PMDD, Pregnancy & Psychopharmacology

Laura G Leahy, DrNPc, APRN, PMH-CNS/FNP, BC
Family Psychiatric Nurse Practitioner
NEIGlobal Master Psychopharmacologist
APNSolutions, LLC—Sewell, New Jersey

Associate Program Director & Advanced Senior Lecturer
University of Pennsylvania-School of Nursing
Course Director, Advanced Psychopharmacology Across the Lifespan

APNA-Clinical Psychopharmacology Institute
21st June 2014-9:45a to 11:15a

Faculty Disclosures

• This presenter has no commercial support to disclose.

• This presenter does receive royalties from American Psychiatric Publishing, Inc. related to the sale of her book

• Discussion of off-label medication uses will occur in this presentation.

Faculty Publications
Objectives

- By the end of this presentation, the audience will be able to:
  - Identify 3 hormones impacting PMS/PMDD symptoms
  - Discuss 2 supplements or complementary treatments for PMDD
  - Discuss 3 dosing options for treating PMDD
  - Discuss 2 classes of psychotropic medications and their impact on pregnancy and lactation

Nodal events in the female lifespan

- Menarche (~ age 9-14)
- Pregnancy & Lactation (typically 20s & 30s)
- Peri-Menopausal Years (typically 40s & 50s)
- Menopause (average age 51...1 day in the life)
- Post-Menopausal Years (all the days after menopause)

Q: Dear Tokli:
   I know I'm walking on eggshells here, but when my girlfriend flies off
   the handle, I'm sure it's not smart to ask the question "Is this PMS
talking or is it you?" But sometimes I can't help myself as she can get
so irrational. Most of the time she is pretty laid back but boy can she
fly off the handle sometimes. I am starting to think it might be related
to her cycles but I am not sure how to bring it up without losing a limb.
I'd like to know if it's her time of the month or if she's actually a
maniac? Is there any way to ask without risking my life?

http://tokiilab.com/pms-or-is-she-really-a-maniac/
Our Inner Eve

80% of all women experience premenstrual exacerbation
(Pearlstein & Steiner, 2008)

Retrospectively, 25-68% of women with mood disorder experience PMS/PMDD
(Pearlstein & Steiner, 2008)

Prospectively, 55-65% of women with mood disorder experience PMS/PMDD
(Pearlstein & Steiner, 2008)

EPIDEMIOLOGY OF PMS/PMDD

- Daughters of women who experience PMS symptoms have 70% chance of experiencing PMS symptoms; likewise, if their mother was symptom free, daughters have a 2/3rds chance of being symptom free (Bueno & Walder, 1972)
- Of the 5% of women who meet criteria for PMDD, almost 6% meet the criteria for Bipolar I Disorder & 5% meet the criteria for Bipolar II Disorder (Shan et al., 2012)

Health Determinants & Risk Factors for PMS/PMDD

- Psychosocial/Cultural/Economic
  - diet & exercise
  - income
  - geographic location
- Biological/Physiological
  - hormones
  - serotonin
  - heredity
- Emotional
  - coping skills
  - lifestyle management
  - occupational stress
  - relational stresss

PMS/PMDD
Impact of PMS/PMDD on Functional Status & Quality of Life

- Symptoms parallel those of psychiatric illness (Yang et al., 2008)
- Quality of Life burden exceeds that of general population & women with chronic back pain (Yang et al., 2008)
- PMS/PMDD Symptoms contribute to significant functional impairment
  - Women who experience PMS/PMDD, regardless of a co-morbid psychiatric mood disorder-depression, anxiety or bipolar, may lose up to 10 years of their life related to their symptoms

Know Thy Body...Know Thy Mood

The menstrual cycle
Evaluating females across the lifespan

- Take a thorough menstrual history
  - Age at menarche
  - Frequency of menstrual cycle
  - Premenstrual Symptoms
    - How many days do symptoms last?
    - Physical, Emotional/Mood Symptoms or Both?
    - Severity of Symptoms
    - Impact of Symptoms on Daily Functioning

Take thorough sexual history

- Sexual orientation
- Age of first sexual intercourse
- Number of partners
- Contraceptive measures
- Pregnancy/Lactation history
- Libido/Orgasm history
- Discomfort during sex
- Sexual/Physical Abuse History
- History of Sexually Transmitted Diseases

