“Mood Disorders in Women: From Menarche to Menopause”

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Life Time Financial Disclosure / Conflict of Interest

Zachary N. Stowe

- No Non-Academic / External Relationships since June 2008
- Off label uses of Medications will be Discussed
- Federal NIH (current):
  - P50-77928 (Stowe) - Perinatal Stress and Gene Influences: Pathways to Infant Vulnerability (TRCBS)
  - MONEAD (Meador) - Neurodevelopmental Effects of ‘in utero’ Exposure to AEDs

Life Time
- Speakers' bureau
  - Eli Lilly and Company; GlaxoSmithKline; Pfizer, Inc; Wyeth-Ayerst Pharmaceuticals, Inc
- Advisory board
  - GlaxoSmithKline, Bristol Myer Squibb
- Faculty Development/Training Advisory Committee
  - Wyeth-Ayerst Pharmaceuticals, Inc
- Research/educational grants
  - GlaxoSmithKline; Pfizer, Inc; Wyeth-Ayerst Pharmaceuticals, Inc
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- Catherine Monk, PhD (Columbia)
Learning Objectives:

• Be familiar with the bi-directional interactions between hormones and mood disorders and/or treatment.
• Understand the unique interactions between the reproductive life cycle and mood disorders.
• Appreciate the impact of maternal mental illness on obstetrical outcome and infant development.
• Recognize the limitations of the currently available classification systems.
• Apply this information to the long term clinical management of women with mood disorders.
# Gender Differences in Psychiatric Illness

**Women**
- Major Depression
- Dysthymia
- Panic Disorder
- Seasonal Affective D/O
- Rapid Cycling Bipolar
- Eating Disorders
- Somatization Disorder
- Borderline Personality

**Men**
- Alcohol Abuse
- Substance Abuse
- Antisocial Personality
- Paraphillias
Gender Differences: Comorbidity with Major Depression

Higher Prevalence in Women
- Panic Disorder
- GAD
- Bulimia Nervosa
- Thyroid Disease
- Migraine Headaches
- Fibromyalgia

Higher Prevalence in Men
- History of Substance Use Disorder
- Obsessive-Compulsive Disorder
- Passive-Aggressive Disorder
- Antisocial Personality Disorder
- Paraphilias

Relative Risk Of Psychiatric Illness

Odds Ratio

Psychiatric Disorder  Anxiety Disorder  Affective Disorder  >3 Psychiatric Disorders

Female  Male

Kessler et al. *Arch Gen Psychiatry.* 1994;51:8.
Results: Sex-Specific Self-Reported Mood Changes by Patients with BD

Gender Difference in Distribution of Time Spent in Mood State

<table>
<thead>
<tr>
<th>Mood State</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed</td>
<td>17%</td>
<td>28%</td>
</tr>
<tr>
<td>Euthymic</td>
<td>64%</td>
<td>6%</td>
</tr>
<tr>
<td>Manic</td>
<td>8%</td>
<td>6%</td>
</tr>
</tbody>
</table>

* p<.001

## Prevalence of Anxiety Disorders in Men and Women

<table>
<thead>
<tr>
<th>Anxiety Disorder</th>
<th>% Women</th>
<th>% Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific Phobia</td>
<td>15.7</td>
<td>6.7</td>
</tr>
<tr>
<td>Social Phobia</td>
<td>15.5</td>
<td>11.1</td>
</tr>
<tr>
<td>Agoraphobia with Panic</td>
<td>7.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Generalized Anxiety Disorder</td>
<td>6.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Panic Disorder (PD)</td>
<td>5.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Post Traumatic Stress Disorder (PTSD)</td>
<td>11.3</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Kessler, *Arch Gen Psychiatry*, 51, 8-19, 1994
Emerging Issues in Psychiatric Diagnoses

• Is it Better Identification, Over Utilization, Justification of Symptoms and/or Treatment?

