Premenstrual Syndrome

Premenstrual Syndrome (PMS) is defined as:

The cyclic recurrence in the luteal phase of the menstrual cycle of a combination of distressing physical, psychological, and/or behavioral changes of sufficient severity to result in deterioration of interpersonal relationships and/or interference with normal activities.

Nearly 200 symptoms have been associated with this definition and it is the clustering of these signs and symptoms that is the hallmark of PMS.
PMCs (Premenstrual Changes) are a common cyclic affective disorder of young and middle-aged occurring in the luteal phase.

PMCs range from mild mood fluctuations, called Premenstrual Syndrome (PMS) to severe mental and physical disturbances, called Premenstrual Dysphoric Disorder (PMDD).

The exact aetiology of PMCs is largely under-explored.

Its diagnosis and management are often difficult.
**Incidence**

Premenstrual syndrome and premenstrual dysphoric disorder are diagnoses of exclusion; therefore, alternative explanations for symptoms must be considered before either diagnosis is made. Milder symptoms are believed to occur in about 30% to 80% of reproductive-age women, while severe symptoms are estimated to occur in 3% to 5% of menstruating women.
Many patients with psychiatric disorders also complain of worsening of their symptoms around the premenstrual phase, called "premenstrual magnification" (PMM).
Premenstrual Syndrome
Modern Definition

Distressing physical, psychological and behavioral symptoms, not caused by organic disease, which regularly recur during the same phase of the menstrual (ovarian) cycle and which significantly regress or disappear during the remainder of the cycle.

Magos & Studd (1984)
Premenstrual Syndrome Diagnosis

- Validated Prospective Symptom Diaries
  - Confirm diagnosis more accurately than retrospective recall
- Moos Menstrual Distress Questionnaire (MDQ/PDQ)
  - Moos 1968, Magos/Studd 1987 (Oestradiol trials)
- Daily Record of Severity of Problems (DRSP)
  - Endicott & Harrison NY State Psych Inst 1990, Arch Women’s Mental Health 2006 (Yaz trials)
- Premenstrual Symptoms Screening Tool (PSST)
  - Steiner et al Arch Women’s Mental Health 2003 (SSRI trials)
Premenstrual Syndrome

TYPES

History

► Primary PMS: Complete resolution of symptoms at onset of menstruation. Dalton (1977)

► Secondary PMS: Improvement of symptoms following menstruation, even if only for a few days.
Patterns of PMS

- Premenstrual symptoms can begin at ovulation with gradual worsening of symptoms during the luteal phase (pattern 1).
- PMS can begin during the second week of the luteal phase (pattern 2).
- Some women experience a brief, time-limited episode of symptoms at ovulation, followed by symptom-free days and a recurrence of premenstrual symptoms late in the luteal phase (pattern 3).
- The most severely affected women have symptoms that at ovulation worsen across the luteal phase and remit only after menses cease (pattern 4). These women describe having only one week a month that is symptom-free.
Some women experience a brief, time-limited episode of symptoms at ovulation, followed by symptom-free days and a recurrence of premenstrual symptoms late in the luteal phase (pattern 3).

The most severely affected women have symptoms that at ovulation worsen across the luteal phase and remit only after menses cease (pattern 4). These women describe having only one week a month that is symptom-free.
Premenstrual Syndrome Symptoms

Over 160 PMS related symptoms Moos (1968)

- **Physical** e.g. breast tenderness, headache, bloating
- **Psychological** e.g. mood swings, irritability, depression
- **Behavioural** e.g. lowered cognitive performance, accidents, suicide attempts
Premenstrual Syndrome
Symptoms — Prevalence

SWS 2007 Sadler Inskip Panay (Submitted)

► >25 000 Women Surveyed
► 30% stated that PMS severely affected their quality of life (cf PMDD 3-8%)
► Positive correlation of PMS with obesity / less exercise / less qualifications
► Less PMS with increasing hormonal contraceptive use
PMDD Definition

(DSM IV - Diagnostic and Statistical Manual of Mental Diseases)

Five or more of the following present premenstrually
(one must be a core* symptom):

- Markedly depressed mood *
- Marked anxiety/tension*
- Marked affective labiality
- Marked anger/irritability*
- Decreased interest in usual activities*
- Difficulty concentrating
- Lethargy/fatigue
- Appetite change/food cravings
- Sleep disturbance
- Feeling overwhelmed
- Physical symptoms (e.g. breast tenderness, bloating)

Symptoms in most menstrual cycles during the last year
(retrospective confirmation) and in at least two cycles as
prospective confirmation

Occur the last week before menses and remit within a few days of
onset of menses

Marked interference with work, social activities, relationship
**Aetiology**

- **Ovarian Steroid Fluctuation**
  Normal cyclic changes in ovarian steroids cause dramatic changes in various body systems.