Other evaluations/testing

- Medical history
- Medication history
  - supplements, vitamins, OTC, oral contraceptives, etc
- Routine lab work
  - CBC w/ Diff, Comprehensive Metabolic, Lipids, Hepatic Functions, Thyroid Functions,
  - βHCG (qualitative & quantitative)
- Reproductive hormone levels
  - Progesterone
  - Estrogen
  - Testosterone
  - Prolactin
  - FSH/LH
Menarche

- The onset of a female's first menstrual period
- Typically around the age of 12
- May occur as early as age 9 and as late as age 16
- Menstrual period may be irregular the first few months
- Menstrual period tends to last 3 to 7 days
- Menstrual periods tend to occur every 21 to 35 days with an average cycle of 28 days

Phases of the Menstrual Cycle

Follicular Phase

- Day 1 of menses to ovulation
- Estrogen increases & stimulates growth of the uterine lining (endometrium)
- Follicle stimulating hormone increases to stimulate growth of ovarian follicles, each containing an egg

http://therotundaramblings.wordpress.com/2008/11/05/premenstrual-syndrome-pms-symptoms-and-treatment/
Ovulatory Phase

- Starts about day 14 after follicular phase
- Midpoint in menstrual cycle
- Rise in estrogen triggers surge in luteinizing hormone
- Dominant follicle releases egg to ovary (Ovulation)
- Increase in amount of mucous from cervix
Luteal Phase

- Starts after ovulation
- Upon release of egg, empty follicle becomes corpus luteum
- Corpus luteum secretes progesterone to prepare fertilized egg for implantation
- If egg is fertilized by sperm, woman is considered pregnant
- If not, egg passes through uterus and uterine lining sheds and the next menstrual period begins

Some females at the period of the catamenia undergo a considerable degree of nervous excitement, morbid dispositions of mind are displayed...a wayward & capricious temper, excitability in feelings, moroseness in disposition, a proneness to quarrel with their dearest relatives & sometimes a dejection of mind approaching to melancholia

JC Pritchard (1835), Page 207
The Role of Hormones

- Many hormones involved in symptoms of PMS/PMDD:
  - Prostaglandins
  - Endorphins
  - Aldosterone
  - Insulin
  - Prolactin
  - Serotonin
  - GABA

Prostaglandins

- Pro-inflammatory Chemicals made in all cells in the body
- Modified forms of Unsaturated Fatty Acids

- Contribute to the following symptoms:
  - Breast pain
  - Fluid retention
  - Cramping
  - Headaches
  - Irritability
  - Depression
Endorphins

- “Feel Good” Hormone released from the pituitary gland
- Decreases contribute to the following symptoms:
  - Increased levels of pain
  - Depression

Aldosterone

Increase in Adrenal Hormone after ovulation
normal

- Fatigue
- Dizziness on standing
- Brain fog
- Low blood pressure
- Dehydration
- Palpitations
- Salt craving

Produces the following symptoms of PMS:
- Fluid retention
- Weight gain
- Breast swelling
- Headaches

INCREASED GLUCOSE UTILIZATION IN THE CEREBELLUM DURING LUTEAL PHASE IN WOMEN WITH PMDD

Insulin
- Hormone produced by the pancreas
- Women tend to be sensitive during premenstrual time through ovulation
- May experience decrease in blood sugar contributing to the following symptoms:
  - Headaches
  - Irritability
  - Changes in mood

Prolactin
- Hormone produced by pituitary gland
- May interfere with ovulation
- Increase causes the following symptoms:
  - Irregular menstrual cycles
  - Breast tenderness
  - Lactation

Serotonin
- One of the Brain's trimonoamine neurotransmitters
- May impact PMS mood related symptoms & sensitivity to changes in estrogen & progesterone
- Reduced levels contribute to the following symptoms:
  - Irritability & Anger
  - Depressed mood
  - Tearfulness
  - Anxiety
GABA (gamma-amino butyric acid)

- Inhibitory neurochemical
- Regulates cognitive function & affect
- May be useful to reduce anxiety & pain related symptoms of PMS/PMDD

