Treatment of Perinatal Depression

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Objectives
- Identify mental health needs during antenatal, perinatal and postpartum periods
- Review concerns with medication use during antenatal, perinatal and postpartum periods

Our Vision
A comprehensive center devoted to the lifelong mental health and wellness of women and their families

Our Mission
1) State of the art clinical care for women and their families in Iowa and the Midwest
2) Quality clinical education and training
3) Support of IDCRC perinatal research

Patient Services
- Diagnostic Assessment
- Medication Management
- Psychotherapy
  - Individual
  - Couples
  - Long and Short-term
- Consultation
- Liaison and Education

Patients Served
- Pregnant
- Postpartum
- Infertility
- NICU
- Pregnancy Loss

Referrals
Call WWC scheduling at
(319) 384-5499

Disclosures
- None
Treatment of Perinatal Depression

Perinatal Mental Health: Unmet Needs
- In OB clinics – nearly 40% of women identified with a mental health disorder
  - Depression – 21-23%
  - Posttraumatic Stress Disorder – 3%
  - Panic Disorder – 1-2%
  - Eating disorders – 5%
  - Substance use disorder – 19%

Symptoms of Depression
1. depressed mood most of the day, nearly every day
2. markedly diminished interest or pleasure in activities
3. change in weight or appetite
4. decreased or increased sleep
5. restlessness or slowing
6. fatigue or loss of energy
7. feelings of worthlessness or guilt
8. diminished ability to think or concentrate
9. recurrent thoughts of death or suicide

Perinatal Adjustment vs. Depression
- Both may have:
  - Changes in appetite
  - Changes in weight
  - Sleep disruption/insomnia
  - Fatigue/low energy
  - Changes in libido
  - Irritability
  - Anxiety
  - Obsessive thoughts (i.e., about the baby’s safety)
  - Ambivalent or negative feelings toward the baby, wanting to flee
  - Doubts or feelings of inadequacy about caring for the baby
  - Thoughts of harming the baby

Additional Symptoms of Perinatal Depression
- Irritability
- Anxiety
- Obsessive thoughts (i.e., about the baby’s safety)
- Ambivalent or negative feelings toward the baby, wanting to flee
- Doubts or feelings of inadequacy about caring for the baby
- Thoughts of harming the baby

Antenatal Depression
- 10-15% of Women
- Increased incidence during first trimester
- Associated with increased use of alcohol, drugs, and cigarettes
- Associated with decreased prenatal care

Antenatal Depression
- Risk Factors:
  - previous episode of depression
  - poor social support
  - “unwanted” pregnancy
  - family history of depression
- Significance of Problem
  - Risk of Prenatal mortality
  - Risk of Low Birth Weight
  - Risk of Postpartum Depression

Postpartum Depression
- 10-15% of new mothers
- All cultures, races, and socioeconomic strata
- Higher risk with high stress, or history of depression or anxiety
- Peak onset 2-3 months
Treatment of Perinatal Depression

Postpartum Depression

- **Risk Factors:**
  - previous episode of depression
  - poor social support
  - "unwanted" pregnancy
  - family history of depression

- **Significance of Problem:**
  - Risk of Attachment Problems
  - Risk of Poor Cognitive Development
  - Risk of Paternal Depression

<table>
<thead>
<tr>
<th>Previous Condition</th>
<th>Risk of PPD</th>
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<tbody>
<tr>
<td>Major depressive disorder</td>
<td>24%</td>
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<tr>
<td>Depression in pregnancy</td>
<td>35%</td>
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<tr>
<td>Previous PPD</td>
<td>50%</td>
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Detection of Perinatal Depression

- Detection rates in Ob-Gyn settings: 15-30%
- Treatment rates: nearly 75% of women screening positive for depression are untreated

- SCREEN for depression and anxiety!
  - EPDS
  - PHQ-9

What treatment do women prefer for perinatal depression?

- Antidepressant medication
- Psychotherapy
- Combined medication and psychotherapy

What treatment for perinatal depression is best supported by empirical data?

- Antidepressant medication
- Psychotherapy
- Combined medication and psychotherapy

Antenatal Depression: Medication Toxicity

- Teratogenic Effects
  - Congenital malformations
  - Spontaneous abortions
  - Birth weight

- Perinatal Effects
  - Labor complications
  - Newborn irritability or sedation

- Neurobehavioral Effects
  - Short and Long-term

Antenatal Depression: Medication Toxicity

- Research Limitations:
  - No prospective studies
  - Small sample sizes
  - Adverse reporting bias
  - Measurement limitations—malformations and cognitive functioning
  - Extrapolation from animal studies

What treatment do women most often receive for perinatal depression?