- **CNS Neurotransmitters**
  Neurotransmitter levels are affected by ovarian steroid changes. The serotonergic, adrenergic, opioid, and GABAergic systems are implicated.

- **Genetic Predisposition**
  Development or severity of premenstrual symptoms may be hereditary.

- **Social Expectations**
  Sociocultural beliefs about menstruation may influence what a woman expects to experience.
[Tentative aetiopathology of PMCs]:

- Progesterone and its congeners → Central GABA system
- Oestrogen → Modulation of metanephrine neurotransmitters in the brain
- Low ACTH

HPA axis dysregulation

- α-MSH, and
- β-ENDORPHIN

Leptin

Bizarre response of the luteal phase of the menstrual cycle due to HPA axis dysregulation

Changes in the affect and physical consortium causing PMCs
Cerebral serotonin neurotransmitter system (5-HTs) is an important component, involved in a large number of psychiatric illnesses where the affect is disturbed.

PMDD is another extreme reflection of the affective disturbances. Therefore, it is interesting to note whether 5-HTs play any role in the development of PMCs.

Studies have shown that post-synaptic serotonergic response possibly is disturbed during the late-luteal-premenstrual phase of the MC or even throughout the cycle in those who have severe vulnerability trait.

Though the gonadal hormone (oestrogen and progesterone)-induced modulation of 5-HTs is a known fact at the backdrop of schizophrenia
Allopregnanolone - Metabolite of progesterone – potent neurotransmitter. Positive modulator of GABA receptor

- **Bimodal Action on mood symptoms**
  - **High levels anxiolytic**
  - **Low levels lead to emotional lability**

Low levels in follicular & luteal phases PMS/PMDD

  - Impaired response to GnRH / ACTH stimulation
  - Impaired steroidogenesis by Corpus Luteum

**GABA** - Major inhibitory system in CNS

- Low levels of GABA in mood disorders
- Low levels in women with PMDD during late luteal phase

**Serotonin** - lower platelet concentrations, lower luteal phase levels, enhanced sensitivity to progesterone.

- Levels elevated by oestradiol
- SSRIs effective for PMDD
## Common Symptoms of PMS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Women with PMS Showing Symptoms (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>92%</td>
</tr>
<tr>
<td>Irritability</td>
<td>91%</td>
</tr>
<tr>
<td>Labile mood with alternating sadness and anger</td>
<td>81%</td>
</tr>
<tr>
<td>Depression</td>
<td>80%</td>
</tr>
<tr>
<td>Oversensitivity</td>
<td>69%</td>
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<tr>
<td>Crying spells</td>
<td>65%</td>
</tr>
<tr>
<td>Social withdrawal</td>
<td>65%</td>
</tr>
<tr>
<td>Forgetfulness</td>
<td>56%</td>
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<tr>
<td>Difficulty concentrating</td>
<td>47%</td>
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</tbody>
</table>
# Common Symptoms of PMS (Continued)

## Physical

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Abdominal bloating</td>
<td>90%</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>85%</td>
</tr>
<tr>
<td>Acne</td>
<td>71%</td>
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<tr>
<td>Appetite changes and food cravings</td>
<td>70%</td>
</tr>
<tr>
<td>Swelling of the extremities</td>
<td>67%</td>
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<tr>
<td>Headache</td>
<td>60%</td>
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<tr>
<td>Gastrointestinal upset</td>
<td>48%</td>
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</tbody>
</table>
Diagnosis

Screening of patients could easily be done by asking the patients to maintain regular menstrual diary for at least two consecutive cycles to note the target symptoms.
Write the date in the first row, starting with today. Circle the days of your menstrual period. Each day, rate the severity of your symptoms: 1 = no symptoms; 2 = mild symptoms; 3 = moderate symptoms; 4 = severe symptoms.

