Doc, It’s My Hormones!
Female Sex Hormones and Common Complaints

Mitra A. Razzaghi, MD

Women’s Integrated Services in Health
“WISH”

www.wishforwomen.org
Female Sex Hormone related medical complaints

- PMDD/PMS
- Migraine headaches
- Weight issues
- Thyroid issues
- Skin and hair issues
I AM THE WARRIOR
I DON’T HAVE PMS
PMDD aka Luteal Phase Dysphoric Disorder

- Cyclic physical and/or behavioral symptoms
- Over 100 symptoms ascribed, 20 confirmed
- Symptoms of anger, irritability and internal tension severe enough to interfere with the woman's life
- Major Sx: Fatigue, Abdominal bloating, Anxiety, Emotional liability, breast tenderness and headache
- Other symptoms: dizziness, weight gain, joint or muscle pain, sleep difficulties, appetite change, trouble concentrating, hot flashes, heart palpitations
## Frequency of Symptoms of PMS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency: percent of cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>92</td>
</tr>
<tr>
<td>Irritability</td>
<td>91</td>
</tr>
<tr>
<td>Bloating</td>
<td>90</td>
</tr>
<tr>
<td>Anxiety/Tension</td>
<td>89</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>85</td>
</tr>
<tr>
<td>Mood liability</td>
<td>81</td>
</tr>
<tr>
<td>Depression</td>
<td>80</td>
</tr>
<tr>
<td>Food cravings</td>
<td>78</td>
</tr>
<tr>
<td>Acne</td>
<td>71</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>70</td>
</tr>
<tr>
<td>Oversensitivity</td>
<td>69</td>
</tr>
<tr>
<td>Swelling</td>
<td>67</td>
</tr>
<tr>
<td>Expressed anger</td>
<td>67</td>
</tr>
<tr>
<td>Crying easily</td>
<td>65</td>
</tr>
</tbody>
</table>
Epidemiology

- PMS: mild 75%, clinically significant 20-30%
- PMDD 3-8%
- PMDD overestimated because of the failure to apply strict inclusion criteria
- Disparity between different ethnic/cultural background
  - Smaller percentage described in diverse cultural settings
  - Blacks vs. Whites 2.9:4 percent
Risk Factors

- Genetic factors
  - Strong correlation with FH of PMDD and PMS
  - No correlation with inheritance of other mood disorders
  - Genetic variation in ESR1 (estrogen receptor alpha) gene
- Lower education
- Smoking
- High “Daily Hassle Score”
- History of traumatic event or anxiety disorder
Pathogenesis

Gonadal steroids

- Comparable concentration of E2 and P in patients with PMS/PMDD with asymptomatic control
- Progesterone receptor antagonist (Mifepristone or ru486) does not alleviate symptoms
- Possible mechanism: abnormal response to normal hormonal changes
Pathogenesis

Neurotransmitters:
- Cyclic fluctuations in circulating estrogen and progesterone cause marked changes in the opioid, GABA and serotonin systems
- Also changes peripheral beta-endorphin levels
- Serotonin depletion plays major player
  - Symptoms of PMS are ameliorated by the serotonin agonist Fenfluramine and aggravated by acute depletion of the serotonin precursor tryptophan
  - Administration of Metergoline, a serotonin antagonist, to fluoxetine-treated women with PMDD causes a return of mood symptoms
Pathogenesis

Vitamins and nutrients

- No differences in serum vitamin E, vitamin A, or vitamin B6 levels in patients and controls or during cycle.
- High intakes of the dietary thiamine and riboflavin -> less likely to develop PMS.
- Treatment with vitamin B6 100mg/day was reported to be more effective than placebo.
- Improvement in total PMS symptom scores and affective symptoms with the administration of magnesium pyrrolidone carboxylic acid (360 mg three times daily in the second half of the menstrual cycle).
Diagnosis

- 40% of women presenting with presumed PMDD, have other diagnosis commonly mood or anxiety disorders

Diagnostic Criteria

- The specific symptom
- Timing of symptoms related to luteal phase
- Severity of symptoms
- Absence of hormone or drug ingestion, exclusion of other diagnoses
Diagnosis

The DSM-IV criteria for diagnosing PMDD: Prospective documentation of physical and behavioral symptoms (using diaries) being present for most of the preceding year.

