Women’s Issues in Psychiatry: Depression through the Reproductive Life Stages

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Disclosures

- Bell Let’s Talk
- CIHR
- Great West Life
- Associates in Psychiatry (TOH)
- University Medical Research Fund
Learning Objectives:

- Describe the phenomenology of Major Depressive Disorder in women during the reproductive life stages.

- To highlight and comment on key gender differences that present throughout the reproductive years.

- To review mood disorders that present at specific time points during the reproductive stages as well as clinically relevant therapeutic options.

- To highlight unique clinical challenges that present during pregnancy and the postpartum.
Background

- The peak period of risk for depression in women occurs between the ages of menarche and menopause.

- Times of particular risk are periods of reproductive change, i.e. the premenstrual period, the puerperium, and the menopausal transition.
Female Reproductive Cycle

Childbearing Years

- Menarche
- Pregnancy
- Perimenopause
- Menopause

Effects Unclear
Premenstrual Dysphoric Disorder
Major Depressive Disorder

Depression related to:
Infertility
Miscarriage
Perinatal Loss

Depression Postpartum Psychosis

Depression Vasomotor Symptoms
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Gender Differences

- Epidemiology

- Clinical presentation

- Pharmacokinetics - absorption, distribution, metabolism, elimination, menstrual cycle effects, drug interactions

- Pharmacodynamics - AD response profile in both sexes
Epidemiology

- Prevalence rates of depression are consistently higher in women.

- World Health Organization (WHO) ranks unipolar depression first in Disability Adjusted Life Years (DALYs) amongst all diseases worldwide for women in their reproductive years.

- The ratio of women to men afflicted with MDD is about two to one.

Epidemiology of Major Depressive Disorder

Results From the National Epidemiologic Survey on Alcoholism and Related Conditions

Deborah S. Hasin, PhD; Renee D. Goodwin, PhD; Frederick S. Stinson, PhD; Bridget F. Grant, PhD, PhD

• Face to face survey 43,000 US adults

<p>| Table 1. Prevalence of 12-Month and Lifetime DSM-IV Major Depressive Disorder by Sociodemographic Characteristics |
|---------------------------------------------------------------|---------------------------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Sociodemographic Characteristic</th>
<th>12-Month MDD, % (SE)</th>
<th>Lifetime MDD, % (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5.28 (0.15)</td>
<td>13.23 (0.3)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3.56 (0.17)</td>
<td>9.01 (0.27)</td>
</tr>
<tr>
<td>Female</td>
<td>6.87 (0.24)</td>
<td>17.10 (0.44)</td>
</tr>
</tbody>
</table>

*The odds ratio F:M - 2.0 to 1.0*
Is the female preponderance in major depression secondary to a gender difference in specific anxiety disorders?

G. PARKER and D. HADZI-PAVLOVIC

• Most studies report female preponderance beginning age 10-12 (puberty).

• Peak differentiation between 15-30.

• Second distinct increase in rates of initial episodes of MDD in late 40’s and early 50’s.

_Psychological Medicine, 2004, 34, 461–470._
Gender Differences - Clinical Presentation

• Women present with more:
  – Atypical features (Psychomotor retardation, ↑appetite, weight gain)
  – Seasonal component
  – Higher level of somatic symptoms, ruminations, feelings of worthlessness and guilt
  – Higher rates of attempted suicides/lower rates of completed suicides

Bigos K et al. Gend Med, 2009, 522-43
Gender Differences - Pharmacokinetics

- Physiologic Factors
  - Absorption: females - ↓ gastric acid secretion, slower gastric emptying, colonic transit time prolonged (Result - increased absorption of AD’s)
  - Distribution: affected by adipose tissue for lipophilic drugs (Result - ↑ half life for lipophilic drugs in female given larger volume of distribution)

Bigos K. et al. Gender Medicine Vol.6, No. 4, 2009: 522-543
Pharmacokinetics

• Metabolism and elimination:
  – CYP enzymes - effects of concomitant medications, menstrual cycle, pregnancy

  – May depend on blood flow to liver and kidney and thought to be reduced in females compared to males (note – blood flow and GFR increases in women during pregnancy)

Deligiannidis KM, Byatt N, Freeman MP. J Clin Psychopharmacol. 2014 Apr;34(2): 244-55;
Bigos K. et al. Gender Medicine Vol.6, No. 4, 2009: 522-543
Pharmacodynamics

• Response to antidepressants
  – Can be quite variable, including differences in adverse effects and time to response.

Despite the differences reported in individual studies, there has been little published work systematically evaluating potential sex differences in antidepressant pharmacokinetics and pharmacodynamics, especially from a population approach

Bigos K. et al. Gender Medicine Vol.6, No. 4, 2009: 522-543
Why the gender difference?

