Treatment of Anxiety and Depression in Pregnancy and while Breastfeeding

Anna Spielvogel, MD, PhD

Learning Objectives:
- Understand maternal and fetal risk associated with untreated mental illness in pregnancy and postpartum period
- Know risk and benefits of psychotropic medication during pregnancy and lactation
- Assess individual patients needs and discuss available treatment options

Public concerns Regarding Psychiatric Disorders
- Confidential Enquiries into Maternal Death in UK (1997-99) psychiatric disorders in general, suicide in particular leading cause of maternal death
- Case reports of infanticide linked to postnatal mood disorders
- Maternal depression/psychosis as risk factor for child neglect, abuse and in rare cases death (Andrea Yates)

FDA Warnings Re: SSRI-Antidepressants
- Paroxetine (Paxil) risk of birth defects
- Antidepressants increase suicidality
- Neonates exposed to SSRI/SNRI antidepressants late in pregnancy have developed adverse effects (PPHN) requiring prolonged hospitalization, respiratory support and tube feeding
Risk Benefit Analysis

- **DIAGNOSIS Need for acute or long term intervention**
- Provider consults woman and family regarding effect of
  - Treatment on
    - Mother
    - Fetus
    - Infant
    - Family
  - No Treatment on
    - Mother
    - Fetus
    - Infant
    - Family
- Pregnant woman's values-priorities --- CHOICE

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Psychiatric Disorders in Pregnancy

**Incidence and Fetal Risk**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Incidence in General</th>
<th>Incidence in Pregnancy</th>
<th>Impact on Obstetric Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety Disorder</td>
<td>13%</td>
<td>Unknown</td>
<td>LBW, SGA, premature delivery, decreased fetal growth</td>
</tr>
<tr>
<td>Major Depression</td>
<td>12% in women</td>
<td>10-16%. 70%</td>
<td>LBW, SGA, premature delivery, decreased fetal growth</td>
</tr>
<tr>
<td>Eating Disorders</td>
<td>0.5-3.7% anorexia</td>
<td>1.1-4.2% bulimia</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LBW, inadequate or excessive weight gain, Miscarriage, hyperemesis gravidarum, premature delivery, cesarean section, low Apgar score</td>
</tr>
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Psychiatric Disorders in Pregnancy

**Incidence and Fetal Risk**

Table 2 of 2

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<tr>
<td>Bipolar Disorder (BP)</td>
<td>1.2%</td>
<td>Unknown. High relapse with medication discontinuation. 50% relapse at 16 weeks GA. High risk for postpartum psychosis.</td>
<td>Not studies, but complications of untreated BP are increased rates of substance abuse, impulsivity and psychosis.</td>
</tr>
</tbody>
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Physiology in anxiety and depression

- Alteration in hypothalamic pituitary adrenal axis (HPA)
- Change in adrenocortiotropic steroid (ACTH)
- Change in endorphins
- Increase in corticotrophin releasing hormone (CRH)
- Increase in cortisol from the placenta
- Increased catecholamine release (anxiety-stress)
Risks of high anxiety or severe stress in pregnancy

- Mother: Substance abuse, suicide, post-partum depression
- Obstetric: Pre-eclampsia, preterm labor, low birth weight
- Fetus: Changes in HPA-axis
  - First/second trimester: Severe maternal stress-birth defects, risk of schizophrenia slightly higher. Long term cognitive, behavioral effects in children
  - Severe anxiety: Behavioral, emotional and cognitive problems in offspring (Egliston KA, 2007)
  - 12-22 weeks GA: HPA axis dysregulation in adolescent offspring’s depressive sx in adolescent females. (Van denBergh BRH, 2008)

Maternal Depression and Child Outcomes I

- Mother: Increased stress, substance abuse, smoking. Strongest predictor of post-partum depression.
- Obstetric: Preterm labor 2-3 fold increase of pre-eclampsia.

