Premenstrual Syndrome (PMS)/Premenstrual Dysphoric Disorder (PMDD)

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- **Potential for conflict(s) of interest: See below**
  - **Wyeth (makers of Effexor/Premarin) – funded me as co-investigator for trial comparing rating scales for depression (HAMD-7 vs. 17) and as facilitator for a contraception talk**
  - **Lundbeck (makers of Celexa/Cipralex/Trintellix) – funded me as co-investigator for study on depression with Celexa as the study drug; funded a presentation given on "Mood Disorders in Women"; funded me to attend advisory meetings on Cipralex/Trintellix**
  - **Warner-Chilcott financially supported presentation on PMS Nov. 26, 13**

Learning Objectives:

- define "premenstrual syndrome"
- describe natural history across the life cycle
- examine the etiology and pathophysiology of PMS
- recognize the impact of PMS on health, wellness and society
- review clinical assessment tools for PMS
- explore hormonal, psychotropic, and alternative treatment options for PMS
- apply learning "pearls" through the review of case

Natural History of PMS:

- Prevalence PMS 13-18 % (up to 30% reported)
- However, 30 % felt need for treatment
- Prevalence PMDD (severe PMS) 2-9 %
- Cumulative lifetime incidence 7.4 %
- Similar prevalence to persistent depressive disorder (previously called dysthymic disorder) and only slightly less than major depression
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PMS Etiology:

- Numerous theories re: etiology abound
- Women who suffer from PMS seem to be inordinately sensitive to the natural fluctuations of hormonal levels of estrogen and progesterone across the menstrual cycle
- There is no difference found in the gonadal steroid levels of women with PMS vs. non-sufferers of the condition
- Neurotransmitter levels in the brain are affected by the fluctuation of hormonal levels throughout the menstrual cycle
- Serotonin, gamma aminobutyric acid (GABA) and endorphins are primarily implicated
- Twin studies suggest genetic predisposition

- Estrogen decreases MAO-A and MAO-B, involved in 5-HT degradation and increases both tryptophan hydroxylase (TPH-1 and TPH-2), involved in **serotonin synthesis and availability**

- Estrogen also regulates 5-HT transport and reuptake from synaptic cleft to the pre-synaptic neuron

- Estrogen promotes down-regulation of 5HT1a auto-receptors and up-regulation of 5HT2a receptors, **increasing the amount of 5-HT in the synapse and the amount available for postsynaptic transmission**

Definition of PMS/PMDD:

- Symptoms must present during the luteal phase (particularly during the last week before the period); resolve during the first few days after menses begins and be absent during the week after the period is finished

- Psychological symptoms must be of sufficient severity to markedly interfere with activities of daily living such as relationships, work, school and social activities

DSM-V:

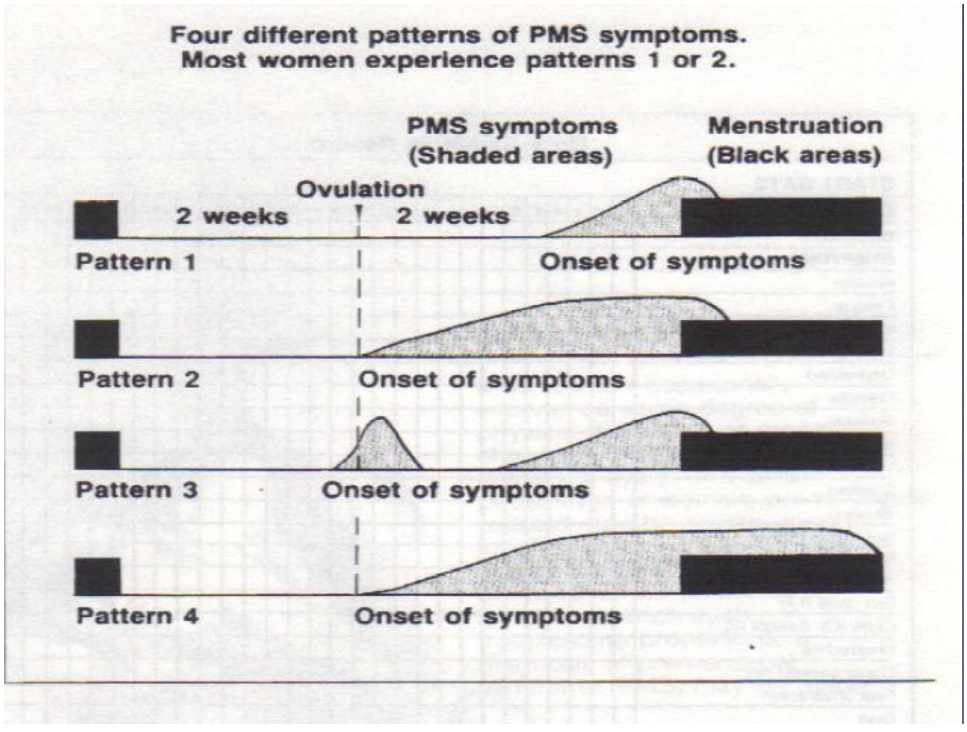
- **Diagnosis rests on having 5 of the following 11 criteria including at least 1 of the first 4 listed:**
- **1) depressed mood; 2) anxiety; 3) mood lability; 4) anger/irritability**
- **5) anhedonia (loss of pleasure in life activities); 6) concentration difficulties; 7) lethargy/fatigue; 8) appetite changes; 9) sleep alterations; 10) sense of feeling overwhelmed/loss of control; 11) physical symptoms like breast swelling or mastalgia, headaches, joint/muscle pain, bloating, weight gain**