- Artifact hypothesis
- ‘Sex role’ hypothesis
- Psycho-Social Factors
- Hormonal model
- Personality Factors
- Neurochemical Theory
Explanations for the gender differences

• Artifact hypothesis

  – Women more likely to seek help, volunteer depressive symptoms, report differentially when seeking help and respond differentially to depression rating measures

  – Discounted in community survey populations

Explanations for the gender differences

- **Sex Role Hypothesis**
  - Gender based role experiences shape development of self and diathesis towards depression/anxiety
    - i.e. pink/dolls vs. blue/war figures → girls “internalize” and are more passive
    - depression vs. “mentally tough”– protected
  - Not supported- if so we’d expect differences to emerge in childhood

Explanations for the gender differences

• Psycho-Social Factors
  – 75% cases of depression has a precipitating life event
  – Women are exposed to greater number of stressful events and/or are more vulnerable to them (i.e. childhood abuse, role conflict, poverty)

  – Existing studies do not support greater exposure to trauma in women, or support sex differences in childhood trauma

Explanations for the gender differences

• Hormonal model
  – Role of estrogen
  – Mood fluctuates with the change of hormones

• Personality Factors
  – neuroticism linked to MDD across all ages, more distinctive in young and middle aged females than in children and very old
  – low self esteem as a vulnerability factor
  – coping styles- self ruminative with sadness vs. distraction

Explanations for the gender differences

• Neurochemical Theory
  – Ie. Stress System/HPA axis- men show greater ACTH response to stressors, no difference in cortisol response; women show smaller saliva cortisol responses but dependent on menstrual cycle phase (follicular smaller; luteal same as men)

  – Interaction of gonadal system with HPA axis - modulate susceptibility to stress related to disorders over the lifetime cyclic changes in ovarian steroids on a monthly basis, increases in pregnancy, puberty, and decreases with childbirth, menopause

  It may be the continually changing steroid milieu is the major factor that sensitizes women to stress.

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• To highlight unique clinical challenges that present during pregnancy and the postpartum.
Female Reproductive Cycle

- Menarche
- Pregnancy
- Perimenopause
- Menopause

Childbearing Years

- Premenstrual Dysphoric Disorder
- Major Depressive Disorder
- Depression related to:
  - Infertility
  - Miscarriage
  - Perinatal Loss

Vasomotor Symptoms

Depression related to:
- Postpartum Psychosis
- Vasomotor Symptoms

Effects Unclear
Question 1

All of the following are necessary for a diagnosis of PMDD except:

(a) prospective daily ratings of at least 3 consecutive symptomatic cycles
(b) the disturbance markedly interferes with work or school or with usual social activities and relationships with others
(c) mood, anxiety, behavioral and somatic symptoms are core features in diagnosis
(d) symptoms onset occurs before onset of menses
Question 2

The prevalence of PMDD over a twelve month span in menstruating women is (DSM-5):

(a) 2-6%
(b) 10-13%
(c) 20-25%
(d) 50%
Question 3

The use of the following may help with fewer premenstrual complaints:

(a) OCP
(b) St. John’s wort
(c) Black cohosh
(d) Vitamin E
Premenstrual Dysphoric Disorder

**DSM-IV**

**Requirements for Diagnosis of Premenstrual Dysphoric Disorder**

A. Symptoms must occur during the week before menses and remit a few days after onset of menses. Five of the following symptoms must be present and include at least one of 1–4.

1. Depressed mood or dysphoria
2. Anxiety or tension
3. Affective lability
4. Irritability
5. Decreased interest in usual activities
6. Concentration difficulties
7. Marked lack of energy
8. Marked change in appetite, overeating, or food cravings
9. Hypersomnia or insomnia
10. Feeling overwhelmed
11. Other physical symptoms (e.g., breast tenderness, bloating)

B. Symptoms must interfere with work, school, usual activities or relationships.

C. Symptoms must not merely be an exacerbation of another disorder

D. Criteria A, B, and C must be confirmed by prospective daily ratings for at least two consecutive menstrual cycles.

Adapted from the *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.*

**DSM-5**

**Table 1: Diagnostic Criteria for Premenstrual Dysphoric Disorder**

A. In the majority of menstrual cycles, at least 5 symptoms must be present in the final week before the onset of menses, start to improve within a few days after the onset of menses, and become minimal or absent in the week postmenses

B. One (or more) of the following symptoms must be present:

1. Marked affective lability (e.g., mood swings, feeling suddenly sad or tearful, or increased sensitivity to rejection)
2. Marked irritability or anger or increased interpersonal conflicts
3. Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
4. Marked anxiety, tension, and/or feelings of being keyed up or on edge

