Women's Mood Disorders:
Before, Between and Beyond Reproduction

First Time Motherhood/New Parent Initiative

EDGECOMBE - HALIFAX – HERTFORD –
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Issues in Women's Reproductive Mental Health

- What reproductive mental health issues specific to women are encountered by health workers?
  - Premenstrual Dysphoric Disorder
  - Perinatal Psychiatry
  - Perimenopause

Mood Disorders in Women in the General Population

- Depressive disorders are very common
- Lifetime prevalence rates range from 4.9 % - 17.1%
- Women report a history of major depression at nearly twice the rate of men
- Depression is now considered the leading cause of disease-related disability among women in the world
- Women of childbearing age are at high risk for major depression

Kessler RC, Epidemiology of Women and Depression, Journal of Affective Disorders, 2003; 74(1):5-13.

DSM-IV Criteria for Major Depression

Five (or more) of nine symptoms:

- Depressed mood
- Loss of interest or pleasure in almost all activities
- Significant weight loss or weight gain
- Insomnia or hypersomnia
- Restlessness or feeling slowed down
- Fatigue
- Worthlessness or inappropriate guilt
- Inability to concentrate
- Suicidal ideation

DSM-IV Criteria for Major Depression (MDD)

- Must be present during the same 2-week period
- Represents a change from previous functioning
- At least one of the symptoms is either

    1) depressed mood or

    2) loss of interest or pleasure

PMS & Premenstrual Dysphoric Disorder

- PMS is common– estimated prevalence is 3% - 10% of general population
- PMDD is less common, prevalence rate of 2% - 5%

Menstrual Related Mood Disorders

- Premenstrual Syndrome (PMS):
  - Constellation of emotional & physical symptoms
  - Occurs during luteal phase (post ovulation)
- Premenstrual Dysphoric Disorder (PMDD)
  - Symptoms must be present during most menstrual cycles
  - Occurs during luteal phase
  - DMS-IV Symptoms include:

    Depressed mood

    Marked anxiety & affective lability

    Marked anger, irritability or interpersonal conflicts

    Other neurovegetative symptoms of depression

Assessment of Premenstrual Complaints

- Assess the reproductive endocrine status
- Rule out underlying medical conditions
- Rule out underlying psychiatric conditions
- Perform **prospective** daily rating scales

Treatment of PMDD

- Non-pharmacologic
  - Calcium supplements (1000mg/day)
  - Magnesium supplements (360mg/day)
  - Aerobic exercise
  - CBT, relaxation
  - Circadian rhythm manipulations
- Hormonal
  - Oral Contraceptive Pills
- Psychotropic Medications

Psychotropic Treatment of PMDD

- Selective Serotonin Reuptake Inhibitors
  - Efficacy of SSRI treatment has been demonstrated in multiple studies with fluoxetine, sertraline and paroxetine
  - Luteal phase dosing vs. standing dosing
- Benzodiazepines
- Other agents

Menopause

- No specific psychiatric disorder has been associated with menopause itself
- However, the relationship between declining estrogen levels and mood symptoms is controversial
- Certain subgroups of women may be more vulnerable to developing psychiatric symptoms

Etiology of Menopause

- Usually occurs naturally with advancing age, between 41-59 yrs
- Can be a direct result of surgical removal of ovaries
- Can result from hormone therapy

Perimenopause

- The “transition” or “change of life” from regular menstrual functioning to menopause
- Usually last 5-10 years
- Decreasing estrogen levels
- Unopposed progesterone
- Increased rate of depressive symptoms

Depression and Menopause

- There is evidence that “estrogen withdrawal” may play a role in the development of mood symptoms
- Women with a history of major depression may be at risk for perimenopausal depression

Psychosocial Issues During Menopause

- Losing one's reproductive functioning
- Changing family roles
- Onset of physical illness
- Aging
- Cultural stereotypes (empty nest) vs. positive feelings of maturity

Treatment of Mood Symptoms during Menopause

- "Usual Care" strategies for treating depressive disorders
  - Psychotherapy
  - Pharmacotherapy
  - Good Psychoeducation
- The ever-changing HRT controversy
  - Review current recommendations