“Yes”

• A trial of treatment is more effective than a trial of diagnosis
Initial Treatment Planning

- Treat all women of reproductive capacity as if they were pregnant from the very first visit.
  - “new and improved = no data”

- The majority of neuropsychiatric illnesses onset prior to family planning.

- Treatment often long term (e.g. > years)
  - Consideration of long term side effects
  - Reproductive health, metabolic syndromes, bone health
Bi-Directional Interactions

Hormones

Medications

Illness
Contraception and AEDs

- 6% failure rate per year of ocp’s with many AEDs
  - increase hepatic metabolism
  - increase binding by SHBG
- Breakthrough bleeding not reliable
- Other routes also affected
- Increase ethinyl estradiol to $>50 \, \mu g$ for 21 days?
- Adjunctive barrier methods
## AED Effects on Hormonal Contraceptive Agents

<table>
<thead>
<tr>
<th>Lowers hormone levels</th>
<th>No significant effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenobarbital</td>
<td>ethosuximide</td>
</tr>
<tr>
<td>phenytoin</td>
<td>gabapentin</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>valproate</td>
</tr>
<tr>
<td>primidone</td>
<td>lamotrigine</td>
</tr>
<tr>
<td>topiramate (&gt;200mg)</td>
<td>levetiracetam</td>
</tr>
<tr>
<td>oxcarbazepine (&gt;1200mg)</td>
<td>zonisamide</td>
</tr>
</tbody>
</table>
Lamotrigine concentrations with & without ocps

With ocps (filled symbols);
Without ocps (open symbols)

Bone Density Loss
Potential Causes in Psychiatric Patients

- **Illness-Related Neurobiological Changes**
  - Hypercortisolemia
  - Proinflammatory Cytokines (IL-6, TNF-α)

- **Illness-Related Behaviors**
  - Hypoactivity
  - Hyperactivity
  - Undernutrition

- **Medications**
  - Neuroleptic-Induced Hyperprolactinemia (if hypogonadal)
  - Supraphysiologic L-thyroxine
  - AEDs
  - +/- SSRIs

AED-Related Bone Disease
Prospective Twin/Sibling Matched Analysis

N=35 female pairs

Bone Density Changes in Children

n=53

$\textit{p}<.005$

Bone Health Recommendations
VPA & Enzyme-Inducing AEDs

• Elemental Calcium
  ▪ 1500 mg in adults; 1300 mg in teens

• Vitamin D
  ▪ 400 to 800 IU daily

• Bone Density Evaluation
  ▪ No established guidelines
Gonadal Steroids Affect CNS 5HT Activity

- ↓ 5-HT₁, ↑ 5-HT₂ receptors¹
- Modulates tryptophan hydroxylase²,³
- ↓ MAO activity⁴

Serotonin

Estrogen

-Progesterone

↑ serotonin uptake and turnover⁵,⁶

Hormonal / Neurochemical Imbalance

• Common clinical complaints

• Limited definitive data to suggest aberrations in hormones or neurotransmitters
  ▪ Probably not worth the clinical time to educate
    • Internet, other clinicians, etc.
  ▪ Rather a reminder to avoid un-needed laboratory testing or results that can not be interpreted
    • e.g. if you run enough tests you will get some abnormal values
Mood and Anxiety Disorders Across the Female Reproductive Cycle

- Premenstrual depression/anxiety (eg, PMDD)
- Depression/anxiety during pregnancy
- Depression/anxiety associated with infertility, miscarriage, or perinatal loss
- Depression/anxiety during the peri-/post-menopausal period
- Depression/anxiety during the postpartum period
PMDD and the Menstrual Cycle

- **Timing:**
  - Gonadal steroids fluctuate throughout cycle
  - Premenstrual symptoms predominately in luteal phase
  - Luteal levels of estrogen and progesterone do not discriminate PMDD from non-PMDD women
  - Hormonal therapies & oophorectomy may act by suppressing ovulation