C. One (or more) of the following symptoms must additionally be present to reach a total of 5 symptoms when combined with symptoms from criterion B above:

1. Decreased interest in usual activities (e.g., work, school, friends, hobbies)
2. Subjective difficulty in concentration
3. Lethargy, easy fatigability, or marked lack of energy
4. Marked change in appetite; overeating; or specific food cravings
5. Hypersomnia or insomnia
6. A sense of being overwhelmed or out of control
7. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of "bloating," or weight gain

**Note:** The symptoms in Criteria A-C must have been met for most menstrual cycles that occurred in the preceding year.

D. The symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships with others (e.g., avoidance of social activities; decreased productivity and efficiency at work, school, or home)

E. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, persistent depressive disorder (dysthymia), or a personality disorder (although it may co-occur with any of these disorders)

F. Criterion A should be confirmed by prospective daily ratings during at least 2 symptomatic cycles (Note: The diagnosis may be made provisionally prior to this confirmation)

G. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition (e.g., hyperthyroidism)

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Women with PMDD, in particular, are more likely to have a past history of mood disorders and other psychiatric disorders, with lifetime estimates ranging from 30% to 70%.

PMDD may predict future MDD.

(Harv Rev Psychiatry 2009;17:120–137.)
Prevalence of Premenstrual Symptoms

Women of Reproductive Age

- Mild Premenstrual Symptoms (75%)
- PMS (20-40%)
- PMDD (3-9%)

Management of PMDD

A. Psychoeducation

B. Lifestyle modification:
   Healthy eating, regular exercise, good sleep hygiene, limit setting and good stress management, moderate alcohol use

C. Dietary supplementation: Calcium, B6

D. Behavioral Treatments (Group psychoeducation, Relaxation therapy)

E. Psychotherapy

F. Pharmacotherapy (SSRIs/ SNRIs)
   - luteal dosing vs. continuous dosing

G. Hormonal treatments

H. Complementary/ Alternative Medicine Options

Vigod S et al. Psychiatr Clin N Amer 33(10) 257-72
Female Reproductive Cycle

Childbearing Years

Menarche
- Effects Unclear
- Premenstrual Dysphoric Disorder

Pregnancy
- Depression Postpartum
- Psychosis

Perimenopause
- Depression related to:
  - Infertility
  - Miscarriage
  - Perinatal Loss

Menopause
- Depression Vasomotor Symptoms

Major Depressive Disorder

Depression related to:
- Infertility
- Miscarriage
- Perinatal Loss
Question 4

Common risk factors for PPD include:

(a) unplanned pregnancy
(b) discontinuation of antidepressant
(c) symptoms of depression in pregnancy
(d) all of the above
Question 5

Which of the following is the best estimate of risk of postpartum psychosis (ppp) following a previous ppp?

(a) 5 %
(b) 15%
(c) 50%
(d) 90%
Question 6

Which medication should be avoided in pregnancy?

(a) Lamotrigine
(b) Divalproex sodium
(c) Lithium carbonate
(d) Olanzapine
Depression in Pregnancy

• Pregnancy does not protect against mental illness.
• Prevalence by Trimester (adult women)
  • 1\textsuperscript{st} – 7.4%
  • 2\textsuperscript{nd} – 12.8%
  • 3\textsuperscript{rd} – 12%
  Mean prevalence in adolescents- 16%

• Postpartum depression often has its onset in pregnancy

Depression During Pregnancy

- Symptom overlap can make diagnosis difficult (e.g. sleep, appetite and energy changes)
- One study found: only 26% of known cases of antenatal depression were identified during prenatal health care visit.
  - Only 2% were referred for treatment.

Postpartum Depression

- The postpartum period represents a time of increased vulnerability.
- DSM-IV TR (with postpartum onset): MDE with onset in the first four weeks following childbirth.
- DSM-5 (with peripartum onset): MDE onset occurs during pregnancy or in the first four weeks following childbirth.
- Clinically: PPD within 12 months of childbirth

**DSM-IV criteria for major depression**

Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning:

1. Depressed mood most of the day, nearly every day
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
3. Significant weight loss when not dieting, or weight gain
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day
9. Recurrent thoughts of death

At least one of the symptoms must be either:

1. Depressed mood
2. Loss of interest or pleasure

Epidemiology

- Prevalence:
  - 10-22% of adult women
  - 26% of adolescent mothers
  - Rates reported from 40-53% in adolescent mothers

- 60% of women have their first depressive episode in the postpartum period.