(Bonari, 2004; Hendrick, 2002)

Maternal Depression and Child Outcomes II

- Child: Psychological
  - Difficulty with emotion regulation
  - Lower self-esteem
  - Aggressive behaviors towards peers & parents
  - Insecure attachments with parents
  - Lower scores on cognitive functioning (Murray, 1997)
- Post-partum:
  - Reduced parental prevention practices (e.g. use of car seats (McLennan 2000)
  - Negative parental behavior
    - Yelling, hitting, smoking
  - For each depressive symptom risk for negative maternal interaction with child rose by 25% (Lyons-Ruth et al, 2000)

Medication in Pregnancy: Risks

- Risk of Teratogenesis
  - Major congenital malformations in newborn caused in first 12 weeks after conception
- Risk of poor obstetric outcome
- Risk of Neonatal Syndromes
  - Physical or behavioral symptoms in acute neonatal period that can be attributed to medication exposure at or near time of delivery
- Risk of Long –Term Effects
  - CNS develops throughout pregnancy and into early years of life; effects of mother’s illness and medication have not been systematically studied
Stages Of Human Development

Conflicting data, cannot rule out small increases in birth defects.

- Benzodiazepines: Craniofacial abnormalities.
- Paroxetine: 2 large registries.
  - 1% increase in birth defects over 3%
  - 1% cardiovascular (mostly ventricular septal defects)

Definitive Teratogenic

- Lithium:
  - definite but increase in C-V defects
  - 0.1 - 1%

- Valproate:
  - definite neural tube defects, craniofacial, IQ
  - 3 - 8%

- Carbamazepine:
  - definite neural tube defects, craniofacial, IQ
  - 2%

Obstetric Complications

- SSRIs:
  - Lower Apgar score
  - Premature birth
  - LBW (Simon 2002; Lattimore 2005; Suri 2007)
- Benzodiazepines - Unknown
Neonatal toxicity/withdrawal

- Benzodiazepine:
  - Neonatal toxicity: floppy infant, hypothermia, poor respiratory effort, feeding difficulties,
  - Withdrawal: tremulousness, apnea, diarrhea, vomiting, hyperreflexia
- SSRI:
  - Tremors, GI disturbance (e.g., feeding problems), irritability, increased muscle tone, constant or absent crying, respiratory difficulties.
  - Persistent Pulmonary Hypertension (PPHN) of newborn.
  - 6 fold increase = 1%.

Long Term –Effects of medication

Has received minimal attention:

- Antidepressants:
  - TCA or Fluoxetine: no change in IQ, language, behavioral or temperment up to 7 years. Other studies do find changes in these parameters
- Benzodiazepines:
  - Possible developmental delays (McElhalter 1994).
- Valproate:
  - Developmental delay 20%, Mental retardation 10% (Levey at al 2004)
- Carbamazepine: conflicting data

Risk Benefit Analysis in practice

32 year old woman who just learned she is pregnant (4 weeks GA) on paroxetine 40 mg a day for recurrent major depressive episodes for last 5 years. Pt currently has no depressive symptoms but has 2 previous suicide attempts while on medication and one previous psychiatric hospitalization. Has stopped medication before but resumed treatment after relapse.

1. Describe to patient – DX, benefit of TX and risks if medication discontinued
2. Describe your own understanding of risk of meds (all)
3. What do you say to patient about risks

Risk of Stopping Paroxetine

- Maternal
  - Withdrawal SX if rapidly stopped
  - Relapse of depression
    - 60-68% (Cohen 1999, 2006)
  - Risks of depression in pregnancy
  - Increased risk of post-partum depression
Switching Paroxetine to Another SSRI

- **Risk**
  - Unclear if equally effective
  - Fetal exposure to 2 medications (no data regarding effect)

- **Advantage**
  - Possible decrease of risk regarding birth defects due to paroxetine exposure

Difference in risk with paroxetine versus alternative SSRI

<table>
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<tr>
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<th>Paroxetine</th>
<th>Fluoxetine, sertraline, citalopram</th>
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<tr>
<td><strong>Teratogenicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital malformations</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Cardiovascular malformations</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Dose above 25mg/day associated with malformation (Berard 2007)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significantly more women had anxiety or panic (Bar-Oz, 2007)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine dose below 25mg equal to other SSRIs Used mostly for depression</td>
<td></td>
<td></td>
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Difference in risk with paroxetine versus alternative SSRI (Table 2 of 2)

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<tr>
<td><strong>Neonatal toxicity and withdrawal</strong></td>
<td>More cases reported (Costi 2002)</td>
<td>Present</td>
</tr>
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FDA Class Labeling for SSRI/SNRI’s