- Five or more of the symptoms must have been present during the week prior to menses
- Resolving within a few days after menses starts
- At least one of the five symptoms must be one of the first four on list
- A valid and reliable prospective symptom inventory is required to make the diagnosis of PMDD e.g. Calendar of Premenstrual Experiences (COPE)
Diagnosis

Diagnostic criteria DSM –IV qualifying symptoms

- **1- Feeling sad, hopeless, or self-deprecating**
- **2- Feeling tense, anxious, or "on edge"**
- **3- Marked liability of mood interspersed with frequent tearfulness**
- **4- Persistent irritability, anger, and increased interpersonal conflicts**
- **5- Decreased interest in usual activities, which may be associated with withdrawal from social relationships**
- **6- Difficulty concentrating**
- **7- Feeling fatigued, lethargic, or lacking in energy**
- **8- Marked changes in appetite, which may be associated with binge eating or craving certain foods**
- **9- Hypersomnbia or insomnia**
- **10- A subjective feeling of being overwhelmed or out of control**
- **11- Other physical symptoms: breast tenderness or swelling, headaches, joint or muscle pain, a sensation of bloating, weight gain**
Diagnosis

**COPE: Calendar Of Premenstrual Experiences**
- 10 most commonly reported physical symptoms
- 12 most commonly reported behavioral symptoms
- Sx rated daily throughout the menstrual cycle
- Total score <40 during days 3 to 9 of the menstrual cycle AND a >42 during the last 7 days of the menstrual cycle is diagnostic

**Validity**
- high degree of correlation between COPE scores and the Profile of Mood States and the Beck Depression Inventory
# Premenstrual Daily Symptoms Diary

Name: __________________________  Month: __________________________

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

| Date | Day of the month | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 |
|------|-----------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|---|
|      |                 |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

- 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
- Feeling overwhelmed
- Headaches
- Breast tenderness or swelling
- Back pain
- Abdominal pain
- Weight gain
- Nausea
- Other (specify)
- Other (specify)
Diagnosis

UCSD for PMS:
- at least one of 6 behavioral symptoms: fatigue, irritability, depression, expressed anger, poor concentration, and social withdrawal
- at least one of 4 somatic symptoms: breast tenderness, abdominal bloating, headache, or swollen extremities
- at least one behavioral symptom and one physical symptom within five days of the onset of menses in two consecutive cycles
- a characteristic symptom-free interval from cycle days 4 through 12 of the idealized 28 day menstrual cycle
Diagnosis

- A variety of medical disorders (e.g., migraine, chronic fatigue syndrome, irritable bowel syndrome) are exacerbated just prior to or during menses.
- History, physical examination, chemistry profile, complete blood count, and serum TSH.
- Irregularity of menstrual cycles needs gynecologic endocrine evaluation.
- Record symptoms prospectively for two months.
- If no symptom free interval in the follicular phase, patient should be evaluated for a mood or anxiety disorder.
Treatment

Non-pharmaceutical
- Regular exercise
- Relaxation therapy
- Avoidance of excess salt and large meals
- NSAIDs
- Chaste Berry 200 mg/day
- Vit B6 100mg/day
- Bright light therapy
Treatment of PMS with Vitex Agnus Castus Extract
“Chaste Berry”

<table>
<thead>
<tr>
<th></th>
<th>Active n=86</th>
<th>Placebo n=84</th>
<th>Difference in mean</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritability</td>
<td>-28.9</td>
<td>-18.2</td>
<td>-10.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Mood alteration</td>
<td>-28.7</td>
<td>-17.6</td>
<td>-11.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Anger</td>
<td>-22.1</td>
<td>-11.7</td>
<td>-10.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Headache</td>
<td>-17.8</td>
<td>-5.9</td>
<td>-11.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Bloating</td>
<td>-12.4</td>
<td>-13.7</td>
<td>1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Breast fullness</td>
<td>-18.6</td>
<td>-9.4</td>
<td>-9.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Responder rate</td>
<td>52</td>
<td>24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Schellenberg BMJ 2001;322:134
Treatment

- **Alprazolam**
  - Alprazolam (0.25 mg three or four times daily) beneficial in double-blind, placebo-controlled crossover studies

- **Luteal phase therapy with SSRI**
  - SSRI on second half of cycle 70-85% response
  - Intermittent therapy starting on cycle day 14-21 to few days after menses for affective symptoms
  - Higher doses of the SSRI needed in some women to adequately treat physical symptoms
Luteal Sertraline in PMDD

Screened and consented (N = 907)

Completed 2-cycle screening (N = 371)

Completed 1-cycle, single-blind placebo run-in (N = 281)

Randomized to sertraline (N = 142)
  Intent-to-treat sample (N = 110, available for at least one drug evaluation)

Randomized to placebo (N = 138)
  Intent-to-treat sample (N = 110, available for at least one drug evaluation)

3 cycles of double-blind sertraline
  Withdrawn (N = 27,)
    Insufficient clinical response (N = 0)
    Intercurrent illness/lab abnormality (N = 0)
    Protocol violation (N = 3)
    Lost to follow-up; Other reason (N = 13)
    Adverse events (N = 11)

