Hormones and Mood in PMDD and Pregnancy

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No other financial disclosures.
Educational Objectives

• Diagnosis/treatment of PMDD vs PMS vs PME
• Better understanding of the menstrual cycle in relation to mood symptoms
• Understanding the second mechanism of SSRI’s
• How to treat depression in pregnancy and risk factors to review with women during pregnancy/delivery
Menstrual Cycle

Sex steroid changes in human menstrual cycle.
Brain Variability Controlled by Ovarian Hormones

Depending on where a woman is in her cycle, there is variability in the following:

- Mood
- Verbal performance
- Sexual interest
- Visual-spatial performance

-L. Brizendine, The Female Brain, 2006
Menstrual Cycle

Sex steroid changes in human menstrual cycle.
Mood Changes Across the Menstrual Cycle

- Best

- Worst

E M L
Follicular

E M L
Luteal

PMDD vs Normal PMS

Normal PMS (Premenstrual Syndrome):
- 80% of women
- Mild to moderate emotional fluctuations

PMDD (Premenstrual Dysphoric Disorder):
- 8-10% of women
- Severe moods swings, depressed mood, irritability, or anxiety and 4 other symptoms (occurring exclusively during the luteal phase (weeks 3-4) and remitting within a few days of the onset of menses)
DSM-IV Research Criteria For PMDD

-It is considered “Depression NOS”

A. In most menstrual cycles during the past year, five (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week postmenses, with at least one of the symptoms being either (1), (2), (3), or (4):
   1. Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
   2. Marked anxiety, tension, feelings of being "keyed up" or "on edge"
   3. Marked affective lability (e.g., feeling suddenly sad or tearful)
   4. Persistent and marked anger or irritability or increased interpersonal conflicts
   5. Decreased interest in usual activities (e.g., work, school, friends, hobbies)
   6. Subjective sense of difficulty in concentrating
   7. Lethargy, easy fatigability, or marked lack of energy
   8. Marked change in appetite, overeating, or specific food cravings
   9. Hypersomnia or insomnia
   10. A subjective sense of being overwhelmed or out of control
   11. Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating," or weight gain

B. The disturbance markedly interferes with work or school or with usual social activities and relationships with others

C. The disturbance is not merely an exacerbation of the symptoms of another disorder (although it may be superimposed on any of these disorders).

D. Criteria A, B, and C must be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles.
Daily Record of Symptoms

Circle the dates of your period.

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Menstrual Cycle Week and All Psychiatric Admissions

- If random, admissions of women to psychiatric hospitals for all psychiatric diagnoses would be 25% on each week of the menstrual cycle

Menstrual Cycle

Sex steroid changes in human menstrual cycle.
PMDD

Progesterone $\rightarrow$ Allopregnanolone (ALLO)

soothing, like Valium

- **ALLO** = a neuroactive metabolite of progesterone and works on GABA (gamma-aminobutyric acid) receptors in the brain
- Hence, ALLO is a powerful anxiolytic, anticonvulsant, and anesthetic agent which decreases anxiety and depression.
- Barbituates, benzodiazepines and alcohol also work at this receptor

-Lisa Griffin, 1999
PMDD

Progesterone → Allopregnanolone (ALLO)

soothing, *like Valium*

-Prozac, Paxil and Zoloft were found not only to increase Serotonin, but also to increase ALLO production by activating the enzyme that converts progesterone to ALLO (by decreasing the enzyme’s $K_m$ 10- to 30-fold)

-Imipramine (Tofranil) had no effect on ALLO production

-Works almost immediately

Journal:

-Lisa Griffin, MD, PhD and Synthia Mellon, PhD.

Selective serotonin reuptake inhibitors directly alter activity of neurosteroidogenic enzymes.

PMDD

2 Main Treatments

- **SSRI’s:**
  - Either 7-10 days before menses to help boost ALLO, or daily if also depressed
  - Or, you can increase SSRI dose in luteal phase

- **Hormones:**
  - Start an OCP, or change to one with a progesterone good for mood
  - Take OCP continuously
    - Women are sensitive to hormones in different ways – some to the hormone fluctuation, some to the amount, and some to the progestin type
# All Possible PMDD Treatments

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Ovulation Suppression</th>
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<tbody>
<tr>
<td>- SSRI*</td>
<td>- OCP’s*</td>
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<tr>
<td>- SNRI*</td>
<td>- GnRH Agonists (Lupron)**</td>
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<tr>
<td>- Clomipramine**</td>
<td>- Danazol (inhibits LH/FSH)</td>
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<td>- Oophorectomy</td>
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<th>Anxiolytics</th>
<th>Other</th>
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<td>- BZD**</td>
<td>- Exercise</td>
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<td>- Buspar**</td>
<td>- Vit B6</td>
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<td>- Calcium**</td>
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<td>- NSAIDS</td>
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<td>- CBT*</td>
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<td>- Diet</td>
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<td>- Chasteberry (may reduce FSH or Prolactin)</td>
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*Efficacy in double-blind studies of PMDD
**Efficacy in double-blind studies of PMS