<table>
<thead>
<tr>
<th>Date</th>
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<th>28</th>
<th>29</th>
<th>30</th>
<th>31</th>
</tr>
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<tbody>
<tr>
<td>Day of the month</td>
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</tbody>
</table>

Irritability or tension
Anger or short temper
Anxiety or nervousness
Depression or sadness
Crying or tearfulness
Relationship problems

Tiredness or lack of energy
Insomnia
Changes in sexual interest
Food cravings or overeating
Difficulty concentrating
Feeling overwhelmed

Headaches
Breast tenderness or swelling
Back pain
Abdominal pain
Muscle and joint pain
Weight gain
Nausea
Other (please specify)
Other (please specify)
Diagnostic Criteria for Premenstrual Syndrome

A 30% increase in the intensity of symptoms of premenstrual syndrome (measured using a standardized instrument) from cycle days 5 to 10 as compared with the six-day interval before the onset of menses and documentation of these changes in a daily symptom diary for at least two consecutive cycles.

University of California at San Diego

- At least one of the following affective and somatic symptoms during the five days before menses in each of the three previous cycles:
  - Affective symptoms: depression, angry outbursts, irritability, anxiety, confusion, social withdrawal
  - Somatic symptoms: breast tenderness, abdominal bloating, headache, swelling of extremities
  - Symptoms relieved from days 4 through 13 of the menstrual cycle
The patient keeps a premenstrual daily symptom diary for two to three months (see Figure 2).

- Are the patient’s symptoms consistent with PMS?
  - Yes
  - No → Evaluate the patient for other physical and psychiatric disorders.

- Are the patient’s symptoms restricted to the luteal phase of the menstrual cycle?
  - Yes
  - No

- Do the patient’s symptoms interfere with daily functioning?
  - Yes
  - No → Premenstrual symptoms

Evaluate the severity of the patient’s symptoms and refer to the diagnostic criteria for PMS and PMDD (see Tables 2 and 3).

- PMS
- PMDD
# Differences Between PMS and PMDD

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Tenth Revision of the International Classification of Disease (ICD-10)</th>
<th>Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Providers using these criteria</td>
<td>Obstetrician/gynecologists, primary care physicians</td>
<td>Psychiatrists, other mental health care providers</td>
</tr>
<tr>
<td>Number of symptoms required</td>
<td>One</td>
<td>5 of 11 symptoms</td>
</tr>
<tr>
<td>Functional impairment</td>
<td>Not required</td>
<td>Interference with social or role functioning required</td>
</tr>
<tr>
<td>Prospective charting of symptoms</td>
<td>Not required</td>
<td>Prospective daily charting of symptoms required for two cycles</td>
</tr>
</tbody>
</table>
The triad of Oestrogen Responsive Depressive Disorders

- Postnatal depression
- Premenstrual depression
- Climacteric depression
## Differential Diagnosis

**Psychiatric disorders**
- Major depression
- Dysthymia
- Generalized anxiety
- Panic disorder
- Bipolar illness (mood irritability)
- Other

**Medical disorders**
- Anemia
- Autoimmune disorders
- Hypothyroidism
- Diabetes
- Seizure disorders
- Endometriosis
- Chronic fatigue syndrome
- Collagen vascular disease
Differential Diagnosis (Continued)

Premenstrual exacerbation

- Of psychiatric disorders
- Of seizure disorders
- Of endocrine disorders
- Of cancer
- Of systemic lupus erythematosus
- Of anemia
- Of endometriosis

Psychosocial spectrum

- Past history of sexual abuse
- Past, present, or current domestic violence
Management of PMCs is often extremely difficult.

 Patients qualified for PMCs could be rated for the symptoms severity under the three-point scale:

 - Mild, moderate and severe.

 According to the symptom rating, the guidelines for the management of PMCs could be adopted as follows.
(A). **Life style modification including counseling or behavioral psychotherapy for coping up with the symptoms when the symptoms are mild,**

(B). **Pharmacotherapy when the symptoms, although mild, are not been tackled by simple life style modification or counseling and psychotherapy or the symptoms are moderate to severe and incapacitating.**
Strategies to cope up PMCs by modifying life styles:

- Doctors often prescribe/advice the followings for their patients with mild PMCs as the first-line of management:
  - Prohibition for caffeine, refined sugars, and crude salt intake,
  - Avoiding alcohol and related beverages
  - Regular exercise, especially isotonic
  - Increase carbohydrate intake in the diet, and
  - Cognitive-behavioral psychotherapy, if required
Though the role of these are quite under tested, the reasons for such age-old prescriptions are probably continuing due to the other benefits and safety.