3 cycles of double-blind placebo
  Withdrawn (N = 33,)
    Insufficient clinical response (N = 4)
    Intercurrent illness/lab abnormality (N = 0)
    Protocol violation (N = 7)
    Lost to follow-up; Other reason (N = 21)
    Adverse events (N = 1)

Completed trial (N = 115)
Completed trial (N = 106)
Luteal Sertraline in PMDD

Halbreich. Luteal Sertraline in PMDD. Obstet Gynecol 2002
Treatment

- OC not better than placebo for treatment of PMS
- Continuous OC’s, or OC’s such as Yaz (20 mcg E2 and 3 mg Drospirenone) shorter placebo interval are effective in some
  - Possible increased risk of VTE with Drospirenone troublesome
  - On Dec 2011 FDA panel voted the benefits of the preparation outweighs risks but recommended better labeling to reflect potential for VTE.

- Cochrane Systematic Review 2009 conclusion:
  - Placebo has large effect
  - Drospirenone + E2 20 mcg (Yaz) may help treat PMDD
Treatment

Danazol

- Inhibits pituitary gonadotropin secretion
- Very effective in treatment of PMS
- The androgenic side effects of Danazol limits its use to patients who fail to respond adequately to the above therapies.
Treatment

Ineffective treatments

- progesterone
- tricyclic antidepressants and monoamine oxidase inhibitors
- lithium

- several popular dietary supplements including
  - Evening primrose oil
  - Essential free fatty acids
  - Ginkgo Biloba
Estrogen Associated Migraine
Prevalence and Burden of Migraine in the United States: Data From the American Migraine Study II

One-year prevalence ratio of migraine and subtypes by age.


www.wishforwomen.org
Estrogen Associated Migraine

- Migraine 3 times more prevalent in women
- Pure menstrual headache
  - 2 days before to 3 day into period in 2/3 of cycles
- Menstrual related migraines
  - Both menstrual and non-menstrual
  - Worse symptoms around menstruation
Pathophysiology

- Trigger: Decline in estrogen concentration after priming
  - Natural: start of menses, postpartum
  - Scheduled withdrawal from exogenous E2
  - Unintentional E2 withdrawal (med interaction)
Pathophysiology

- Estrogen effect on CNS
  - Facilitation of **serotogenic** and **glutameric** systems
  - Fall In E2 level causes fall in serotonin
  - Release of **calcitonin gene-related peptide** and **substance P** from trigeminal nerves
  - Vasodilation of cranial vessels, sensitization of meningeal afferents of trigeminal nerves
  - Effect on NO, Mg, Prostaglandins that modulate neurotransmission balance

JAMA. 2006;295(15):1824
Epidemiology

- Increased incidence in girls with onset of puberty
- Common in perimenopausal period, peak early 40’s
- Migraine up to 41% of women by age 50, fall by half after menopause.
  - Chronic daily headaches worsen initially
- High incidence of chronic migraine in patients with endometriosis
Migraine association with PMS


www.wishforwomen.org
Characteristics

- Menstrual migraines are more severe, last longer, less responsive to acute treatment
- Usually not associated with aura due to relatively low estrogen environment with menses
- Pure menstrual migraine less common than menstrual related (21% vs. 56%)
Treatment Algorithm for Migraine in Women

Migraine in Women

Menstrual Migraine

- Usually Without Aura
- Occurs on Days -2 to -3 of Menstruation or Other Times of the Month Predictable

- Acute Treatment as Needed
  - Simple Analgesics (NSAIDs, Acetaminophen)
  - Combination Analgesics
  - Ergots
  - Triptans

  - Inadequate Response
    - Short-term Preventive Treatment
      - Triptans Beginning 2 d Before Anticipated Menses for 5-6 d

Nonmenstrual Migraine

- With or Without Aura
  - Not Associated With Menstruation
  - Intrequent and/or Hard to Predict
  - Short Episodes (<1 d)

  - Acute Treatment as Needed
    - Simple Analgesics (NSAIDs, Acetaminophen)
    - Combination Analgesics
    - Ergots
    - Triptans

  - Inadequate Response
    - Rescue Therapy
      - Corticosteroids
      - Opiates

- With or Without Aura
  - Not Associated With Menstruation
  - Frequent (>2/wk)
  - Long Episodes (2-3 d)

  - Acute Treatment as Needed
    - Simple Analgesics (NSAIDs, Acetaminophen)
    - Combination Analgesics
    - Ergots
    - Triptans

  - Inadequate Response
    - Daily Preventive Therapy
      - Anticonvulsants
      - ß-Blockers
      - Tricyclic Antidepressants
      - Calcium Channel Blockers