Differential Diagnosis

- Postpartum Anxiety Disorders
- Baby Blues
- Postpartum Depression
- Postpartum Psychosis
Postpartum Blues

• Prevalence: 50 - 85%

• As many as 25% of these women are at risk for development of PPD within the first year

• Mild and transient

• Symptoms: low mood, crying, mood lability, irritability, anxiety, insomnia, memory & concentration problems
Postpartum Blues

• Course:
  – begins 3-4 days after delivery
  – peaks at day 5-6
  – back to normal in 2-3 weeks

• Mother’s functioning usually preserved

• Treatment limited to support and reassurance
Postpartum Psychosis

A Psychiatric Emergency!!!

- Incidence: 1-2/1000 births
- Onset:
  - mean ~ 2-3 weeks pp
  - usually within 8 weeks of delivery

Recurrence Rates high

Postpartum Psychosis

• Symptoms:
  – Early:
    • insomnia, mood lability, restlessness
  – Later:
    • Marked memory & concentration impairment
    • Incoherence
    • Suspiciousness
    • Irrational/obsessive concerns
    • Delusions and hallucinations
Biological Risk Factors for Perinatal Depression

- Prior history of a MDD/PPD
- Current depression or anxiety in pregnancy
- Psychiatric illness in family members
- Discontinuation of medications
- Significant medical/obstetrical problems

Psychosocial Risk Factors for Perinatal Depression

- Lack of partner, family and social support
- Stressful life events
- Breastfeeding difficulties
- Colicky babies / infant health problems
- Unplanned pregnancy
- Socio-economic status
- Abuse Issues

151 depressed mothers and their children (7-17 years)

Remission of maternal depression after 3 months of medication Rx was significantly associated with reductions in children’s depressive, anxiety & disruptive behavior disorders and symptoms.
Screening and Diagnosis

• Women should be screened for symptoms of PPD early.

• When undiagnosed and untreated, PPD can cause marked suffering and dysfunction in family, disruption of bonding, & adverse cognitive-behavioral developmental effects in newborn.

• Guilt, shame and fear of negative consequences may prevent women from disclosing their emotional distress during what is supposed to be a happy time.
SCREENING

• NB: Somatic symptoms of depression are not reliable because they are also present in non-depressed pregnant women (sleep, appetite, energy, and libido changes).

• Look for:
  – Anxiety
  – Lack of interest in the pregnancy / baby
  – Guilty ruminations
  – Profound anhedonia / social withdrawal
  – Inability to sleep
Screening: EPDS
(Edinburgh Postnatal Depression Scale)

• 10 question, self-report screening tool

• Well validated: threshold of 12:
  – sensitivity 88%, specificity 92%

• Has also been validated for antenatal depression and in adolescent mothers.

Management

- Psychotherapy
- Pharmacotherapy
- Combination (Meds + therapy)
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The Psychiatrist’s Dilemma
No Decision is Risk Free

Exposure to Medications

versus

Exposure to Illness

Get me a lawyer!
Non-pharmacological

• Psychoeducation:
  – Patient and family education is key.
  – Discuss vulnerability, precipitating and maintaining factors
  – Family strategies within and outside the home

• Psychotherapy (group vs. individual)
  – Supportive
  – Cognitive Behavioural Psychotherapy (CBT)
  – Interpersonal Psychotherapy (IPT)

Medications in pregnancy

- Placental transfer from mom to baby
- Highest risk of teratogenicity in 1st trimester
- 1-3% baseline incidence of anomalies
- Avoid stopping “cold turkey” b/c discontinuation syndrome, risk of relapse
- Often higher doses required in 3rd trimester
Pharmacotherapy: Which antidepressant to choose?

- All antidepressants are equal in efficacy, differ in side effects
- Personal and family history of response
- Cost
- Side effect profile
- Drug interactions
- Monotherapy
### Pregnancy Categories

<table>
<thead>
<tr>
<th>A</th>
<th>Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk and AWC studies in pregnant women have not during the first trimester (and there is no evidence of risk in later trimesters).</td>
</tr>
<tr>
<td>C</td>
<td>Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.</td>
</tr>
<tr>
<td>D</td>
<td>There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).</td>
</tr>
<tr>
<td>X</td>
<td>Studies in animals or humans have demonstrated fetal abnormalities OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).</td>
</tr>
</tbody>
</table>
Shortcomings of Current Labeling

- Pregnancy Categories
  - Incorrectly seen as a grading system where risk increases from A → B → C → D → X.
  - Do not convey the relative range of reproductive risk

- Clinically not very informative

- Updates with human data are rare
A newly designed system (FDA, expected June 2015) will abolish the letters. Labeling will be required to include the following three subsections: Pregnancy, Lactation, and Females and Males of Reproductive Potential. Each must include a summary of the risks and a discussion of the data available and provide relevant information so that health care providers may make more informed treatment decisions:

FDA and Health Canada Warnings

- Teratogenicity: paroxetine data – now category D
- Neonatal Toxicity/Withdrawal
- Abnormal muscle movements (EPS)/ Withdrawal
- Persistent Pulmonary Hypertension of the Newborn

Paroxetine:
FDA Category Change from C to D
(2005)

SUMMARY OF FINDINGS
An independent epidemiological study of delivery outcome following maternal use of SSRI antidepressants in early pregnancy was conducted utilizing the Swedish national registry data (n=5,123 women).