Impact of the Menstrual Cycle on Emotional Well-being

Premenstrual tension syndrome\(^1,2\)

Premenstrual exacerbation of depression or anxiety disorders\(^3\)

Clinical dilemma: Diagnostic uncertainty

Premenstrual dysphoric disorder (PMDD)\(^1,2\)

Depression May Underlie Premenstrual Emotional Symptoms

Diagnostic Profile of Subjects Initially Seeking Treatment for Premenstrual Complaints

- No depressive or anxiety disorder: 61.2% (n=126)
- Depressive disorders: 23.3% (n=48)
- Comorbid depressive and anxiety disorders: 7.3% (n=15)
- Anxiety disorders: 8.2% (n=17)

PMDD = premenstrual dysphoric disorder.

* Generalized anxiety disorder (GAD), panic disorder (PD), and obsessive-compulsive disorder (OCD).
† Major depression, dysthymia, and bipolar depression.

PMDD: Background

- 75% of women report minor, isolated, or occasional premenstrual changes
- 20% – 50% report “premenstrual syndrome”
- 3% – 8% of reproductive-age women have PMDD

Paroxetine is not FDA-approved for treatment of PMDD.

PMDD = premenstrual dysphoric disorder.

| Symptom                                | 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 |
|----------------------------------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Imatility                              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Sudden mood changes                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Tension                                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Sadness                                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Decreased interest in usual activities |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Feeling overwhelmed                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Difficulty concentrating              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Bloating                               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Breast tenderness                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Food cravings                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Lack of energy                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Change in sleep                        |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Relationship problems                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Other: Headache                        |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
### Premenstrual Daily Symptom Chart

**Name:** Jane Doe  
**Month:** March

1. Circle the days of your menstrual period in the row labeled Day of Month.
2. Begin your ratings today. For example, if today is the 12th day of the month, mark your symptoms in the column labeled 12. At the same time each day, use a marker or pen to fill in the column numbered 0 to show how severe each symptom was over the past 24 hours. Leave the symptom blank if you had no problem with that symptom. See example on the right. If you forget to fill in a day, place an X in the Day of Month bar to signify that you did not fill in the chart for that day.
3. Continue on new page on the first day of the next month.

#### Example:

<table>
<thead>
<tr>
<th></th>
<th>none</th>
<th>mild</th>
<th>moderate</th>
<th>severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

#### Symptoms:

- **Irritability**:  
- **Sudden mood changes**:  
- **Tension**:  
- **Sadness**
- **Decreased interest in usual activities**
- **Feeling overwhelmed**
- **Difficulty concentrating**
- **Bloating**
- **Breast tenderness**
- **Food cravings**
- **Lack of energy**
- **Change in sleep**
- **Relationship problems**
- **Other: Clumsy**

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Depression
PMDD / PMS: TREATMENT

• Antidepressants – First Line Therapy
  ▪ SSRI preferred
  ▪ Rapid response
  ▪ Intermittent vs. Continuous Dosing
  ▪ Frequent Relapse when discontinued

• Hormonal Therapies
  ▪ Oral Contraceptives: limited data, safety concerns
  ▪ GnRH Agonists: reserved for severe cases

• Diet & Nutritional Supplements
  ▪ Calcium carbonate (1200 mg / day)
  ▪ Magnesium
  ▪ Low fat vegetarian diet

• Psychotherapy
  ▪ CBT
  ▪ Relaxation Training
Premenstrual Exacerbation (PME)

- Prospective Monthly Charting for accurate Diagnosis
- Worsening of symptoms during luteal phase of menstrual cycle
- Distinction from PMDD is presence of ongoing symptoms during follicular phase of cycle
- Premenstrual exacerbation of symptoms may be seen with many disorders, including
  - Anxiety disorders
  - Eating disorders
  - Substance abuse
  - Seizures
  - Migraines
  - Asthma

PMDD=premenstrual dysphoric disorder.
Rates of Menstrual Abnormalities among Women with Bipolar Disorder

