from using the term 'just PMS' for women having devastating PMDD symptoms. Further research may help to reduce the need for medical and surgical menopause for this incapacitating condition.

Take home message

1) PMDD is a severe form of PMS and is a legitimate diagnosis.
2) Prospective symptom recording provides objectivity to the diagnosis.
3) Consider multidisciplinary care for patients with PMDD, including gynaecologists and psychiatrists with special interest in the condition.

Additional source of information: **NICE CKS** has a recently updated guidance on the diagnosis and management of women with Premenstrual Syndrome, for the target audience of healthcare professionals working within the NHS in the UK and providing first contact or primary healthcare.

Box 4. Selective Serotonin Reuptake Inhibitor (SSRI)/ Selective Nor-epinephrine Reuptake Inhibitor (SNRI) (Off-label use)

Regimens - 1) Continuous
2) Luteal phase (Day 15-28)

Doses - Fluoxetine 20 mg a day / Sertraline 50 mg to 100 mg a day / Citalopram 20 mg a day / Escitalopram 20 mg a day / Paroxetine 20 mg a day

Side effects - Nausea, insomnia, somnolence, fatigue, reduced libido

How to discontinue treatment –
Luteal phase regimen – discontinue at any time.
Continuous regimen – Taper dose over a period of time to avoid withdrawal symptoms

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