-Teri Pearlstein, M.D. Warren Alpert Medical School of Brown University, APA Conference 2008
Advantages of SSRI’s

- Fluoxetine, Sertraline and Paroxetine CR are FDA approved for PMDD
- Both continuous and intermittent dosing effective
- Intermittent Fluoxetine is effective for mood symptoms at both 10 and 20 mg. 20 mg is more effective for physical symptoms than 10 mg.*
- No discontinuation symptoms with intermittent dosing
- Dosing strategies can be tailored to a woman’s preferences

-Teri Pearlstein, M.D. Warren Alpert Medical School of Brown University, APA Conference 2008
Intermittent Fluoxetine in PMDD

Mean change from baseline

DRSP Mood Cluster

DRSP Physical Cluster

DRSP Social And Functional Impairment Cluster

Placebo

Fluoxetine 10 mg

Fluoxetine 20 mg

DRSP = Daily Record of Severity of Problems
Concerns With SSRI’s

- Potential long-term effects: weight gain, sexual SEs
- Lower doses are less effective for physical symptoms than for mood/anxiety symptoms
- Tolerance to dose over time?
- Symptom recurrence after dose discontinuation?
- Pregnancy during treatment (may not want to choose Paroxetine CR if pregnancy is a possibility)

-Teri Pearlstein, M.D. Warren Alpert Medical School of Brown University, APA Conference 2008
Other Luteal Phase Treatments

- Alprazolam up to 0.25 mg tid prn (taper at menses), or Ativan 0.5 mg prn
- Spironolactone 50 mg bid for edema
- Bromocriptine 2.5 mg for breast pain/tenderness (mastalgia)
- NSAIDS for cramps/leg pain

-Teri Pearlstein, M.D. Warren Alpert Medical School of Brown University, APA Conference 2008
Which birth control pill is good for mood?

- Lower progestin potency:

  Ortho Evra patch
  Ovcon 35
  Ortho-TriCyclen
  Othro-Cyclen
  Brevicon
  Modicon

  Necon 1/35
  Alesse
  Levlite
  Tri-Levlen
  Triphasil
  Trivora

Which OCP is good for mood?

- Women are sensitive to hormones in different ways – some to the progestin, some to the amount and some to the hormonal fluctuation.

- Seasonale or any monophasic OCP taken continuously can stabilize mood.

- Women who are sensitive to hormonal fluctuation should avoid triphasic OCP’s.

- It takes about 2 cycles to see if a certain OCP will work.
• Contains:
  – Drospirenone 3 mg
  – Ethinyl estradiol 20 µg (Yasmine has 30 µg)

• Shortened hormone-free interval:
  – 24 active pills, 4 inactive pills (Yasmine has 21 active/7 inactive pills)

• Efficacy was expected for physical symptoms. But, surprisingly, efficacy in mood and irritability was also seen with YAZ

Drospirenone

- Derived from 17 alpha spirolactone
- Analogue of spironolactone
- Has antimineralocorticoid activity (leads to water diuresis)
- Increases K+ retention, Na+ and water excretion
- Has antiandrogenic activity
All OCPs (with estrogen) Can Lower Libido

• The oral estrogen in OCPs increases SHBG (Sex Hormone Binding Globulin)

• Increased SHBG → lower free testosterone

• Oral estrogen and thyroid increase SHBG
  – Oral estrogen passes through the liver (vs some patches or endogenous estrogen) and binds up SHBG, increasing production of SHBG. Progesterone is bound by transcortin.

PMDD In Summary

- PMDD: 8-10% of women
- The current hypothesis: women who experience PMDD are sensitive to the change in estrogen and progesterone
- SSRIs are effective treatments with daily or luteal phase dosing—higher doses are more effective for physical symptoms
- YAZ® has similar efficacy to SSRI’s, both for physical and mood symptoms
- The big question: should women with PMDD be treated with OCP’s or SSRI’s first?
Disorders with Premenstrual Exacerbation (PME)

- Affective disorders
- Anxiety disorders
- Psychotic disorders
- Eating disorders
- Personality disorders
- Substance abuse
- Migraine
- Allergies
- Asthma
- Seizures
Sample Question:

Premenstrual dysphoric disorder (PMDD):

A. is associated with hormonally abnormal menstrual cycles
B. is associated with abnormal levels of hormones
C. is associated with changing levels of sex steroids that accompany ovulatory menstrual cycles
D. is seen in approximately 50% of women
E. is not treated with SSRI’s
F. all of the above
Sample Question:

Premenstrual dysphoric disorder (PMDD):

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D. is seen in approximately 50% of women
E. is not treated with SSRI’s
F. all of the above
Sample Case: “Help my PMDD”

• 27 y/o married woman
• “I have a serious case of PMDD. I get low energy, irritable and depressed. I start fights with my husband and often have to skip work. Then, when my period comes, I feel fine.”
• “I have been using YAZ OCP and Effexor XR. It kinda helps, but not 100%.”
Things to Consider

- PMS charting
- Check labs: TSH, cbc to r/o anemia
- Meds: educate about SSRIs being 1st choice for PMDD (and safety in pregnancy since she’s a young, married woman)
  
  - Effexor not ideal: SSRIs are 1st line (though some data that Effexor and Clomipramine also help with PMDD)
  
  - Since Effexor not working great anyway, consider Zoloft 25 mg or Prozac 10 mg
  
- Discuss her future plans for pregnancy
- Therapy
Things to Consider

- **Ask about libido**: She’s on YAZ, which can lower her libido (via 2 mechanisms!!!)
- If unsure, you can also check libido labs:
  - Free and total testosterone
  - SHBG
  - TSH
  - Prolactin
  - DHEA-S
- May want to switch to another OCP or the Mirena or Copper IUD.
The Mommy Brain: Hormones, Pregnancy and Mood

- The smell of a newborn baby stimulates the woman to produce oxytocin – a love potion creating baby lust
  - Oxytocin is also released when talking to friends, or creating a connection
  - “A feel good” hormone – released in bonding and during orgasm

- Throughout pregnancy, a woman is marinated in neurohormones manufactured by the fetus and placenta

-L. Brizendine, The Female Brain, 2006
The Mommy Brain: Hormones, Pregnancy and Mood

• **Progesterone**: Spikes from 10-100x normal!

• Thirst and hunger centers on full blast

• Women become sensitive to smells, especially of foods—to avoid eating something that could harm the fragile fetus

-L. Brizendine, *The Female Brain*, 2006
The size and structure of a woman’s brain change during pregnancy.

- Between 6 months to the end of pregnancy, fMRI scans show that her brain is shrinking!
  - Restructuring and building new maternal circuits

This state gradually returns to normal 6 months after giving birth.

Depression and Pregnancy

• 1-2 out of every 10 pregnant women have symptoms of major depression

• Women who have been depressed before are at higher risk

• Range of treatments:
  – Support groups, light therapy, medications and ECT
  – Individual therapy is highly recommended

Depression and Pregnancy

• Depression carries serious risks:
  – poor nutrition
  – poor self-care
  – substance abuse
  – SI

• Can lead to premature birth, low birth weight and developmental problems

• Depressed mothers are often less able to care for themselves and/ or their children, or to bond with their children
What are the symptoms of PPD?

• MDE symptoms 1 month to 1 year postpartum

• Things other than depression can cause some of these symptoms
  – Changes in appetite and trouble sleeping are common in pregnancy
  – Medical conditions, such as anemia and hypothyroidism, can cause low energy
Depression and Pregnancy

- What I tell women: the risks…
  - During pregnancy
  - During delivery
  - After delivery
During Pregnancy

• 2006 study—pregnant women with MDD are very likely to become ill again if they stop taking their medication

• Many studies have found no link between antidepressants and serious malformations in newborns

• 2005—FDA issued a warning about Paxil: taking the drug during the first three months of pregnancy may increase the risk of birth defects, particularly heart defects

During Pregnancy

- SSRI’s have been linked to small increased risks of:
  - **heart defects** (0.9% for 1 SSRI, 2.1% >1 SSRI, vs 0.5%)
  - **hydronephronsis** (kidney defects)
  - **cleft palate** (5% vs 2-4%)

- 2012 study—found
  - Untreated maternal depression was associated with slower rates of fetal body and head growth
  - Fetuses from mothers treated with SSRIs had no delay in body growth but did have delayed head growth and were at increased risk for preterm birth

During Pregnancy: Autism Risk

• 2011 study—examined fetal SSRI exposure in 298 children with autism spectrum disorders (ASDs) and 1507 control children

• Possible association between SSRI exposure and childhood ASD

• Things to consider
  – Rx use not confirmed
  – dx from records not interview
  – factors not controlled for (tobacco, alcohol, drug use)
  – mothers of ASD kids were much older
  – need to distinguish role of meds vs underlying dz

During Pregnancy (cont)

- "Clinicians and patients need to balance the small risks associated with SSRIs against those associated with undertreatment or no treatment."
  -Sept 2009, Pederson et al., *British Medical Journal (BMJ)*