(N = 80)

Prior to Treatment

- Amenorrhea, 8%
- Oligomenorrhea, 18%
- Intermenstrual Bleeding, 6%
- Frequent Bleeding (polymenorrhea), 6%
- No Menstrual Abnormalities, 40%
- Heavy Flow (Menorrhagia), 26%

Current Treatment

- Heavy Flow (Menorrhagia), 39%
- Frequent Bleeding (polymenorrhea), 12%
- Intermenstrual Bleeding, 15%
- Oligomenorrhea, 20%
- Amenorrhea, 8%
- No Menstrual Abnormalities, 28%
Genes?  
PCOS  
Environment?
Polycystic Ovarian Syndrome (PCOS)

- PCOS is among the most common endocrine disorders in women of reproductive age, affecting 4% to 6% of them

- PCOS is the leading cause of anovulatory infertility and hirsutism

PCOS Diagnostic Criteria
Revised 2003 Rotterdam Criteria - 2 out of 3

- **Ovulatory Disturbance**
  1. Oligomenorrhea (<9 menses/year)
  2. Anovulation

- **Hyperandrogenism**
  1. Clinical signs (hirsutism, acne, balding)
  2. Biochemical signs

- **Polycystic Ovaries & Exclude Other Etiologies** - Congenital Adrenal Hyperplasia, Androgen Secreting Tumors, Cushing’s Syndrome

Fertil Steril, Hum Reprod 2004
Emergence of PCO Symptoms
Association with AED Treatment

N=72

Signs and Symptoms of Reproductive Health Dysfunction for Women on AEDs

- Weight gain of more than 20%
- Hirsutism (in women)
- Abnormal menstrual cycle (<23 days, >35 days)
- Midcycle menstrual bleeding
- Difficulty conceiving or history of early-term miscarriage
Background

- > 4,000,000 deliveries in US annually
- > 50% inadvertent conception
- Maternal Age Increasing
  - Longer time to develop illness prior to pregnancy
- Neuropsychiatric Illnesses in Pregnancy
  - >500,000 women annually
  - 8 health care databases: 6.6% of women prescribed AD at some point in pregnancy (Andrade et al 2007)
    - e.g. >250,000 exposed annually
- Uniform support for Breast Feeding
Psychopharmacology during Pregnancy and Lactation – Common Situations

- Inadvertent conception on medication
- Conceived on medication and patient has already discontinued
- Psychiatically stable and approaching delivery and wants to breast feed
- Symptom worsening during pregnancy and/or breast feeding
- Pre-conception counseling
CRITICAL PERIODS IN HUMAN DEVELOPMENT*

<table>
<thead>
<tr>
<th>Main Embryonic Period (in weeks)</th>
<th>Fetal Period (in weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
</tr>
<tr>
<td>7</td>
<td>38</td>
</tr>
</tbody>
</table>

### Neural tube defects (NTDs)
- TA, ASD, and VSD
- Amelia/Meromelia
- Amelia/Meromelia
- Cleft lip
- Low-set malformed ears and deafness
- Microphthalmia, cataracts, glaucoma
- Enamel hypoplasia and staining
- Cleft palate
- Masculinization of female genitalia

### Mental retardation

### CNS

### Heart

### Upper limb

### Lower limb

### Upper lip

### Ears

### Eyes

### Teeth

### Palate

### External genitalia

---

**Common site(s) of action of teratogens**
- Less sensitive period
- Highly sensitive period

---

**Major congenital anomalies**

**Functional defects and minor anomalies**

---

TA — Truncus arteriosus; ASD — Atrial septal defect; VSD — Ventricular septal defect

---

when major birth defects may be produced.
Antenatal Depression: Maternal & Neonatal Consequences

- Non-compliance with prenatal care
- Self medication with drugs, EtOH, and tobacco
  - 10-12% use tobacco
  - 14-15% use EtOH
  - 3% use illicit drugs
- Not bonding with baby
- Effects on family
- Suicide
- Postpartum Depression