- All SSRI’s/SNRI’s used to be Cat C (caution, not enough data), Paroxetine to Cat D, definite concern in humans
- Neonates exposed to SSRI/SNRI antidepressants late in the third trimester have developed adverse events requiring prolonged hospitalization respiratory support and tube feeding
- Physicians will be advised to taper dosages of SSRIs during the last trimester, so women are medication free for 7-10 days prior to delivery
Risk Benefit Analysis in practice
- 23-y old single woman with a history of anxiety (GAD) and panic attacks starting 4 years ago. Hx of alcohol and MJ abuse 14-17, pt had excellent response to clonazepam and is continuing. Had only partial response to sertraline. She is 12 weeks pregnant.
- What do you tell her about risk of birth defects?
- What are long term effects
- What are neonatal toxicity and withdrawal effects

When to stop or switch medication?
- Much less known about benzodiazepines than SSRI’s.
- Teratogenicity controversial but considered low (Levey 2004).
- 33 cases of infants with maternal clonazepam exposure, no birth defects, (Lin 2004)
- Benzodiazepine syndrome (dysmorphic features, growth and CNS abnormalities controversial (Iqbal, 2002)
- Neonatal toxicity and withdrawal well documented-floppy infant
- Benefit of effective medication-outweighs risk-can consider very slow taper 4 weeks before delivery if patient can tolerate.

Mental illness in the postpartum
- Highest period of active mental illness
  - 20 times higher
- 10-15% Postpartum depression
  - 25-50% with HX
- 0.2% Postpartum psychosis
  - risk BP
- Untreated bipolar disorder
  - 50-80% relapse
  - 10-20% postpartum psychosis

Psychotropics in breastfeeding
- Placental passage of medication 70% of maternal serum
- All present in breast milk
- Infant exposure magnitude of order less
- None are FDA approved for breastfeeding
- All have limited safety data
- Unknown what if any is safe level for infants
### Antidepressants in Breast Feeding Mothers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Infant serum drug level</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Detected in some</td>
<td>Limp, irritable, Reduced infant weight over control</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Most not detected</td>
<td>None</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Most not detected</td>
<td>None</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Detected in some</td>
<td>Uneasy sleep (1)</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Not detected</td>
<td>None</td>
</tr>
</tbody>
</table>

(Gjerdingen 2003)

### Benzodiazepines in Breast-feeding Dyad

<table>
<thead>
<tr>
<th>Drug</th>
<th>1/2 life in mother (hrs)</th>
<th>Infant serum level</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>12-15</td>
<td>Not detected</td>
<td>None reported</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>18-50</td>
<td>Detected but might be due in utero exposure</td>
<td>Some reported</td>
</tr>
<tr>
<td>Diazepam</td>
<td>240</td>
<td>Detected</td>
<td>Lethargy, sedation, poor suckling</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>10-20</td>
<td>Not detected</td>
<td>None reported</td>
</tr>
</tbody>
</table>

(Malone 2004)

### Postpartum depression/Anxiety Treatment

- **Effective treatments:**
  - SSRIs: Use sertraline or paroxetine
  - TCA: Nortriptyline
  - Benzodiazepines: Monitor infant (can accumulate)
  - Estrogen: (controlled study 6 months)
  - Individual psychotherapy

(Gjerdingen 2003)

### Psychotherapeutic Treatment options for anxiety and depression in pregnancy and post-partum

- Mild to moderate SX with minimal functional impairment;
- Psychotherapy, CBT, IPT, increased social support
- Post-partum Mother-Infant therapy long term most beneficial for secure infant attachment and normal cognitive and behavioral development in children
- Treatment rates of HX of MDD-recurrent or current depression low -20%, women who do not take medication rarely receive adequate psychotherapy (Flynn, 2006)
SUMMARY

- No decision is risk free
- Inform women about known risks of medication and illness
- Serious symptoms require treatment
- Treat to remission

FDA Use-in-Pregnancy Ratings

- **A:** Controlled studies in women show no risk
- **B:** Animal studies show no risk but there are no controlled studies in humans, or animal studies show adverse effect that has not been confirmed in human studies
- **C:** Animal studies show risk but there are no controlled studies in humans, or studies in animals & humans are not available
- **D:** There is evidence of risk in humans, but the drug may have benefits that outweigh the risk
- **X:** Risk outweighs any benefit