The findings showed ~ 2-fold increased risk of cardiac malformations (VSD and ASD) in infants exposed to paroxetine, compared with the total registry population (approximately 2% incidence vs. 1%, respectively).

Kallen B, Olausson, P: Reproductive Toxicology 2006; 21:221-222; Diav-Citrin et al. (Abstract) Repro Toxicology 2005; 20:453-491;
Evaluation of the Risk of Congenital Cardiovascular Defects Associated With Use of Paroxetine During Pregnancy

Adrienne Einarson, R.N.
Alessandra Pistelli, M.D., Ph.D.
Marco DeSantis, M.D.
Heli Malm, M.D.
Wolfgang D. Paulus, M.D.
Alice Panchaud, Ph.D.
Debra Kennedy, M.D.
Thomas R. Einarson, Ph.D.
Gideon Koren, M.D.

Objective: In 2005–2006, several studies noted an increased risk of cardiovascular birth defects associated with maternal use of paroxetine compared with other antidepressants in the same class. In this study, the authors sought to determine whether paroxetine was associated with an increased risk of cardiovascular defects in infants of women exposed to the drug during the first trimester of pregnancy.

Method: From teratology information services around the world, the authors collected prospectively ascertained, unpublished cases of infants exposed to paroxetine early in the first trimester of pregnancy and compared them with an unexposed cohort. The authors also contacted the authors of published database studies on antidepressants as a class to determine how many of the women in those studies had been exposed to paroxetine and the rates of cardiovascular defects in their infants.

Results: The authors were able to ascertain the outcomes of 1,174 infants from eight services. The rates of cardiac defects in the paroxetine group and in the unexposed group were both 0.7%. The rate in the database studies (2,061 cases from four studies) was 1.5%.

Conclusions: Paroxetine does not appear to be associated with an increased risk of cardiovascular defects following use in early pregnancy, as the incidence in more than 3,000 infants was well within the population incidence of approximately 1%.

(Am J Psychiatry 2008; 165:749–752)
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.

Safety Announcement

The new drug labels now contain more and consistent information about the potential risk for abnormal muscle movements (extrapyramidal signs or EPS) and withdrawal symptoms in newborns whose mothers were treated with these drugs during the third trimester of pregnancy.

Antipsychotic drugs are used to treat symptoms of psychiatric disorders such as schizophrenia and bipolar disorder, and have been shown to improve daily functioning in individuals with these disorders. Common brand names for antipsychotic drugs include Haldol, Clozaril, Risperdal, Zyprexa, Seroquel, Abilify, Geodon, and Invega (see List of Antipsychotic Drugs below).

Healthcare professionals should be aware of the effects of antipsychotic medications on newborns when the medications are used during pregnancy. Patients should not stop taking these medications if they become pregnant without talking to their healthcare professional, as abruptly stopping antipsychotic medications can cause significant complications for treatment.

The symptoms of EPS and withdrawal in newborns may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty in feeding. In some newborns, the symptoms subside within hours or days and do not require specific treatment; other newborns may require longer hospital stays.
SSRI exposure > 20 weeks associated with ↑ risk of PPHN
- Fluoxetine, sertraline, paroxetine
- No association with use of non-SSRI antidepressants

Odds ratio 6.1
Background risk: 1-2/1000
Mortality 10%
Estimated increased risk: 6-12/1000

** Multiple Methodological Issues **
“FDA has reviewed the additional new study results (6 studies) and has concluded that, given the conflicting results from different studies, it is premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN. FDA will update the SSRI drug labels to reflect the new data and the conflicting results.”
Antidepressants in Pregnancy

**SSRIs:**

**TCAs:**
3 prospective, 10 retrospective studies, <700 cases. Altshuler et al. Am J Psychiatry 1996

**Venlafaxine:**
Einarson et al Am J Psychiatry 2001 N=150

**Trazodone/Nefazodone:** Einarson et al, Can J Psychiatry 2003 n= 150

**Bupropiron:**
Chan et al, Am J Obs Gynecol 2005 n = 136;
Cole JA. et al. Pharmacoepidemiol Drug Saf. 2006 n= 1213

**Mirtazepine:**
Djulus et al, J Clin Psychiatry Aug 2006 n= 104

NO increase risk for major malformations found with ANY antidepressant to date
Longterm Neurobehavioural Studies

- Fluoxetine and tricyclics
  - First trimester use only
  - Exposed throughout pregnancy
- 4 year follow-up by neurologist, psychologist, pediatrician
- No differences between exposed and non-exposed babies

Benzodiazepines in Pregnancy

• Early studies (1960’s and 70’s) found an increased risk for major malformations, in particular oral cleft

• A meta-analyses with pooled data from cohort studies showed no association between fetal exposure to benzodiazepines and the risk of major malformations or oral cleft. However, with pooled data from case-control studies, there was a significant increased risk for major malformations or oral cleft alone. OR = 1.79 (1.13-2.82)

Benzodiazepines in Pregnancy

More recently…..