- Although *relative risks* for certain anomalies are elevated with SSRI use, *absolute risks* are low. For example, excess risk for a major cardiovascular anomaly attributable to SSRI use is 37 additional cases per 10,000 women.
  -July 2011, Malm et al., *Obstetrics and Gynecology*
During Delivery

**Neonatal Abstinence Syndrome (NAS):**
- Baby “withdrawal” from SSRIs
  - breathing or feeding problems, jerky movements, seizures, irritability, abnormal crying, tremor
  - Sx usually subside from 48 hours to a few days

**Persistent Pulmonary Hypertension of the Newborn (PPHN):**
- 2006 study—babies exposed to SSRIs in late pregnancy (after 20 weeks) may be more likely to have PPHN
- Since then, we have 7 studies total: 3 showed no link between PPHN and SSRI’s, the other 4 showed some increased risk
- FDA will update their SSRI drug label to reflect the conflicting results
- **Key point:** Factors associated with depression itself (vs. SSRI exposure) can increase PPHN risk (obesity, smoking, premature birth, cesarean section)

-Ruta Nonacs. “SSRI’s and PPHN: the FDA revises its warning.” MGH Center for Women’s Health website, Jan 17, 2012.
During Delivery (cont)

- Both untreated depression/ anxiety and SSRI exposure have been correlated with early or preterm birth
- 2009 study—SSRI use in late pregnancy correlated with an elevated risk of gestational hypertension and preeclampsia in the mother

After Delivery

• No link to serious problems with language, behavior or intelligence

• There has been no data reported on long term effects of antidepressants on the baby’s well being

Choosing an Antidepressant

• We don't know all the answers. No drug is entirely safe. A woman and her health care team must look at her case and carefully weigh risks/benefits of:
  – The drug
  – Other treatments
  – The risk of untreated depression

• If a woman has been or is currently stable on a certain SSRI, that medication is usually continued (unless it is Paxil, which is generally contraindicated)

• Zoloft and Prozac are often chosen b/c Zoloft has the lowest levels in breast milk and Prozac’s long half-life
Important Points

• Pt should be followed closely by psychiatrist and ob/gyn
• Prenatal vitamins and folic acid
• Check thyroid, CBC and other lab work
• Deliver the baby in a hospital to adequately monitor and assess any possible delivery complications
• Stress reduction techniques and individual therapy
• Be on the lowest number of meds and the lowest dose necessary
• Start low and go slow
Within the first month after giving birth: 10% of women will have had ‘Postpartum Depression’

- Huge ‘crash’ in hormones after pregnancy

- **Postpartum**: the brain and ovaries experience the re-establishment of menstrual cycle hormone pulses just as during the onset of puberty
Psychiatric Admissions in 2 Years Before and After Delivery

*Rate of psychiatric admissions in the 2 years before and after delivery in a population of 470,000 people with 54,087 births in a 12-year period
Postpartum Depression

- **Postpartum Depression:**
  - Technically, onset is within 4 weeks after childbirth, but can be seen up to 1 yr later (in DSM, it’s a specifier: “With Postpartum Onset”) 
  - 10-15% of women will experience postpartum depression within the 1st month after giving birth

- ‘Baby blues’:
  - Affect up to 80% of women during the 10 days postpartum (usually lasts 2 weeks)
  - These are transient, do not impair function, and don’t meet MDD criteria
Sample Question:

Which antidepressant is found to be transmitted in the lowest amounts in breast milk?

A. Prozac  
B. Celexa  
C. Zoloft  
D. Lexapro  
E. Klonopin
Sample Question:

Which antidepressant is found to be transmitted in the lowest amounts in breast milk?

A. Prozac
B. Celexa
C. Zoloft
D. Lexapro
E. Klonopin
Sample Case: “I want to stop my meds”

- 33-year-old married woman
- Had a MDE 1 yr ago
- She responded well to Zoloft 100 mg and has been symptom free for 9 months.
- She wants to stop her Zoloft so she can get pregnant.
- What do you do?
Consider a Trial off Meds If:

- There was only one previous MDE
- It occurred more than 9 months ago
- It resolved quickly with medication
- She has been functioning well for more than 6 months
- No family history
- No current stressors
- Good financial and emotional supports
- Good insight into her illness so she can recognize early signs
- She is cooperative with treatment and willing to restart meds if needed
- At its worst, there was no significant decompensation or SI
Educational Objectives

• Diagnosis/treatment of PMDD vs PMS vs PME.
• Better understanding of the menstrual cycle in relation to mood symptoms.
• Understanding the second mechanism of SSRI’s.
• How to treat depression in pregnancy and risk factors to review with women during pregnancy/delivery.
The End

Thank You!

A special thank you to Dr. Louann Brizendine