- Preterm labor
- Premature birth (<37 weeks)
- Low birth weight
- Small for gestational age, smaller head circumference
- Low APGAR scores
- Neonatal Complications
- Admission to NICU
- Fetal demise

References:

Treatment Options

✓ Medications
✓ Psychotherapy
✓ ECT
✓ Light Therapy
✓ TCMS

“Paper or plastic?”
PLACENTAL PASSAGE OF MEDICATIONS (n=512)

(Neport et al AJP 2007; Stowe et al unpublished data)
## FDA Pregnancy Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Controlled studies show no risk: adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus</td>
</tr>
<tr>
<td>B</td>
<td>No evidence of risk in humans: either animal findings show risk, but human findings do not; or, if no adequate human studies have been done, animal findings are negative</td>
</tr>
<tr>
<td>C</td>
<td>Risk cannot be ruled out: human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk</td>
</tr>
<tr>
<td>D</td>
<td>Positive evidence of risk: investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh risks</td>
</tr>
<tr>
<td>X</td>
<td>Contraindicated in pregnancy: studies in animals or humans, or investigational or postmarketing reports, have shown fetal risk that clearly outweighs any possible benefit to the patient</td>
</tr>
</tbody>
</table>
Perinatal Product Labeling

"Use in pregnancy is not recommended unless the potential benefits justify the potential risks to the fetus."

"When manufacturers & official agencies warn against drug treatment during pregnancy, their warnings serve to protect themselves and are of little use to clinically responsible physicians."

## Prospective Studies

### Antidepressants & Major Malformations

<table>
<thead>
<tr>
<th>Registry / Antidepressant</th>
<th>(n)</th>
<th>% Major Malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>NY Dept of Health (95-01)</td>
<td>1,816,343</td>
<td>4.09%</td>
</tr>
<tr>
<td>Swedish Registry (95-01)</td>
<td>637,651</td>
<td>3.50%</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>4,679</td>
<td>2.69%</td>
</tr>
<tr>
<td>Sertraline</td>
<td>3,393</td>
<td>1.95%</td>
</tr>
<tr>
<td>Citalopram</td>
<td>2,688</td>
<td>2.72%</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>2,687</td>
<td>3.50%</td>
</tr>
<tr>
<td>Bupropion</td>
<td>2,550</td>
<td>2.20%</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>771</td>
<td>1.82%</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>235</td>
<td>3.40%</td>
</tr>
</tbody>
</table>

1 [http://www.health.state.ny.us/nysdoh/cmr/docs](http://www.health.state.ny.us/nysdoh/cmr/docs)  
2 [http://www.sos.sos.se/epc/epceng.htm](http://www.sos.sos.se/epc/epceng.htm)
Antidepressant Neonatal Toxicity, Withdrawal, Abstinence Syndrome

• Original Report in 1973 (Webster 1973)

• Increased attention (Stiskal 2001; Laine 2003; Kallen 2004; FDA 2004; Sanz 2005, JAMA 2006)
  ▪ All data derived from cross sectional assessments
  ▪ Infant evaluator not blind to maternal medication
  ▪ Highly variable time of symptoms – birth to several days
  ▪ Symptoms range from CONFUSION to CONVULSIONS

• Withdrawal physiologically unlikely
  ▪ Fetal Dosing to point of delivery via umbilical cord

• Warrants further study, with some modest degree of scientific methodology
**Nonteratogenic Effects** — Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring “prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying”.