Definitions of Premenstrual Syndrome (PMS) & Premenstrual Dysphoric Disorder (PMDD)

- Premenstrual Syndrome (PMS)
  - Severe symptoms: anger, irritability, mood swings, cramping, bloating, sadness-occurring in the luteal phase which cause distress & impact functioning

- Premenstrual Dysphoric Disorder (PMDD)
  - ≥ 5 luteal phase symptoms with at least 1 mood symptom (anger, irritability, depression, anxiety, lability)
  - 2 cycles of daily charting confirming symptoms
  - Evidence of functional impairment

Differential Diagnosis of PMDD

- Affective disorders
- Anxiety, panic attacks
- Personality disorders
- Anorexia/ Bulimia
- Endometriosis
- Anemia
- Polycystic ovarian syndrome
- Thyroid disorders
- Hyperprolactinemia

13 THINGS PMS STANDS FOR:
1. PASS MY SHOTGUN
2. PSYCHOTIC MOOD SWING
3. PERPETUAL MUNCHING SPREE
4. PUFFY MID-SECTION
5. PEOPLE MAKE me SICK
6. PROVIDE ME with SWEETS
7. PARDON MY SOBBLING
8. PIMPLES MAY SURFACE
9. PASS MY SWEATS
10. PISSEY MOOD SYNDROME
11. POOR MEN SUX
12. PACK MY STUFF
13. POTENTIAL MURDER SUSPECT

http://www.butterfunk.com/pictures-13-pmsquotes.htm
### Impact of Psychiatric Illness on Pregnancy Outcomes

<table>
<thead>
<tr>
<th>Illness</th>
<th>Teratogenic Effects</th>
<th>Obstetric</th>
<th>Neonatal</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>No studies</td>
<td>Low dev scores, slow mental</td>
<td>Low forces, fetal distress, preterm delivery,</td>
<td>Benzoes, antidepresants, therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>development, inadaptability</td>
<td>miscarriage</td>
<td></td>
</tr>
<tr>
<td>Major Depression</td>
<td>No studies</td>
<td>Low birth wgt, postnatal</td>
<td>Crying, NICU, cortisol &amp; catecholamine</td>
<td>Antidepressants, psychotherapy, ECT</td>
</tr>
<tr>
<td>Bipolar</td>
<td>No studies</td>
<td>Same as major depression, high risk for post partum psychosis</td>
<td>Same as major depression</td>
<td>Lithium, anticonvulsants, antipsychotics, ECT</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Congenital malformation especially CV</td>
<td>Preterm delivery, low birth wgt, placental abnormalities, antenatal hemorrhage</td>
<td>Same as postnatal death</td>
<td>antipsychotics</td>
</tr>
</tbody>
</table>

### Pregnancy & lactation

- Mood changes are common during pregnancy
  - Typically flares between 6 & 10 weeks gestation
  - Eases during second trimester
  - Increases again toward end of pregnancy
  - Pregnancy is not protective against MDD relapses
Fluctuations in hormones & neurotransmitters
- Increased estrogen maintains uterine lining
- Increased progesterone produced by the placenta
- Increased circulating levels of estrogen & progesterone contribute to “emotional rollercoaster” some women experience during pregnancy whether or not they had mood symptoms prior to pregnancy

Severe drop in progesterone & estrogen after birth so that milk production can begin may also contribute to the “baby blues” or the more serious post-partum depression
- During lactation women produce lower levels of stress response hormones in the hypothalamus which may protect women who are vulnerable to depression
- Hormone Oxytocin may have anti-depressant &/or stress reducing properties

Treating females across the lifespan
FDA Approved Medications for Premenstrual Dysphoric Disorder

- Serafem (fluoxetine)
- Paxil CR (paroxetine controlled-release)
- Zoloft (sertraline)
- YAZ (drospirenone/ethinyl estradiol OCP)

SSRI Dosing strategies

- Continuous Dosing
  - Maintain same dose continuously throughout month

- Intermittent (Luteal Phase) Dosing
  - Luteal phase dosing
  - Dosed 10 to 14 days prior to menses & 1 to 2 days after

- Semi-intermittent Dosing
  - Most complex regimen, least studied
  - Continuous dosing with increased dose during luteal phase