Perinatal Mood Disorders: Etiology

- Caused primarily by changes in levels of estrogen and progesterone
- Life stressors, such as moving, illness, poor partner support, financial problems, and social isolation can negatively affect the woman's mental state
- Strong emotional, social, and physical support can greatly facilitate her recovery

Childbirth and Postpartum

At childbirth and during the transition to the postpartum period the following occur:

- Estrogen and progesterone rapidly decline
- There is blunted HPA axis activity due to suppressed hypothalamic CRH secretion
- These normal changes are altered in women with PPD

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Background: Perinatal Depression

COMMON

- **10% - 15% prevalence**
- 4,000,000 women give birth annually in U.S., 500,000 with PPD
- Most common, unrecognized complication of perinatal period
- Compare to prevalence rate of gestational diabetes at 2% - 5%

Gavin NI et al., Perinatal Depression: A Systematic Review of Prevalence and Incidence, Obstetrics and Gynecology, 2005;(106):1071-83. Gaynes BN, Gavin N, Meltzer-Brody S, et al., Perinatal Depression: Prevalence, Screening Accuracy, and Screening Outcomes, AHRQ Publication No. 05-E006-1, February 2005.

Background: Perinatal Depression

MORBID

- Devastating consequences for patient and family
  - Low maternal weight gain, preterm birth
  - Impaired bonding between mother and infant
  - Increased risk of suicide and infanticide

MISSED

- No practice guidelines or routine screening
- Symptoms often different from “classic DSM-IV depression”

Gavin NI et al., Perinatal Depression: A Systematic Review of Prevalence and Incidence, Obstetrics and Gynecology, 2005; (106):1071-83. Gaynes BN, Gavin N, Meltzer-Brody S, et al., Perinatal Depression: Prevalence, Screening Accuracy, and Screening Outcomes, AHRQ Publication No. 05-E006-1, February 2005.

Mood Symptoms in the Perinatal Period

Distinguishing characteristics are:

- Anxiety or agitation
- Depressed mood
- Sadness, weepiness
- Irritability
- Lack of interest in the newborn
- Impaired concentration or feeling overwhelmed
- Feelings of dependency

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Risk Factors for Perinatal Mood Symptoms

"Giving birth is like taking your lower lip and forcing it over your head." *Carol Burnett*

- Rapid hormonal changes
- Physical and emotional stress of birthing
- Physical discomforts
- Emotional letdown after pregnancy and/or birth
- Awareness and anxiety about increased responsibility
- Fatigue and sleep deprivation
- Disappointments including the birth, spousal support, nursing, and the baby

Postpartum Psychosis

- A rare but **devastating** condition, with an estimated prevalence of 0.1% - 0.2% (one to two per thousand)
  - Women with Bipolar Disorder, risk is 100 times higher at 10% - 20%
  - **Psychiatric emergency** & requires immediate treatment with a mood stabilizer & antipsychotic
- Onset usually 2-3 days postpartum
- Has a 5% suicide and 4% infanticide rate
- Risk for recurrent episode with subsequent pregnancy is 90%

Screening Instruments

- Edinburgh Postnatal Depression Scale (EPDS)
  - Most commonly employed screening tool
- Beck Depression Inventory (BDI)
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Hamilton rating Scale for Depression (HRSD)
- Nine Symptom Depression Checklist of the Patient Health Questionnaire (PHQ)

Edinburgh Postnatal Depression Scale (EPDS)

- Most commonly employed screening tool for PPD
- 10 questions self-rated instrument
- Validated and developed specifically to identify women experiencing postnatal depression
- English and Spanish versions
- Please see handout of complete screening tool

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Treatment of PPD

- Critical for the well being of the woman, baby and family
- Effective treatments are readily available
- Skilled assessment and treatment by mental health professionals in perinatal psychiatry makes a difference in outcomes!!