These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see Monoamine oxidase inhibitors under CONTRAINDICATIONS). When treating a pregnant woman with SSRIs/SNRIs during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.
Persistent Pulmonary Hypertension (PPHN) and SSRI Exposure

• Chambers CD et al 2006
  – 377 PPHN matched with 836 controls
    ➔ SSRI Exposure after 20 weeks gestation
    ➔ Odds ratio 5.1
• Kallen et al 2008
  – 506 PPHN, 831,324 controls
    ➔ SSRI Exposure
    ➔ Odds Ratio 2.2
• Andrade et al 2009
  – WHO Registry
    ➔ Odds Ratio 1.4
Fetal AED Exposure: Heightened Educational Needs

Children exposed to VPA in utero are over 3 times more likely to have developmental difficulties than those exposed to other AEDs.

Adab et al. J Neurol Neurosurg Psychiatry 2001
High-Dose Maternal Anticonvulsant-Exposure vs. Child IQ

Lamotrigine (n=52, 300 mg/d)

Phenytoin (n=28, 450 mg/d)

Carbamazepine (n=37, >750 mg/d)

Divalproex (n=22; 1500 mg/d)

Psychiatric Admissions in 2 Years
Before and After Delivery

Postpartum Mental Illness

- **Postpartum "blues"**
  - 50%-70% of adult women within 10-14 days
  - Transient, considered nonpathologic

- **Postpartum depression (PPD)**
  - 10% of adult women
  - 2/3 have onset by 6 weeks postpartum
  - Serious and disabling

- **Postpartum psychosis (PPS)**
  - 1-2/1000 live births
  - 70% are affective (bipolar D/O, depression)
  - Medical emergency

D/O = disorder.
Postpartum Depression: Clinical Predictors

Incidence (%)

- No History of Depression
- Past history major depression
- MDD during pregnancy
- Past history postpartum depression

### PPD: Treatment Studies

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marital counseling</td>
<td>IPT</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Estrogen</td>
</tr>
<tr>
<td>Antidepressants (TCAs)</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Sertraline</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Venlafaxine</td>
</tr>
</tbody>
</table>

**Recurrent Psychosis**
- Lithium >> haloperidol
Support Breast Milk as Ideal Form of Nutrition

- American Academy of Pediatrics
- American College of Obstetrics and Gynecology
- American Dietetic Association
Lactation Safety Classification Schemes

- **American Academy of Pediatrics**
  - Usually compatible with breastfeeding
  - Unknown but of concern
  - Assoc’d with significant side effects & should be used with caution
  - Requires cessation of breastfeeding

- **Thomas Hale, *Medications and Mothers’ Milk***
  - L1 - SAFEST
  - L2 - SAFER
  - L3 – MODERATELY SAFE
  - L4 – POSSIBLY HAZARDOUS
  - L5 – CONTRAINDIENCED
## Lactation: Comparing the Data & the Safety Ratings

<table>
<thead>
<tr>
<th>Drug</th>
<th>Exposed Infants (N)</th>
<th>Hale Rating</th>
<th>American Academy of Pediatrics Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>202</td>
<td>L3/L2</td>
<td>Unknown but of concern</td>
</tr>
<tr>
<td>Sertraline</td>
<td>180</td>
<td>L2</td>
<td>Unknown but of concern</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>105</td>
<td>L2</td>
<td>Unknown but of concern</td>
</tr>
<tr>
<td>Citalopram</td>
<td>69</td>
<td>L3</td>
<td>Unknown but of concern</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>143</td>
<td>L2</td>
<td>Usually compatible with breastfeeding</td>
</tr>
<tr>
<td>Valproate</td>
<td>41</td>
<td>L2</td>
<td>Usually compatible with breastfeeding</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>42</td>
<td>L3</td>
<td>Unknown but of concern</td>
</tr>
<tr>
<td>Lithium</td>
<td>32</td>
<td>L4</td>
<td>Significant side effects; should be given with caution</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>16</td>
<td>L2</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>3</td>
<td>L3</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1</td>
<td>L4</td>
<td></td>
</tr>
</tbody>
</table>
DEPRESSION or MENOPAUSE?