Brandes, J. L. JAMA 2006;295:1824-1830

www.wishforwomen.org
Treatment

Abortive:
- Fast-acting triptan early in mild pain stage
  - Study with Sumatriptan 50% complete response, 42% severity decreased by 50%
- NSAID such as Mefenamic acid 500 TID
- Combined Triptan and NSAID
- Positive studies with long acting triptans:
  - Naratriptan (Amerge, half-life 6h, 1-2.5 mg/dose, max dose 5mg/day)
  - Frovatriptan (Frova half-life 26h, 2.5 mg/dose, max 7.5mg/day)
Treatment

- Preventive treatment
  - Magnesium 120mg TID x 2 wks starting day 15th of cycle
    - Small DBPC study in Italy, over 50% response after 3 months. Effect decreased with open study in the same group
  - Extended-cycle E/P combined contraceptives
  - Cyclic E/P contraception with supplemental estrogen
  - Natural cycles with supplemental estrogen
  - Non-hormonal therapy: long-acting triptan BID

Headache. 2009;31(5):298

www.wishforwomen.org
Estrogen Based Therapies

- Peri-menstrual transdermal E2 patch/gel for a week
  - Estradiol Patch 0.1 mg/24 hr, or Estradiol gel 1-1.5 g/d just before period
  - Timing is very important – starting too early or stopping too soon can cause HA

- SERM, GnRH agonists and progestins not safe or effective

Neurology. 2008; 70(17):1555 and 2006;67(12):2159
Peri-menopause Migraines

- 3-7 year prior to menopause
- Menstrual irregularities and vasomotor symptoms
- Increase in migraine headaches and chronic daily headaches
- After menopause, migraines improve but CDH do not due to sleep and mood disruptions
Migraine and stroke

Data from observational studies: migraine may be a risk factor in developing stroke

Women with migraine with aura: up to 2-fold risk of ischemic stroke
  - Risk higher in smokers and OCP users

No increased risk of myocardial infarction

Schurks, BMJ. 2009;339:b3914

www.wishforwomen.org
Forest plot of the studies of migraine and ischaemic stroke


www.wishforwomen.org
Contraception and migraine

Women with migraine without aura
- Low dose OCP (<50mcg E2) acceptable if no other risk factors

Women with migraine with aura
- No OCP
- Barrier methods, surgical methods if not desiring pregnancy, IUDs including Mirena IUD
<table>
<thead>
<tr>
<th>Variable</th>
<th>ACOG Guidelines</th>
<th>WHO Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker, &gt;35 yr of age</td>
<td>Risk unacceptable</td>
<td>Risk usually outweighs benefit</td>
</tr>
<tr>
<td>15 cigarettes/day</td>
<td>Risk unacceptable</td>
<td>Risk unsuitable benefit</td>
</tr>
<tr>
<td>≥15 cigarettes/day</td>
<td>Risk unacceptable</td>
<td>Risk unacceptable</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Risk acceptable; no definition of blood-pressure control</td>
<td>Risk usually outweighs benefit if systolic blood pressure is 140–159 mm Hg and diastolic blood pressure is 90–99 mm Hg</td>
</tr>
<tr>
<td>Blood pressure controlled</td>
<td>Risk unacceptable; no definition of uncontrolled blood pressure</td>
<td>Risk unacceptable if systolic blood pressure is ≥160 mm Hg or diastolic blood pressure is ≥100 mm Hg</td>
</tr>
<tr>
<td>History of stroke, ischemic heart disease, or venous thromboembolism</td>
<td>Risk unacceptable</td>
<td>Risk unacceptable</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Risk acceptable if no other cardiovascular risk factors and no end-organ damage</td>
<td>Benefit outweighs risk if no end-organ damage and diabetes is of ≤20 yr duration</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Risk acceptable if LDL cholesterol &lt;160 mg/dl and no other cardiovascular risk factors</td>
<td>Benefit-risk ratio is dependent on the presence or absence of other cardiovascular risk factors</td>
</tr>
<tr>
<td>Multiple cardiovascular risk factors</td>
<td>Not addressed</td>
<td>Risk usually outweighs benefit or risk unacceptable, depending on risk factors</td>
</tr>
<tr>
<td>Migraine headache</td>
<td>Risk usually outweighs benefit</td>
<td>Risk usually outweighs benefit</td>
</tr>
<tr>
<td>Age ≥35 yr</td>
<td>Risk unacceptable</td>
<td>Risk unacceptable</td>
</tr>
<tr>
<td>Focal symptoms</td>
<td>Risk usually outweighs benefit</td>
<td>Risk usually outweighs benefit</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Risk unacceptable</td>
<td>Risk unacceptable</td>
</tr>
</tbody>
</table>

Petitti, NEJM 2003; 349:1443-1450

www.wishforwomen.org