• A study from the Swedish Medical Birth Register analyzed 1944 cases of infants exposed to various benzodiazepines in the 1st trimester.

• An increased risk for preterm birth and low birth weight was detected in the exposed population, however there was no increased risk for orofacial clefts or other major malformations.

Wikner BN et al Pharmacoepidemiol Drug Saf Nov 2007
Conventional Antipsychotics

- 1309 children were examined who were exposed to phenothiazines during pregnancy. No differences were found in rates of congenital malformations, perinatal mortality rate, birth weight as compared to the population.
  

- 215 women followed up exposed to haloperidol. No increase risk for major malformations.
  
Atypical antipsychotics

Manufacturers registries:
Olanzapine = 242 Quetiapine = 446
Clozapine = 523 Risperidone = 250

Case reports:
Clozapine = 74 Olanzapine = 69
Quetiapine = 3 Risperidone = 12
Yeager et al Am J Psych 2006

Prospective comparative study
151 women followed up exposed to these drugs:
Olanzapine = 60 Risperidone = 49
Quetiapine = 36 Clozapine = 6
McKenna et al, J Clinical Psychiatry April 2005

- No increased risk for major malformations;
- Possible increased risk for low birth weight
Mood Stabilizers

Lithium may be considered the safest alternative

• Mother
  – Hypothyroidism
  – Increase in polydipsia and polyuria
  – Nephrogenic diabetes insipidus (rare)
• Baby
  – Ebstein’s anomaly 1:1000
    • Cardiac U/S recommended at 16-20 weeks
  – Fetal goiter
  – baby Neonatal toxicity
    • Lethargy
    • Floppy syndrome

Cohen, 1994; AAP, 2000; Viguera 2000; Warner, 2000; Iqbal, 2001;
Pinelli, 2002; Yonkers, 2004; Alexander, 2004; Newport, 2005; Stowe, 2007; Viguera, 2007
Mood Stabilizers

Valproic acid (monotherapy): recent study found overall rate of malformations (10.7%) NTD (2.9%)
Wyszynski et al. Neurology 2005

- In addition, the potential for lower IQ has also been documented
  Genton et al. Drug Saf. 2006

Carbamazepine: NTD (1%); no increase risk for adverse neurodevelopmental effects
Nulman et al. Drugs 1999

* Lamotrigine: has been associated in one pregnancy registry with an increased risk for major malformations (oral clefts). However, this trend has not been observed in other registries
Medications in Breastfeeding

- Clear benefits to breastfeeding (AAP recommendations)
  - neonate: decrease incidence of acute/chronic disease
  - mom: reduces risk of breast CA in premenopausal women, reduces pp blood loss

- All medications excreted in breast milk
  - Side effects in breast feeding infants rare

- Percent of dose transfer to baby under 10% considered low
  - Sertraline and Paroxetine have the least secretion in breast milk.

- Risk vs Benefit
- Guilt of not breastfeeding

Medications in Breastfeeding

- **Antidepressants**: generally considered safe

- Sertraline recommended as first line in ppd in breastfeeding moms: trace or undetectable levels in infant sera

- **Benzodiazepines**:
  - Not contraindicated but should be used cautiously during lactation
  - Prolonged use not recommended.
  - Aim for minimum doses for maternal symptom relief
    - Low doses of medications with no active metabolites (Clonazepam or Lorazepam) preferred
    - Monitor baby (sedation)- use cautiously
Medications in Breastfeeding

• Antipsychotics:
  Typical: N=35
  - Reports of toxicity and developmental delays
  - Use cautiously

Atypical:
  - Clozapine: high accumulation in breast milk but no infant data; report of infant seizure
  - Risperidone, olanzapine, quetiapine: few cases but no toxicity.