Mortola Criteria for PMS 1990:

- **Patient must report at least 1 of the affective and somatic symptoms in 3 prior menstrual cycles during the 5 days before the onset of menses**
- **The Sx must resolve within 4 days of onset of menses and not recur until after day 12 of cycle**
- **Sx must be present in at least 2 cycles during prospective recording**
- **Sx must adversely affect social or work-related activities**

- **These symptoms must be cyclic in nature**
- **PMS can be diagnosed using self-administered rating scales such as a PRISM calendar, Daily Record of Severity of Problems (DRSP), Self-Assessment Disk, Premenstrual Assessment Form, Calendar of Premenstrual Experience (COPE), Prospective Record of the Impact and Severity of Menstrual Symptoms, Premenstrual Syndrome Diary (OMSD), Visual Analog Scale or Penn Daily Symptom Rating**

PRISM calendar can be found on-line for you and patients to use. Get your patient to chart at least 2 menstrual cycles.



- Self-assessment tools must be used over a period of 2-3 cycles to chart symptoms during consecutive days of the menstrual cycle
- There are no confirmatory laboratory tests/investigations to make a diagnosis
- Other medical/psychiatric conditons in the differential diagnosis must be excluded

Differential Dx:

- Psychiatric: depression, dysthymia, anxiety, panic disorder, BPD, somatoform disorder, personality disorder, substance abuse
- Medical: anemia, autoimmune diseases, chronic fatigue syndrome, diabetes, seizure disorders, hypothyroidism, endometriosis, allergies, ovarian cysts

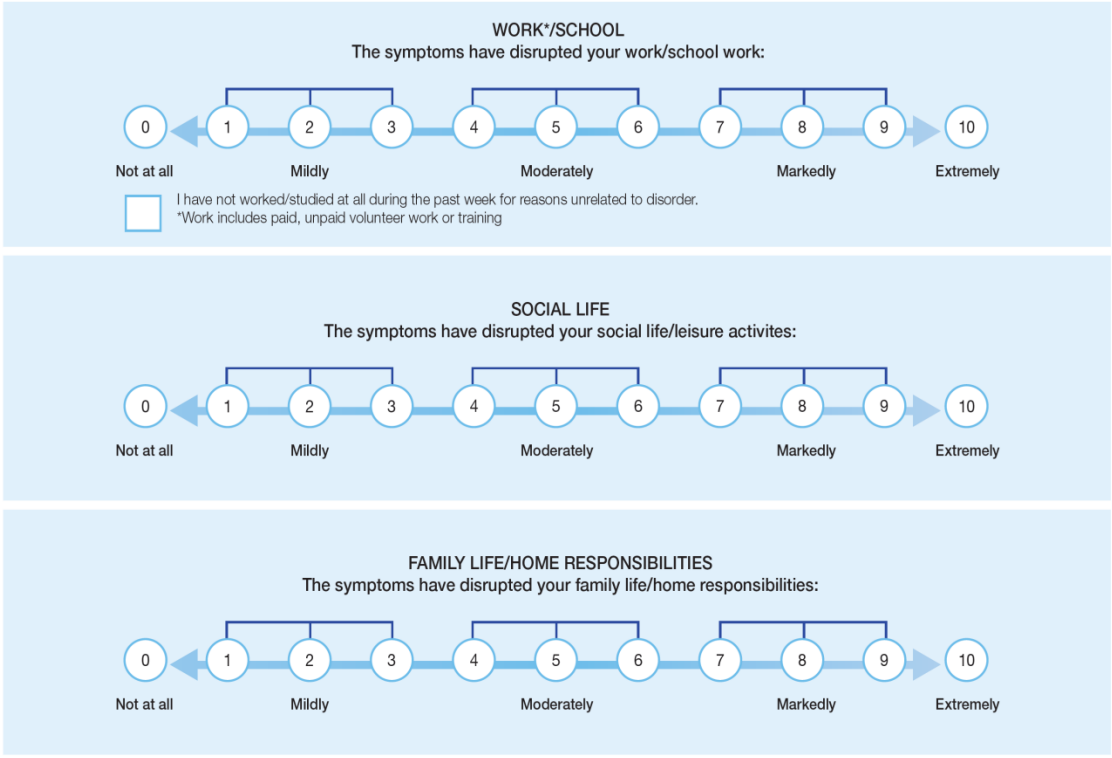
Risk Factors for PMS:

- Advancing age
- Genetics
- Previous psychological trauma especially in childhood
- Co-morbidity with other psychiatric illness
- More prevalent in Caucasians (PMDD in 2.9% of black women vs. 4.4% white women), smokers, obese, lower educational level

Biopsychosocial Impact of PMS:

- Obesity (BMI > 30) 3-fold ↑ in PMS population
- Criminal activity
- Nicotine addiction
- Alcoholism
- ↓ work productivity
- ↑ # days work/school missed for ANY health reasons
- Interference with hobbies, social life, relationships
- Significant ↑ in healthcare provider visits/year
- Significant $$$ to society, healthcare system, insurance, etc…
- Average delay in diagnosis 5.3 years
- Cronje (2004) PMS x 10 years prior to Tx, then delay of 3.5 years for referral after failed Tx
- Approximately 3.75 clinicians to diagnose PMS

Assessing and Monitoring Function: Sheehan Disability Scale



DAYS LOST

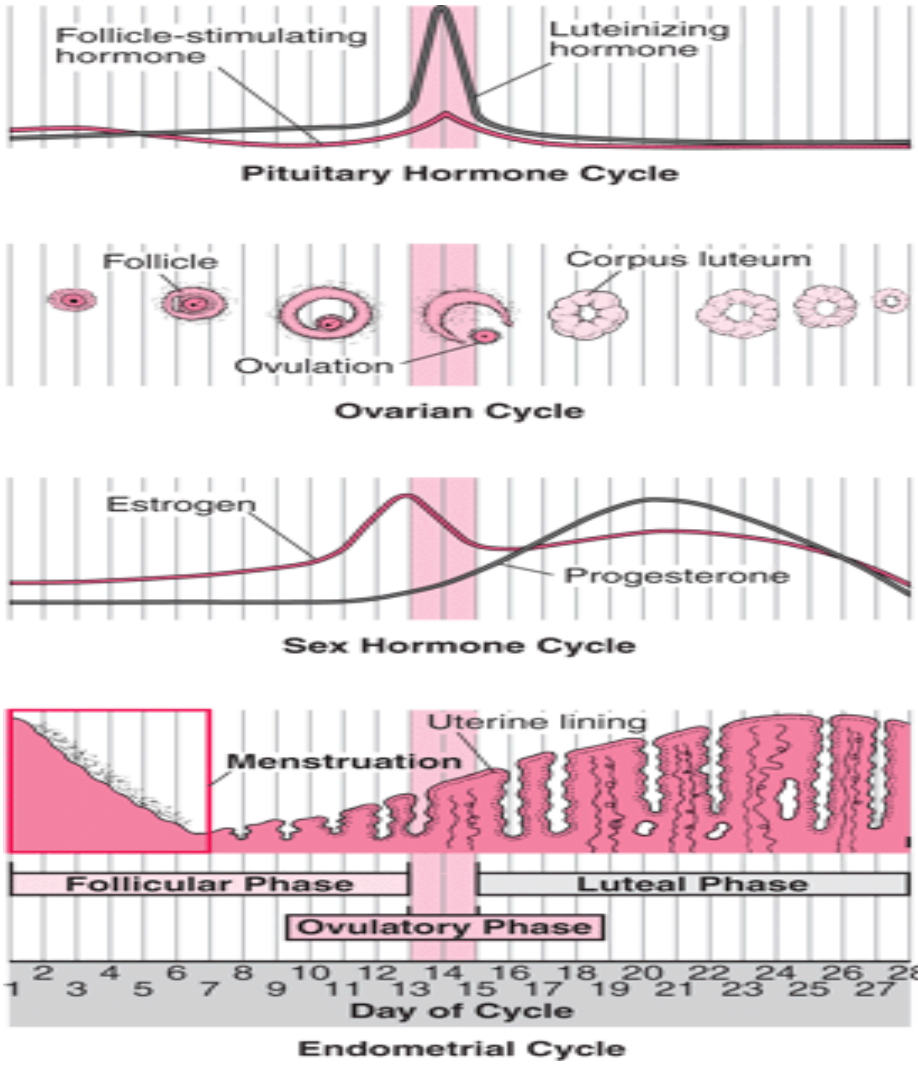
On how many days in the last week did your symptoms cause you to miss school or work or leave you unable to do your normal daily responsibilities? _____