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Treatment of Perinatal Depression

- Treatment must include both psychological and/or biological interventions
  - Psychotherapy (individual and/or group)
  - Increased social supports
  - Exercise, good nutrition, adequate sleep
  - Antidepressant medications if appropriate
  - Careful monitoring

Risk of Relapse of Major Depression in Pregnancy

- High risk of depressive relapse following antidepressant discontinuation during pregnancy
  - Of 201 women in the sample, 86 (43%) experienced a relapse of major depression during pregnancy
  - Women who discontinued medication relapsed more frequently (68% vs 26%) compared to women who maintained medication
  - Pregnancy is not "protective" with respect to risk of relapse of major depression

Cohen L, Altshuler L, et al., Relapse of Major Depression During Pregnancy in Women Who Maintain or Discontinue Antidepressant Treatment, JAMA, 2006; 295(5):499-507.

Pharmacotherapy in Pregnancy

- All psychotropics cross the placenta and none are approved by the FDA for use during pregnancy
- Unethical to conduct randomized placebo controlled studies on medication safety in pregnant women
- Thus, most information about the reproductive safety of drugs comes from case reports and retrospective studies
- Prevalence of SSRI use in pregnancy is 6% - 8%

SSRI Use During Pregnancy

Important issues to consider:

- First trimester exposure
- Third trimester exposure and risk of "discontinuation syndrome"
- Must weigh risk/benefit ratio
  - Consider untreated or inadequately treated maternal depression vs. risk of antidepressant exposure

Antidepressants Treatment in Pregnancy

Neonatal Outcomes:

- SSRI withdrawal is possible but usually these are transient (restlessness, rigidity, tremor)
- Late SSRI exposure carries an overall risk ratio of 3.0 (95% CI, 2.0-4.4) for a neonatal behavioral syndrome
- Neonatal behavioral syndrome in 31.5% of infants in late-exposed group, 8.9% in early-exposure group for fluoxetine

Moses-Kolko EL, Bogen D et al., Neonatal Signs After Late In Utero Exposure to Serotonin Reuptake Inhibitors: Literature Review and Implications for Clinical Applications, JAMA, 2005; 293(19):2372-83.
Chambers CD, Johnson KA et al, Birth Outcomes in Pregnant Women Taking Fluoxetine, NEJM 1996; 335(14):1010-5.

Primary Pulmonary Hypertension of the Newborn

- In 2006, a case control study showed SSRI exposure after 20 weeks gestation increased risk (4-5x higher) of PPHN with absolute risk of <1%

  (Chambers C, Hernandez-Diaz S, Van Marter L, Werler M, Selective Serotonin Reuptake Inhibitors and Risk of Persistent Pulmonary Hypertension of the Newborn, New England Journal of Medicine, 2006; 354(6):579-87.)

- Recent studies show increased risk of PPHN with multiple other risk factors and absolute low risk with SSRI exposure

  - C-section, high maternal BMI, AA or Asian heritage
  - Study concluded that large BMI and C-section had greater risk than SSRI exposure

    (Hernandez-Diaz S, Van Marter L, Risk Factors for Persistent Pulmonary Hypertension of the Newborn, Pediatrics, 2007; Aug;120(2):e272-82.)
  - Swedish Medical Birth Register– 3rd trimester exposure showed increased risk of 2.4

    (Kallen B, Olausson PO, Maternal Use of Selective Serotonin Reuptake Inhibitors and Persistent Pulmonary Hypertension of the Newborn, Pharmacoepidemiology and Drug Safety, 2008; Aug;17(8):801-6.)

    (Andrade SE, McPhillips, Antidepressant Medication Use and Risk of Persistent Pulmonary Hypertension of the Newborn, Pharmacoepidemiology and Drug Safety, 2009; Mar;18(3):246-52.)

What to do?