Yoshida, 1998; Barnas et al, 1994; Goldstein et al, 2000; Ilett, 2004; Hill, 2000; Patton, 2002; Croke, 2002; Lee, 2004; Misri 2004; Misri 2006
Medications in Breastfeeding

- **Mood Stabilizers:**
  - Lithium: not recommended. high level passed (rule of ½’s). Monitor baby tsh, renal function, lithium level
  - CBZ/epival: compatible
  - Lamotrigine: high infant serum levels 30%. Monitor for rash
Female Reproductive Cycle

Childbearing Years

- Menarche
  - Effects Unclear
  - Premenstrual Dysphoric Disorder

- Pregnancy
  - Major Depressive Disorder
  - Depression related to: Infertility, Miscarriage, Perinatal Loss
  - Depression Postpartum Psychosis

- Perimenopause
  - Vasomotor Symptoms

- Menopause
Question 7

Common risk factor’s for depression during midlife?

(a) Presence of hot flashes
(b) Disturbed sleep
(c) Previous episode(s) of depression
(d) all of the above
Question 8

What is considered the most effective treatment of hot flashes?

(a) Acupuncture
(b) Estrogen therapy
(c) phytoestrogens
(d) venlafaxine
Menopausal Transition

- Transition commences with the onset of the first menstrual irregularity, and ends with the final menstrual period (FMP).

- Ovary loses the ability to produce hormones after FMP (including estrogens and androgens).
Menopausal Status

- This is defined according to bleeding patterns:
- Premenopause- regular menstrual periods with predictability.
- Early Perimenopause- A woman is considered to have entered the “early” transition if she has either skipped a menstrual period or has noted an increase in irregularity of her cycles by 2-7 days. Increased quantity of menstrual flow and midcycle spotting.

Menopausal Status

- **Late Perimenopause**: Skipped periods or longer cycles are common. Marked by 3-11 months of amenorrhea.

- **Postmenopause**: 12 months or more have elapsed without menses.

- **Women** who have experienced 3 months of amenorrhea are highly likely (about 95%) to become postmenopausal.

Menopausal Transition

• Length from regular cycling to complete cessation of menses ranges from 3-9 years

• During this time, the pattern of menstrual cycles including duration, frequency, and amount of bleeding becomes less predictable
Menopausal Transition

- Up to 90% of women may experience the onset of change in menstrual patterns between the ages of 40-44 years.

- Median age of inception of late perimenopause estimated at 47-48 years.
What is the evidence of an association between the menopausal transition and depression?

- The majority of women do not develop depression during the menopausal transition.

- Depressive symptoms have been observed more frequently in some perimenopausal women compared with postmenopausal women in several (but not all) longitudinal, community-based studies.
The Evidence

- A multiethnic community-based cohort study (SWAN study) showed that mood symptoms and irritability were more likely to occur in peri-menopausal vs. premenopausal women.

- In addition, reports of persistent mood symptoms remained higher after adjustment for potential confounding factors such as vasomotor symptoms and sleep disturbances.

The Evidence

- Freeman and colleagues identified an increased risk for significant depression during the perimenopause compared with the premenopause or postmenopause.

- The association remained after adjusting for several variables, including past history of depression, severe premenstrual syndrome, poor sleep, and hot flashes.

- One obvious weakness of this study was that only 3% of the sample (approximately 10 women) were followed through to the postmenopausal phase.
The Evidence

- In a recent prospective observational study, 29 asymptomatic premenopausal (defined by self-report) women were followed until 6 to 12 months after their FMP to determine the timing of onsets of mood disorders relative to specific stages of the menopausal transition.

- A 14-fold increase in the rate of onset of depression was observed during the 12 months before and the 12 months after the FMP, suggesting an increased risk of depression in women during both the late menopausal transition and the early postmenopause relative to the premenopause.

Risk for New Onset of Depression During the Menopausal Transition

The Harvard Study of Moods and Cycles

Lee S. Cohen, MD; Claudio N. Soares, MD, PhD; Allison P. Vitonis, BA; Michael W. Otto, PhD; Bernard L. Harlow, PhD

Context: Transition to menopause has long been considered a period of increased risk for depressive symptoms. However, it is unclear whether this period is one of increased risk for major depressive disorder, particularly for women who have not had a previous episode of depression.

Objective: To examine the association between the menopausal transition and onset of first lifetime episode of depression among women with no history of mood disturbance.

Design: Longitudinal, prospective cohort study.

Setting: A population-based cross-sectional sample.

Participants: Premenopausal women, 30 to 45 years of age, with no lifetime diagnosis of major depression (N=460), residing in 7 Boston, Mass, metropolitan area communities.

Main Outcome Measure: Incidence of new onset of depression based on structured clinical interviews, Center for Epidemiologic Studies Depression Scale scores, and an operational construct for depression.

Results: Premenopausal women with no lifetime history of major depression who entered the perimenopause were twice as likely to develop significant depressive symptoms as women who remained premenopausal, after adjustment for age at study enrollment and history of negative life events. The increased risk for depression was somewhat greater in women with self-reported vasomotor symptoms.