If these are found to be ineffective or inadequate, or the symptoms are severe, pharmacotherapy remains the mainstay of the treatment.
Strategies for opting for the pharmacological agents

- Vitamins and minerals as dietary supplements,
- Psychopharmacological drugs, and
- Hormonal agents:
- Vitamins and minerals
Treatment of PMS

NOT EFFECTIVE
✓ Progesterone, Pyridoxine, Bromocriptine, Combination Oral contraceptives (OCPs)

POSSIBLY EFFECTIVE
✓ Diet, Aerobic exercise, Psychological approaches, Magnesium, Evening Primrose Oil, Vitamin E, Spironolactone, Non Steroidal Anti-inflammatory, Ovulation Suppression

EFFECTIVE
✓ Calcium, Selective Serotonin Reuptake Inhibitors

NATURAL THERAPIES
✓ Black Cohosh, Borage Seed oil, Dandelion, Dong Quai
<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50-150 mg/day</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10-30 mg/day</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>25-75 mg/day (14 days before menses)</td>
</tr>
<tr>
<td><strong>Anxiolytics</strong></td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>1.2 µg/day (6-14 days before menses)</td>
</tr>
<tr>
<td>Buspirone</td>
<td>25-60 mg/day (12 days before menses)</td>
</tr>
<tr>
<td><strong>Ovulation suppression</strong></td>
<td></td>
</tr>
<tr>
<td>GnRH agonists</td>
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</tr>
<tr>
<td>Buserelin*</td>
<td>400-900 µg/day (intranasal)</td>
</tr>
<tr>
<td>Leuprolide</td>
<td>3.75-7.5 mg/monthly</td>
</tr>
<tr>
<td></td>
<td>(intramuscular injection)</td>
</tr>
<tr>
<td>Danazol</td>
<td>200-400 mg/day (at onset of symptoms until onset of menses)</td>
</tr>
</tbody>
</table>

*Not available in the US.
Management of Mild / Moderate PMS

- Healthier lifestyle
- Nutrition
  - Stress management
  - Counselling/support
  - Mild medications
    - Evening primrose
    - Diuretics
  - Vitamins & minerals
    - B6, A & D
    - Magnesium
    - Zinc
Moderate / Severe PMS

Psychological/physical
??Progesterone

Psychological/physical
COC/ Oestradiol /Other

Psychological
SSRI's / SNRIs

Resistant PMS
GnRHa + add-back

Resistant PMS
TAH BSO HRT
Oestrogen Therapy

100µg patches tried subsequently

- As effective
- Fewer symptoms of breast discomfort and bloating
- Less anxiety about high dose estrogen therapy

Smith RNJ, Studd JWW et al; BJOG 1995
Premenstrual Syndrome Treatment - SSRI's

Steiner M. et al 1995 NEJM

- **Fluoxetine in treatment of premenstrual dysphoria**
- **405 women in 2 month placebo washout phase**
- **313 women randomised to fluoxetine 20mg, 60mg or placebo**
- **Both doses significantly superior to placebo in reducing tension & irritability.**
Premenstrual Syndrome Treatment - SSRI’s

- **Luteal phase fluoxetine** as effective with fewer side-effects

*Dimmock et al Lancet 2000*
Efficacy of selective serotonin-reuptake inhibitors in premenstrual syndrome: a systematic review.

- **Take home tip:**
  Mildest SSRI therapy

  Citalopram 10 – 20mg luteal phase (D15 – D28)
Premenstrual Syndrome Treatment - GnRH Analogues

- Very effective for PMS - also diagnostic
- Unsuitable for long term use alone
- HRT add back to prevent menopausal symptoms and bone loss

Leather, Studd Gyne Endocrinol 1999
Premenstrual Syndrome: Pathophysiology, Definition of the Disease and Treatment Options

Summary

► Prevalence of severe PMS/PMDD 10 – 30%

► E2/serotonin and Prog:Allo /GABA most plausible aetiologies in genetically vulnerable women

► Confirmation of severe PMS/PMDD by validated rating scales essential
Premenstrual Syndrome: Pathophysiology, Definition of the Disease and Treatment Options

Summary

► Training of Health Professionals of paramount importance to aid recognition of condition

► Management ideally should be by multidisciplinary teams

► Moderate/severe PMS usually needs medical intervention - sooner rather than later to avoid unnecessary suffering
Premenstrual Syndrome

Future Aims

- **Confirmation of benefits of new COCPs/long cycle COCPs**

- **Licensing of**
  - Yaz® for PMS/PMDD in Europe
  - Long Cycle COCPs
  - Transdermal oestradiol
  - GnRHα + add-back for severe PMS
COCP

- Little benefit with COCP despite ovulation suppression.
  - Progestogenic PMS-like side effect & pill free week
- Rapkin (2003) Psychoneuroendocrinol
  - Anti-androgenic, anti-mineralocorticoid progestogen, drosperinone – Yasmin COCP showing promise