- SSRIs (especially fluoxetine and sertraline) and TCAs relatively safe even during first trimester
- SSRIs (especially sertraline) and TCAs relatively safe in breast-feeding. (Risk of fluoxetine accumulation in breastmilk and TCA-induced seizures)
- Avoid Paroxetine (unless risk/benefit analysis dictates otherwise)
- Insufficient information about newer antidepressants (SNRI's), and trazodone
- Bupropion: FDA risk category changed from B to C

Psychotherapy During Pregnancy

- Psychotherapy can be an important form of treatment of depression during pregnancy and the postpartum period
- Good data available for use of Cognitive-Behavioral (CBT) and Interpersonal Psychotherapy during pregnancy
- Requires weekly visits and motivation/compliance by the patient

Pregnant Women with Bipolar Disorder

- Present a complex clinical challenge
- Goal is to minimize the risk to the fetus, while limiting the impact of the psychiatric illness on the mother and her family
- Decisions surrounding psychotropic use are difficult and associated with risks

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Lithium vs. Anticonvulsants

LITHIUM

- Ebstein's cardiac malformation
  - 0.05% risk vs. 0.1% base rate
- Neonatal hypothyroidism
- Diabetes Insipidus (rare)
- Polyhydramnios (rare)
- FDA Pregnancy Category D

VALPROIC ACID

- Spina bifida (1%-5% risk)
- Structural defects of the heart, limbs and face
- FDA Pregnancy Class D

CARBAMAZEPINE

- Spina bifida (1% risk)
- Structural defects of the face (dysmorphic facies)
- Secreted in breast milk
- FDA Pregnancy Category C

Newer Anticonvulsants

- Limited data is available with the “newer" agents such as gabapentin, lamotrigine, oxcarbazepine and topiramate
- Lamotrigine has good safety record to date. No increased risk of birth defects
- The benzodiazepines may have increased risk of cleft lip and palate (0.7%)
- All are secreted in breast milk
- FDA pregnancy class C

Antipsychotics

- Teratogenic risks are probably low with the traditional neuroleptics (Haloperidol is safest)
- There is inadequate information available to ascertain risk of newer atypical antipsychotics, although safety profile is promising to date
- Quetiapine has lowest transmission in breast milk (All are secreted in breast milk)
- FDA pregnancy class C (except for clozaril)

Psychotropic Use During Lactation

Risk-Benefit Assessment for Lactation

- The majority of women plan to breastfeed
- 5% - 17% of nursing women take medications
- Breastfeeding is beneficial for the infant
- All psychotropic medications studied to date are secreted in breast milk
- Untreated maternal mental illness has an adverse effect on mother-infant attachment and infant development

Lactation - Mood Stabilizers/ Antipsychotic Medications

- **Lithium:**
  - The AAP cautions against Lithium during lactation
  - Consistently found in high concentrations in breast milk (24%-72% of maternal serum levels)
- **Valproic Acid and other Anticonvulsants**
  - Until recently AAP states they are compatible with breastfeeding
  - Newer studies raise concerns with Valproic Acid
  - Lamotrigine appears safe to date
- **Atypical Antipsychotics**
  - Literature is sparse
  - Quetiapine appears to have a low transmission into breast milk (0.1% of maternal dose) and no adverse effects

Infant Monitoring

- Most centers lack the clinical laboratory assays to detect typical infant serum concentrations
- Infant serum concentrations are uninterpretable
- Routine infant serum monitoring is **not routinely** recommended:
  - Except in the child who has potential medication side effects
  - Small proportion of breastfeeding children may be metabolic outliers for a particular medication and accumulate it

Conclusions: Treatment

- Perinatal psychiatric illness requires immediate intervention
- Coordination of care between OB-GYN and trained mental health professionals is critical
- Antidepressant medications can be safely used during pregnancy and lactation - assess risk of untreated illness vs. greater risk of exposure
- Chronic mental illness must be treated during pregnancy to prevent severe PPD
- Patients with preexisting psychosis must be treated as a **"high risk pregnancy"** during and after delivery

UNC Center for Women's Mood Disorders: Perinatal Psychiatry Program

Clinical and Research Program that provides assessment, treatment and support for women in the perinatal period

Collaboration of doctors, nurses, midwives, therapists, & social workers who provide services for in patient and out patient units

www.womensmooddisorders.org

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Patient Resources

- Postpartum Support International
  www.postpartum.net

- “Down Came the Rain” by Brooke Shields

- “This Isn’t What I Expected: Overcoming Postpartum Depression” by Karen Kleiman & Valerie Raskin

- “Beyond the Blues” by Bennett & Indman

For More Information

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