Conclusions: The current study suggests that within a similarly aged population of women with no lifetime history of depression, those who enter the menopausal transition earlier have a significant risk for first onset of depression. Further studies are needed to determine more definitively whether other factors, such as the presence of vasomotor symptoms, use of hormone therapy, and the occurrence of adverse life events, independently modify this risk. Physical symptoms associated with the menopausal transition and mood changes seen during this period may affect many women as they age and may lead to a significant burden of illness.

Arch Gen Psychiatry. 2000;63:385-390

- All women enrolled were premenopausal without history of depression
- Two fold increase in depression in women entering the perimenopausal timeframe
- Increased rate of depression also noted in those reporting hot flashes
Risk Factors

• Studies in women who become depressed during midlife have identified several variables associated with risk for depression:
  • Previous episodes of depression
  • Longer duration of the perimenopause
  • Presence of hot flashes
  • Retrospective reports of premenstrual depressive symptoms or postpartum depression
  • Complaints of poor health
  • History of smoking
  • Disturbed sleep
  • Reduced parity
  • Absence of a partner
Alternative and complementary therapies for the menopause

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b Complementary Medicine, Peninsula Medical School, Universities of Exeter & Plymouth, 25 Victoria Park Road, Exeter EX2 4NT, UK

<table>
<thead>
<tr>
<th>CAM therapy</th>
<th>Clinical evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acupuncture</td>
<td>Two systematic reviews [47,48]</td>
<td>No evidence of any significant effect on menopausal symptoms</td>
</tr>
<tr>
<td>Calcium</td>
<td>Several RCTs and a systematic review [84]</td>
<td>Significant reduction of bone loss</td>
</tr>
<tr>
<td>DHEA</td>
<td>Several RCTs</td>
<td>Results inconsistent</td>
</tr>
<tr>
<td>Fibre</td>
<td>Several RCTs</td>
<td>Discrepancy in results on hypocholesterolemic effects</td>
</tr>
<tr>
<td>Herbal remedies a</td>
<td>/ Systematic review [54]</td>
<td>/ No conclusive evidence of a benefit on vasomotor symptoms</td>
</tr>
<tr>
<td>Homeopathy</td>
<td>Systematic review [89]</td>
<td>No evidence of effects on vasomotor symptoms</td>
</tr>
<tr>
<td>Physical exercise</td>
<td>Several systematic reviews [92–94]</td>
<td>Combination of walking with other exercise modalities has positive effect on bone mineral density</td>
</tr>
<tr>
<td>Plant sterols and stanols</td>
<td>Several RCTs</td>
<td>Effective in reducing LDL-C and total cholesterol plasma levels</td>
</tr>
<tr>
<td>Probiotics and prebiotics</td>
<td>Several RCTs</td>
<td>Discrepancy in results</td>
</tr>
<tr>
<td>Vitamins</td>
<td>Systematic reviews [72,73,83]</td>
<td>Vitamin D (in combination with calcium) and vitamin K significantly reduce the incidence of fractures</td>
</tr>
</tbody>
</table>
Pharmacologic Treatment

- HRT: Some studies suggest that women with peri-menopausal depression may respond to specific interventions, such as estrogen therapy (ET).

- ET has been used widely to treat menopausal symptoms and may be the most effective treatment of hot flashes.*

Pharmacologic Treatment

• Antidepressants remain the treatment of choice for the management of most depressive and anxiety disorders during the peri-menopausal and postmenopausal years.

• HRT improves depressive symptoms and menopause-related complaints (e.g., vasomotor symptoms, sexual dysfunction, sleep disruption) and better overall functioning and quality of life.

Recap of Learning Objectives:

• Describe the phenomenology of Major Depressive Disorders in women during the reproductive life stages.

• To highlight and comment on key gender differences that present throughout the reproductive years.

• To review mood disorders that present at specific time points during the reproductive stages as well as clinically relevant therapeutic options.

• To highlight unique clinical challenges that present during pregnancy and the postpartum.
Summary

• MDD may be influenced by reproductive events
• Clinicians should screen for depressive symptoms routinely
• Pregnancy is not protective for depression
  – Treat like past depressive episodes, higher doses of antidepressants in last trimester
  – Optimal control of the psychiatric disorder should be maintained during pregnancy, the post partum period and thereafter

• Higher risk for MDD during the menopausal transition
  – Effective treatments available for vasomotor and mood symptom
Perinatal Resources

• Motherisk
  – 416-813-6780
  – www.motherisk.org

• Postpartum Support International
  – www.postpartum.net

• BC Reproductive Mental Health Program
  – www.bcwomens.ca/healthservices/reproductivementalhealth

• MGH Centre For Women’s Mental Health
  - www.womensmentalhealth.org
Questions?