Sarafem (fluoxetine) Dosing

- Continuous
  - Daily dosing of 20 to 80mg/day

- Intermittent (Luteal Phase)
  - 20mg/day on days 15 to 28 of cycle & 1st day of menses
  - No proven benefit above 20mg/day

- Semi-Intermittent (OFF LABEL)
  - Base dose of 20 to 60mg/day
  - 5 to 14 days prior to menses increase dose by 20mg/day
  - Resume base dose at onset of menses
**Paxil CR (paroxetine CR) Dosing**

- **Continuous**
  - Daily dosing of 12.5mg qAM
  - May increase by 12.5mg per cycle to max of 37.5mg/day
- **Intermittent (Luteal Phase) – OFF LABEL**
  - Dose 12.5 to 25mg daily on days 15 through 28 of cycle
- **Semi-Intermittent (OFF LABEL)**
  - Base dose of 12.5 to 50mg per day
  - 5 to 14 days prior to menses increase dose by 12.5 to 25mg daily, at onset of menses resume base dose

**Zoloft (sertraline) Dosing**

- **Continuous**
  - Take daily in doses from 50mg to max 150mg/day
  - Increase by 50mg each cycle if no relief
- **Intermittent (Luteal Phase)**
  - Daily dose of 50mg on days 15 to 28 of cycle
  - Max 100mg/day
  - Begin each cycle with 50mg x 3 days
- **Semi-Intermittent (OFF LABEL)**
  - Base dose of 25mg to 200mg daily
  - 5 to 14 days prior to menses, increase dose by 50 to 100%
  - At onset of menses, decrease dose back to base dose

### SSRI Dosing Guidelines for PMDD

<table>
<thead>
<tr>
<th>SSRI Antidepressant</th>
<th>Starting Dose</th>
<th>PMDD Dosing Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine (Prozac/Serafem)</td>
<td>10mg</td>
<td>10-60mg</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>25mg</td>
<td>25-200mg</td>
</tr>
<tr>
<td>Paroxetine CR (Paxil CR)</td>
<td>12.5mg</td>
<td>12.5-25mg</td>
</tr>
<tr>
<td>Citalopram (Celexa)</td>
<td>10mg</td>
<td>10-20mg</td>
</tr>
<tr>
<td>Escitalopram (Lexapro)</td>
<td>5mg</td>
<td>5-20mg</td>
</tr>
</tbody>
</table>
YAZ (drospirenone/ethinyl estradiol)

- Continuous Dosing
  - Must be taking on a daily basis to regulate menstrual cycle by altering hormonal levels
  - Drospirenone, analog of diuretic spironolactone, serves as diuretic to relieve symptoms
  - 24 active tablets + 4 placebo

- Side Effects/Risks
  - Category X for pregnancy DO NOT USE
  - Headache, nausea, weight changes, bloating, breakthrough bleeding, breast tenderness, elevated BP, thromboembolism, myocardial infarction, stroke/TIA

OFF LABEL Psychotropics for PMDD

- Celexa (citalopram)
- Lexapro (escitalopram)
- Remeron (mirtazapine)
- Effexor XR (venlafaxine)
- Anafranil (clomipramine)
- Luvox/Luvox XR (fluvoxamine)
- Paxil (paroxetine non-controlled release)

Off label Anxiolytics for PMDD

- Studies show Luteal phase dosing may decrease PMS symptoms
- Dosing BID to TID at onset of symptoms to cessation of symptoms (1 to 2 days after start of menses)
  - Xanax (alprazolam) 0.125 to 0.5mg/dose
  - Klonopin (clonazepam) 0.25-0.5mg/dose
  - Ativan (lorazepam) 0.25-0.5mg/dose
Complementary Treatments

- **Vitamin B₆ 50-100 mg/day**
  - One systematic review of 9 RCTs suggests that Vitamin B₆ supplementation relieved PMS sx by more than 2-fold compared with placebo

Vitamin B₆
Food sources of vitamin B₆ (pyridoxine) include beans, legumes, nuts, eggs, meats, fish, breads and cereals.