- Antidepressant medication
- Psychotherapy
- Combined medication and psychotherapy
Treatment of Perinatal Depression

**Clinical Considerations** — When treating pregnant women with PROZAC, the physician should carefully consider both the potential risks and potential benefits of treatment, taking into account the risk of untreated depression during pregnancy. Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy and who continued antidepresant medication, there was no evidence of teratogenicity following administration of fluoxetine at doses up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times the maximum recommended human dose (MRHD) on a mg/m2 basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m2 basis) throughout organogenesis. However, one prospective cohort study conducted by the European Network of Teratology Information Services reported an increased risk of cardiovascular malformations in infants born to women (N = 253) exposed to fluoxetine during the first trimester of pregnancy compared to infants of women (N = 1,359) who were not exposed to fluoxetine. There was no specific pattern of cardiovascular malformations. Overall, however, a causal relationship has not been established.

PROZAC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes regardless of drug exposure.

Treatment of Pregnant Women during the First Trimester — There are no adequate and well-controlled clinical studies on the use of fluoxetine in pregnant women. However, fluoxetine is known to cross the placenta. Animal reproduction studies using fluoxetine at doses up to approximately 15 mg/kg/day (1.5 times the maximum recommended human dose (MRHD) of 80 mg on a mg/m2 basis) did not reveal evidence of malformation potential. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m2 basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m2 basis) during gestation and lactation.

**Antenatal Medication Background**

- Incidence of major birth defects in US: 2 – 4%
- 65 – 70% of unknown cause
- 2 – 4% medication related
- Maximum vulnerability for structural and neurochemical abnormalities of CNS is 14 to 35 days post conception

**What happens to the untreated?**

Less than 1/3 of depressed perinatal women are treated

Cohen et al. 2006
- Relapse risk
  - 26% of women who maintained treatment relapsed
  - 68% of women who stopped treatment relapsed

**OLD FDA Medication Classification for Use during Pregnancy**

- A: Fetal risk not revealed in controlled studies in humans
- B: Fetal risk not confirmed in animals but inadequate human studies
- C: Fetal risk revealed in animals but not established or studied in humans; may use if benefits outweigh risk to fetus
- D: Fetal risk shown in humans; use only if benefits outweigh risk to fetus
- X: Contraindicated; benefit does not outweigh risk

**SSRI's Teratogenicity - Paroxetine**

- FDA warning - increased risk of cardiac defects
- Berard et al. 2007
  - 1403 women
  - Paroxetine OR = 1.38 vs. other 0.89 (not significant)
- Einarson et al. 2008
  - 3,000+ infants - cardiac malformations
  - Paroxetine group 0.7%
  - Unexpected group 0.7%
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SSRI's Teratogenicity
- Alwan et al, 2007
  - N = 9622 with major birth defects
  - N = 4062 without birth defects
  - No overall congenital heart defects
  - As a group, increased risk of:
    - Anencephaly (OR 2.4)
    - Craniosynostosis (OR 2.5)
    - Omphalocele (OR 2.8)
  - Absolute risks small

SSRI's Teratogenicity
- Louik et al, 2007
  - N = 9849 infants with birth defects
  - N = 5860 infants without birth defects
  - No overall birth defects for SSRIs as a group
  - Sertraline
    - Septal defects (OR 2.0)
  - Paroxetine
    - Cardiac defects (OR 3.3)
  - Absolute risks small

SSRs Teratogenicity
Cardiac Septal Defects
- Pedersen et al 2009
  - SSRIs OR 1.99
  - Sertraline OR 3.25
  - Citalopram OR 2.52
  - Fluoxetine OR 1.34
  - >1 SSRI 4.70
  - Absolute Risk low – overall 0.5%, SSRI 0.9% and >1 SSRI 2.1%

SSRI's Prematurity, Birth Weight
- Increased risk
  - Chambers et al 1996: compared 228 women exposed to Prozac to 254 controls
  - Simon et al 2002: retrospectively medical records for 185 women exposed to SSRI’s compared with matched unexposed women
  - Wisner et al. 2009: 238 women with SSRI exposure, prematurity but not low birth weight

SSRI's Prematurity, Birth Weight
- Oberlander 2006:
  - Accounted for illness severity SSRI exposure only linked to low birth weight and respiratory distress (NOT preterm delivery)
  - Oberlander 2008:
    - Accounted for illness severity
    - Accounted for duration of exposure
    - No difference between early and late exposure on outcome
      - Longer duration – risk for LBW, gestational age, respiratory distress

Neonatal Abstinence Syndrome
- Tremors
- Feeding difficulties
- Irritability
- Increased muscle tone
- Respiratory problems
- Increased reflexes
- Increased crying
- Sleep changes

Neonatal Abstinence Syndrome
- Neonatal abstinence syndrome occurs in up to 30% of neonates exposed to SSRIs in utero
- Monitor for 48 hours after birth, transient
- Possible dose-dependent relationship with paroxetine
- Should SSRI be tapered prior to delivery? SSRI exposed infants w/ and w/o exposure 14 days prior to delivery
  - When illness severity accounted for, no difference in outcomes (neonatal adaptation) between groups