Depressed / Irritable
Anhedonia
Thoughts of Death
Worthlessness

Energy
Concentration
Sleep
Weight
Libido

Hot Flushes
Perspiration
Vaginal Dryness
The ovaries after long years of service have not the ability of retiring in graceful old age, but become irritated. Transmit this irritation to the abdominal ganglia which in turn transit this irritation to the cerebral tissue - produces disturbances such as extreme nervousness or even an outburst of actual insanity.

-Farnum 1887
Perimenopausal Depression & Hot Flashes


Perimenopause = Irregular cycles OR amenorrhea < 12 mos.

**Prevalence (%) Vasomotor**

- **Older Pre-Menopause** (n=184)
- **Peri-Menopause** (n=141)
- **Post-Menopause** (n=151)

**OR(MDD|HF): 4.3 [95%CI, 1.4-13.8]**

\[ p < .01 \]
Perimenopausal Depression: Efficacy of 17 β-estradiol

Results

MADRS Scores

Placebo

Estradiol

Soares, C.N. et al Archives of General Psychiatry 2002
Antidepressants For Hot Flashes: Results of Controlled Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Venlafaxine XR</strong></td>
<td>Placebo</td>
<td>↓ 27% HFS score</td>
</tr>
<tr>
<td>Breast Cancer Survivors</td>
<td>37.5 mg</td>
<td>↓ 37% HFS score</td>
</tr>
<tr>
<td></td>
<td>75 mg</td>
<td>↓ 61% HFS score</td>
</tr>
<tr>
<td></td>
<td>150 mg</td>
<td>↓ 61% HFS score</td>
</tr>
<tr>
<td><strong>Fluoxetine</strong></td>
<td>Placebo</td>
<td>↓ 36% HFS score</td>
</tr>
<tr>
<td>Breast Cancer Survivors</td>
<td>20 mg</td>
<td>↓ 50% HFS score</td>
</tr>
<tr>
<td><strong>Paroxetine CR</strong></td>
<td>Placebo</td>
<td>↓ 37% HFS score</td>
</tr>
<tr>
<td>Natural Menopause</td>
<td>12.5 mg</td>
<td>↓ 62.2% HFS score</td>
</tr>
<tr>
<td>Dube et al, 2002 †††</td>
<td>25 mg</td>
<td>↓ 64.4% HFS score</td>
</tr>
</tbody>
</table>

††† Dube et al. *JAMA* 2003
Summary

- **Psychiatric Disorders** –
  - Co-Morbidity is the rule not the exception
  - Age of Onset Typically Prior to Family Planning
  - Illnesses do not ‘go away’ During Pregnancy
- **Fluctuations in Hormones May Affect Illness/Treatment**
  - Changes in BCP, Hormonal Therapy (e.g. Provera Tamoxifen)
- **Treatment may Influence Fertility**
  - Interaction with BCP
  - Anxiety/ Stress reduces Fertility
  - Libido
Summary

• > 50% of Pregnancies are Unplanned
  ▪ Folic Acid – March of Dimes, CDC
  ▪ Treatment Planning – should plan for potential pregnancy

• Long Term Treatment Planning
  ▪ Calcium supplementation

• Medication Use during Pregnancy and Lactation
  ▪ Considerable data on both illness and medication
General Approach

- **Interview** –
  - Treatment response can run in families

- **Laboratory Evaluation** –
  - Thyroid: TSH > 2.5
  - Anti-thyroglobulin/Antimicrosomal Antibodies in Postpartum women

- **Working Diagnosis** –
  - Does have to be right .... Just close
General Approach

• Antidepressants
  ▪ Learn to use 2-3 (throw the rest away)
    • Potential Pregnancy
    • Most data:
      ▪ Fluoxetine, sertraline, citalopram
  ▪ Start lowest dose (can always give more, but once given – never less)
  ▪ At 4 weeks – if no change, then change dose or medication
General Approach

- Change only one thing at a time
- Treat for 9-12 months from achieving wellness
  - Never reduce medication at holidays
  - Taper by the menstrual cycle
Questions?