DAYS UNDERPRODUCTIVE

On how many days in the last week did you feel so impaired by your symptoms, that even though you went to school or work, your productivity was reduced? _____

- **10-point self-rated scale in 3 spheres of function – work, home and social life**
- **Maximum score 30/30; if completely functional 0/30**

Pathophysiology of PMS:
Condition seems to be connected with more dramatic drop in the level of estradiol and possibly progesterone fluctuations at certain times in the menstrual cycle ie. at ovulation and in the pre-menstrual period



Genetics:

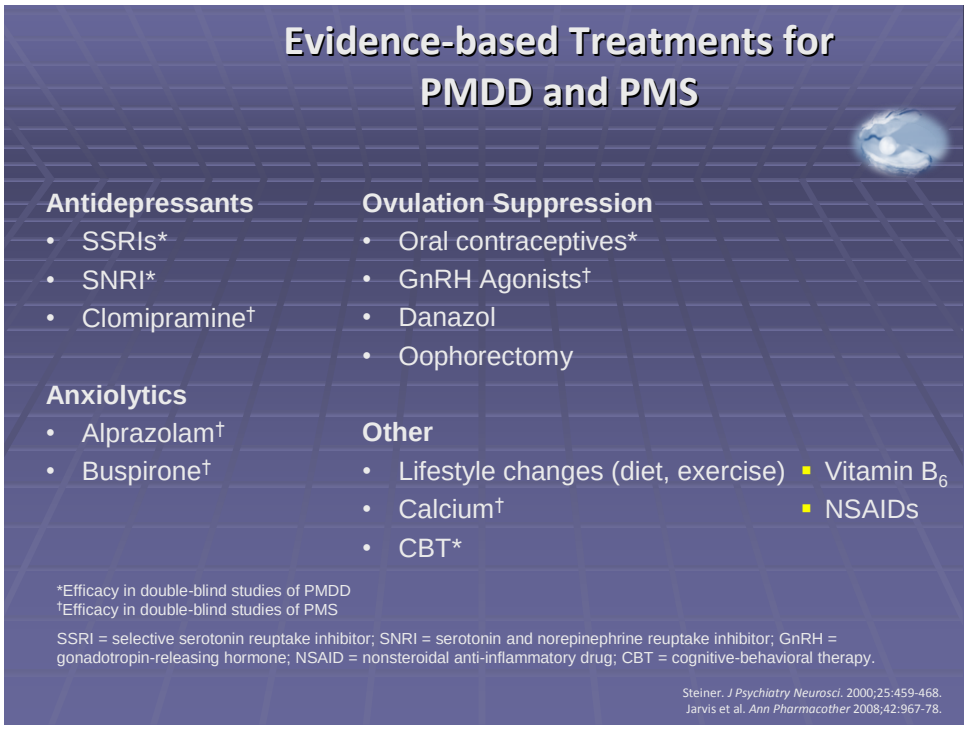
- major twin studies
  - *Condon 1993*
  - Correlation coefficient: monozygotic 0.55; dizygotic 0.28
  - *Kendler 1998*
  - Heritability 56 % in large (1312 twins) 6 year study
  - *Treloar 2002*
  - Genetic correlation between PMS and neuroticism was 0.62 and 0.70 for lifetime major depression
  - *Jahanfar Oct. 2011*
  - Prevalence of PMS 43.0% and 46.8% in monozygotic and dizygotic twins respectively

Treatment:

- Many similarities to treatment for other depressive disorders
- Treatment options include: counseling for patients and their families, lifestyle modifications, medications, surgery in select cases

Lifestyle changes:

- Decrease salt/carbs intake/drink ++ fluids – data limited
- Limit caffeine/carbonated drinks/ETOH – no good trials
- Avoid stress especially when Sx worsen
- Consider light treatment/acupuncture
- Exercise 30 minutes/d at least 5 days of the week/engage in relaxation therapy
- Stop Smoking
- CBT vs. placebo better after 4 weeks/effects lasted up to 18 months
- Educate family/friends/co-workers re: PMS



Supplements:

- Calcium carbonate/citrate – 1200 mg/d in divided doses – Nurses' Health Study II (B - level of evidence)
- Mg – 200-400 mg/day decreases fluid retention; helps mood/migraine – evidence mixed
- Vit. B6 – 50-100 mg/d - mixed data re: effectiveness (B); too much associated with peripheral neuropathy
- Vit. E – mixed data; 400-600 I.U./day
- Vit. D – 800-1000 I.U./d good for bones & PMS
- ***Can J Clin Pharmacol. 2009 – Whelan et al
- Folate 1-5 mg/d a good idea for women in child-bearing years to prevent neural tube defects but no data to support use in PMS
- **effectiveness of other supplements questionable (including dong quai, black cohosh, wild yam, St. John's wort, kava, evening primrose); chasteberry?
- ***Can J Clin Pharmacol. 2009 – Whelan et al

Pharmacotherapy:

- Ovarian suppression for broad range of behavioral and physical symptoms
- Psychotropic meds most effective for irritability and anxiety symptoms
- Combination therapy with ovarian suppression and psychotropic meds may be required

Ovarian suppression:

- Goal is to abolish variability in circulating levels of reproductive steroids, especially in luteal phase
- May be accomplished by a multitude of hormonal manipulations

- **Choice should depend on:**
- Comfort, compliance, complexity, cost…
- Need for contraceptive or wish for pregnancy
- Tolerance of side-effects
- Relative vs absolute contra-indications
- Severity of symptoms

- **Hormonal Contraceptives**
  - Monophasic
  - Continuous
  - Oral, patch, ring, injectable formulations
  - Careful selection of progestin
    - 19-nortestosterone derivatives
    - Drosperinone (Cochrane Database 2009 Lopez found it effective in combination with EE 20 ug)

- 60 % response rate
- Broad range of behavioral and physical symptoms
- Most efficient for PMS vs PMDD

- **Danazol**
  - 17 α ethinyl testosterone
  - Suppresses ovarian steroidogenesis
  - Masculinizing side-effects
  - Halbreich 1991
  - Prospective study
  - 20/23 vs 6/32 cycles were symptom-free
  - P=0.0002

- **GnRH agonist**
  - Pseudo-menopause
  - Side-effects
  - Cost
  - Eventually need add-back HT if long-term
  - Ideal as challenge test prior to BSO

- **Bilateral oophorectomy**
  - Definitive therapy
  - Cronje 2004
    - TAH BSO
    - 6 year prospective study
    - PMS x 10 years
    - 93.6 % complete resolution
    - Treatment with E+T post-op

- **Cyclic progesterone**
  - Replacement of luteal phase progesterone, to stabilize or increase circulating metabolites

  - **Baker 1995**
    - 200 mg micronized progesterone vaginal suppository
    - 7 month double-blind placebo controlled study
    - Beck depression, Hamilton anxiety scales
    - No significant Δ overall <u>BUT</u> significant improvement related to tension, irritability, mood swings, anxiety, lack of control
  - **Magill 1995**
    - 400 mg BID vaginal or rectal progesterone suppository
    - Luteal phase x 14 days, 4 cycles
    - Double-blinded, placebo-controlled
    - Clinical and statistical significance in highest scoring PMS in treated vs placebo

- **Cochrane 2006**
    - 17 studies, only 2 analysable
    - 115 patients
    - Could not combine for analysis
    - Statistically significant improvement in progesterone treated vs placebo

- **Antidepressant Rx:** most SSRIs and SNRIs have data to support use for PMS; however… However, in 2005, FDA gave paroxetine category D rating for potentially causing congenital cardiac defects; it should be avoided in women of childbearing age if they are not using reliable contraception
- Cochrane Database review; Brown Jan. 2009 found all SSRIs were effective in luteal phase only treatment or if used continuously
- Daily use of SSRIs or SNRIs with increased dose during the luteal phase is another alternative for treatment
- ***9 D's*** common S/E of SSRIs/SNRIs:
- Dizziness
- Drowsiness
- Diarrhea/constipation
- Dry mouth
- Difficulty sleeping
- Dysfunction sexually
- Dyspepsia
- Diaphoresis
- Dreaming
- ***SNRIs tend to cause more constipation; citalopram and escitalopram typically cause softer stools
- Benzodiazepines – alprazolam (Xanax) studied for use in the luteal phase – I am not a big proponent of this for obvious reasons
- Buspirone used continuously decreases irritability as well as physical Sx (83% vs. 54% compared to placebo)
- Spironolactone improved mastalgia, bloating, weight gain and depressed mood compared to placebo