SSRIs and Persistent Pulmonary HTN
- N = 377 women with PPHN infants, 836 matched controls
- 14 PPHN infants exposed to SSRI after 20 weeks gestation (n = 6 for controls)
  - OR = 3.1 (95% CI: 2.2-16.8)
  - 1-2/1000 to 6-12/1000

SSRIs and Persistent Pulmonary HTN
- FDA revised warning:
  - Data are conflicting
  - Case-control studies may overestimate
  - Prospective are usually underpowered
  - Other factors associated with depression (smoking, obesity, PTD, C-section) may account for the association
### Treatment of Perinatal Depression

#### Depression During Pregnancy: Neurodevelopmental Effects
- **Nulman et al 1997:** Prospective study of 80 women taking tricyclics, 55 taking fluoxetine, 84 controls
- Children's IQ and language development evaluated between 16 and 86 months
- No differences in development between groups
- No differences in temperament, mood, arousability, or behavioral problems

#### Tricyclic Antidepressants
- No apparent increased risk for malformation
  - Swedish Registry study – increased risk of PTD, LBW, ASD, VSD
  - Unable to control for maternal depression
- Reported withdrawal symptoms late in pregnancy, symptoms in neonate
- Require increased dose in last trimester

#### Mirtazapine
- **Djulus 2006**
  - N = 104
  - Higher rate preterm births (p = 0.04)
  - mirtazapine 16%
  - other AD 7%
  - known meds 2%
  - Higher rate spontaneous abortions (not statistically significant)
- **Lennestal & Kallen 2007**
  - Higher rate preterm birth (OR 1.6)

#### Bupropion
- **Alwan et al 2010**
  - Left outflow tract heart defects
  - N=483 cases (case-control)
  - OR 2.6
- **Chun-Fai-Chen 2005**
  - N = 136
  - Higher rate of spontaneous abortions
  - 14.7% vs. 4.3%
  - No other differences (malformations, birth weight, etc)

#### Trazodone/Nefazodone, Venlafaxine
- **Einaron et al, 2003**
  - N = 147 exposure during 1st trimester
  - No statistical differences between TRD and NFZ group and control groups (SSRI and other drugs)
- **Einaron et al, 2001**
  - N = 150 exposure during 1st trimester
  - No statistical differences between venlafaxine group and control groups (SSRI and other drugs)

#### Depression During Pregnancy: Medication Treatment Trials

#### Antenatal Depression: Rational Treatment
- Conventional wisdom is to avoid all medications during the first trimester if possible
- Psychotherapy
- Use previously effective antidepressants
- Maintenance and preventive treatment
- Response rate appears to be similar to non-pregnancy related depression

#### Antenatal Depression: General Guidelines
- Use lowest effective dose
- Use as few medications as possible
- Use previously effective medication(s)
- Don’t expose to BOTH antidepressants and depression
- Individualized risks and benefits
- Account for severity in recommendations
  - Consider alternatives

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Postpartum Depression: Medication Treatment Trials

- Stowe et al 1995: Sertraline (n=26)
- Cohen et al 1998: Venlafaxine (n=16)
- Suri et al 2001: Fluvoxamine (n=6)
- Nonacs et al 2005: Buproprion (n=8)
- Appleby et al 1997: Fluoxetine & "BT" (n=87)
- Misri et al, 2004: Paroxetine & CBT (n=35)

Infant Dose Depends On:
- Maternal dose
- Drug characteristics
- Time of administration in relation to breastfeeding

Newborn Accumulation Depends On:
- Absorption
- Rate of elimination

Antidepressants and Lactation

- Weissman 2004
  - 57 studies, n = 337 cases, n = 238 infants
  - Looked at maternal plasma, breast milk, infant levels
  - No detectable levels in infant
  - Increased levels
    - Citalopram 17 % of the cases
    - Fluoxetine 22 % of the cases

Medication risks decrease with infant age
Use antidepressant that has worked previously
Psychotherapy
Carefully consider risks of non-treatment
Discuss treatment options with patient and document rationale for treatment

"Evidence Guided" vs "Evidence Based"

Risk and Benefit Discussion Critical

- Risks of untreated depression
- Benefits of treatment
- Risks of medication
- Benefits of breastfeeding
- Personal history
  - treatment experience, severity
  - Access to care
  - Perception of risk

Empirical "Stepwise" Treatment

Intervention Intensity  Depression Severity
  Psychoeducation  At Risk
  Peer Support  Subthreshold
  Activity Scheduling
  Active Listening  Mild
  Interpersonal Psychotherapy  Moderate to Severe
  Medication

Referrals
Call WWC scheduling at
(319) 384-5499