Complementary Treatments

- Calcium 1000 to 1200 mg/day has been shown to reduce PMS symptoms
- A 2009 systematic review of 62 studies of herbal supplements, vitamins, and minerals with claims of PMS symptom relief found that data was:
  - Insufficient to evaluate the effectiveness of ginkgo, saffron, St John's wort, soy, or vitamin E
  - Sufficient to suggest that chasteberry and vitamin B6 may reduce PMS sx
    - (Whelan, Jurgens, & Naylor, 2009)

Complementary Treatments

- Chasteberry
  - Small tree grown in southern Europe
  - RCT (N=170) women treated with 20mg to 100mg of chasteberry daily were more likely to have a decrease in PMS sx compared to placebo (52% vs 24%)
  - No patients withdrew from the study due to adverse effects
    - Schellenberg (2001)
Prescribing during pregnancy

- **RISKS**
  - Most medications Pregnancy Category C
  - Limited clinical trials with pregnant women
  - Potential transfer of drug causing adverse effects in newborn
  - If possible, avoid during 1st trimester with rapid fetal neural tube development

- **BENEFITS**
  - Decreased mood lability
    - A stressed mom = A stressed baby
    - Stressed mom’s are at risk for premature &/or lower birth weight infants
  - Improve mother's level of functioning
  - Many retrospective studies of mothers & infants
  - Potentially protective for post-partum depression

Prescribing during lactation

- **Risks**
  - Potential transfer of minute amounts of drug to infant
  - Limited clinical trials in women who nurse their babies

- **Benefits**
  - May protect mother against post-partum depression
  - Potentially greater milk production if mother is not stressed or anxious
  - May decrease the mother’s anxiety allowing for a better breast feeding experience
Antidepressants During Pregnancy & Lactation

- Most Medications Category C
  - Selective Serotonin Reuptake Inhibitors (SSRIs)
  - Tricyclic Antidepressants (TCAs)
- Literature defining SSRI Efficacy and Safety in Pregnancy & Lactation
  - Dr Zachary Stowe, Emory University
- No confirmed Birth Defects or Delivery Complications
- Decreased serum concentrations across pregnancy
- Potential Neonatal “withdrawal” symptoms

Wellbutrin (bupropion)

- Category C—previously Category B
- May improve maternal energy, motivation & interest
- May continue throughout 3rd trimester
- Continue/titrate dose upon delivery to minimize post-partum depression

Zoloft (sertraline)

- Dose at lowest possible strength to reduce maternal symptoms, attempt to reduce dose ~ 1 week prior to delivery date
- Potential newborn “withdrawal” symptoms, especially at maternal higher doses
- Resume maternal dosing after delivery to minimize risk of post-partum depression
Prozac (fluoxetine)

- Category C—previously category B
  - Use caution if pregnancy > 20 weeks gestation
    - Neonatal persistent pulmonary HTN > 20 weeks gestation
    - Neonatal withdrawal &/or serotonin syndrome 3rd trimester
    - Long half-life & active metabolites

Paxil/CR (paroxetine/CR)

- Category D in Pregnancy
  - Previously category C now Category D
    - Teratogenicity in 1st trimester
    - Neonatal persistent pulmonary HTN > 20 weeks gestation
    - Neonatal withdrawal &/or serotonin syndrome in 3rd trimester
    - Positive evidence of human fetal risk
    - Congenital malformation
    - Cardiovascular risk
    - Maternal benefit may outweigh fetal risk in serious or life-threatening situations

Impact of SSRIs on Infants exposed during Woman’s Pregnancy

- May experience serotonergic “overstimulation” effects during first 4 days of life
- Observed symptoms included:
  - tremor
  - restlessness
  - rigidity
- Despite impact on infant, SSRI use is recommended to avoid severe, desabling depression in pregnant women

Laine K, Heikkinen T, Ristikari T, Lair R J. Effects of exposure to maternal antidepressants on platelet 5HT2 receptors in newborns. Arch Gen Psychiatry. 2003;60:720–726
Impact on Children born to Women who took Antidepressants during Pregnancy

- Evaluations of children between 18 & 86 months of life
- Exposed children experienced no significant differences in:
  - Intelligence quotient
  - Temperament
  - Mood
  - Activity levels
  - Distractibility
  - Behavior

Nulman I, Rovet J, Stewart DE, et al. Neurodevelopment of children exposed in utero to antidepressant drugs. *N Engl J Med.* 1997;336:258–262

Anxiety & Insomnia During Pregnancy & Lactation

- Benzodiazepines Category D
  - Avoid During 1st Trimester
  - Ativan (lorazepam) may be best
    - no active metabolites
    - Shorter half-life
  - Possible Cleft Lip/Palate
  - Floppy Infant Syndrome
  - Neonatal Withdrawal Syndrome
  - Infant lethargy during nursing → weight loss

- Buspar (buspirone) Category B
  - No known impact
- Benadryl (diphenhydramine) Category B
  - Possibly safest anxiolytic & hypnotic
- Ambien (zolpidem) Category C—prior B
  - Favored during nursing due to rapid excretion
  - No known impact
- Trazodone Category C
  - Presumably safe with no known impact
Bipolar During Pregnancy

- **Most Medications Category D**
  - Lithium
  - Anticonvulsants
    - Lamictal (lamotrigine)
    - Tegretol (carbamazepine)
    - AVOID Depakote (Valproate)
  - Antipsychotics
    - First Generation (Conventional)
    - Second Generation (Atypicals)

**Impact of Lithium on Pregnancy & Lactation**

- Best to use Sustained Release Lithium
- Increased incidence of heart defects
- Decreases serum concentration across pregnancy
- IV fluids during delivery to ↓ risk of toxicity
- If Nursing, monitor CBC, Thyroid hormones, BUN, Creatinine & Li**+** level in both mother & infant

**Impact of Anticonvulsants on Pregnancy & Lactation**

- Best options are lamotrigine (Lamictal) & carbamazepine (Tegretol)
- Increased incidence of birth defects
- Decreases serum concentration across pregnancy
- Supplement Folate & Vitamin K during pregnancy
- No issues noted during delivery
- Newborn may require Vitamin K at birth
- If Nursing, monitor CBC, Liver Functions & Drug level, if applicable, for both mother & infant
Impact of Antipsychotics on Pregnancy & Lactation

- Best option is haloperidol (Haldol)-long history
- Newer Atypicals have shown safety & efficacy in anecdotal studies
- No confirmed incidence of birth defects
- Avoid anticholinergics for SEs during pregnancy
- Possible risk for neuroleptic malignant syndrome & intestinal obstruction in newborn
- No evidence of complications with lactation

Jenny

- Began “episodes” around age 11 at onset of puberty
- Started menses at age 13.3 years
- Menses irregular x 14 months
- Jenny is now 16 ½ years old
- At least monthly episodes of anger & irritability coupled with sadness & crying lasting about 9 days then symptoms abruptly stop day 2 of menses
- Jenny’s mother just turned 50 years old
- Jenny’s maternal grandmother is 71 years old

- Mom: “these episodes are tearing our family apart...I’m ready to send her away...she must be Bipolar, she had all the symptoms I read in the women’s magazine”
- Jenny: “I can’t help it, my stomach hurts, I’m miserable, I need to sleep, I can’t concentrate, everything makes me so mad, then it just stops”
- Jenny’s grandmother: “I think they all have the family curse, the way they go at it, my daughter’s [Jenny’s mom] just as moody”
Fluctuations in female hormones across the lifespan may mimic &/or induce alterations in mood, behavior & cognition.

Psychotropic medications, especially the SSRI’s, have proven safe & effective in relieving symptoms of PMS/PMDD, reducing risk of post-partum depression & minimizing discomfort of peri-menopausal symptoms.

Working with your patient on creative management strategies may improve the female’s quality of life despite the hormonal influences.
References

- http://www.ePocrates.com
- http://www.healthopedia.com/drugs/detailed/benzodiazepines
- http://iheartguts.com/tag/follicle-stimulating-hormone

Faculty Contact

Laura G. Leahy, DrNPC, APRN, PMH-CNS/FNP, BC
Family Psychiatric Nurse Practitioner
NEIGlobal Master Psychopharmacologist

APNSolutions, LLC
123 Egg Harbor Road
Suite 703 Tower Commons
Sewell, New Jersey 08080
Phone/Text: 856.556.0860
Fax: 856.956.1116
Email: LGLeahy@APNSolutions.com
Website: www.APNSolutions.com