Psychotropic Medications and Pregnancy

Renee M Bruno, MD
(beginning shortly)
Psychotropic Medications and Pregnancy

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“Decisions about what constitutes reasonable risk during pregnancy requires shared responsibility but ultimately rests with the informed patient.”

- Informed choices
- Close psychiatric follow up
- Coordinated care with OB

*Cohen, Nonacs* Mood and Anxiety Disorders in Pregnancy and Postpartum 2005; 24:54
Outline

- Background & Context
- Planning
- Guidelines (ACOG, APA)
- Effects of maternal illness
- Medications
  - Major Depression- antidepressants
  - Bipolar illness- mood stabilizers, antipsychotics
  - Schizophrenia- antipsychotics
  - Anxiety Disorders- benzodiazepines
Facts

- Antidepressant discontinuation in pregnancy, relapse common (75% in first trimester)
- Antenatal anxiety complicates depression
- Postpartum Mood and Anxiety disorders, intense and require aggressive treatment
- Bipolar Disorder may first present as Postpartum Psychosis
- Postpartum Psychosis is a Psychiatric Emergency
Shared goal

Maximize maternal & fetal wellbeing while minimizing exposure to:

• Medications
• Maternal illness
• Environmental toxins
Planning

- Symptom free for 6 months minimum
- Slow taper 25% q 1-2 weeks
- Mild
- Moderate to severe
Treatment Planning

• Self care
• Vitamins
• Planned contraception, conception
• Planned delivery
• Breast feeding intent
• Illness history
• Medication risk; risk of untreated illness
Bipolar Meds and Oral Contraceptives (OCP)

- Carbamazepine > 1200mg
- Oxcarbazepine > 1200mg
- Topiramate > 200mg

Induce cytochrome P40 enzymes = ineffective OCP’s

OCP’s can decrease Lamotrigine levels

Am J Psychiatry 2004; 161: 608-620
Folic Acid for ALL

- Antidepressants: Folic acid 1 mg daily
- Other (anticonvulsants) : Folic acid 2-4 mg daily
Decision making

- Has the baby already been exposed?
- Has the medication been optimized?
- What trimester is she?
- What works?
- Will she breastfeed?
Conundrums

• No decision is risk-free
• No psychotropic drugs approved for use during pregnancy
• Childbearing women & research studies
• Emphasis on error of commission rather than omission
• Risks more heavily weighted than benefits
• FDA labeling system inadequate
## Safety Ratings

<table>
<thead>
<tr>
<th>FDA Categories</th>
<th>FDA Proposal</th>
</tr>
</thead>
<tbody>
<tr>
<td>A no risk</td>
<td>Fetal Risk Summary</td>
</tr>
<tr>
<td>B no evidence risk</td>
<td>Clinical Considerations</td>
</tr>
<tr>
<td>C risk cannot be ruled out</td>
<td>Data</td>
</tr>
<tr>
<td>D positive evidence of risk</td>
<td>Breastfeeding section</td>
</tr>
<tr>
<td>X contraindicated</td>
<td></td>
</tr>
</tbody>
</table>
CRITICAL PERIODS IN HUMAN DEVELOPMENT*

- Age of embryo (in weeks) vs. fetal period (in weeks) vs. full term

1. Period of dividing zygote, implantation & bilaminar embryo
2. Not susceptible to teratogens
3. CNS.
   - Heart
   - Limbs

4. Eye
5. Heart
6. Ear
7. Palate
8. External genitalia
9. Brain
10. Central nervous system

- Major congenital anomalies (red)
- Functional defects & minor congenital anomalies (yellow)

* Red indicates highly sensitive periods when teratogens may induce major anomalies.
Resources

• Developmental and Reproductive Toxicity: www.toxnet.nim.nih.gov (DART database NLM)

• Organization of Teratology Information Specialists (OTI’s): www.otispregnancy.org (866)-626-OTIS


• MGH Center for Women’s Mental Health: www.womensmentalhealth.org
Good Practice

• Be familiar with risks of meds AND risks of maternal illness
• Be familiar with guidelines
• Document
• Communicate
• Collaborate, refer
• Include spouse/support
Guidelines for Antidepressant Use During Pregnancy

- Nonpharmacologic treatments ineffective
- History of serious decompensation when antidepressants discontinued
- Suicidal ideation, past attempts
- Psychosis
- History of serious disabling depression during previous pregnancy
- Inability to follow prenatal instructions (weight loss, missed visits)
- Serious lapses in judgment
- Severe and disabling anxiety
- Family history; perinatal depression, suicide

Burt V. Woman’s Health in Psych 2006; Vol. 2 No 5: 7 - 14
ACOG Guidelines

1. Single medication in a higher dose favored over multiple medications

2. Changing medications increases exposure

3. Selection of medication
   - prior exposure during pregnancy
   - available reproductive safety data
   - history of effectiveness
   - higher protein binding = less placental passage

4. Abrupt discontinuation discouraged
Untreated Perinatal Depression

- Poor prenatal care
- Cigarette/alcohol/drug abuse
- Preeclampsia
- Shorter gestation, motor maturity lower, cortisol higher
- Lower birth weight
- Suicide
- Shorter periods of breastfeeding
- More abusive
- Impaired attachment
- Cognitive behavioral disturbances in children

Orr ST et al. Pediatric and Perinatal Epidemiology 2000;14: 309-313
Young EA et al Biol Psychiatry 2006;60:831-836
Stress/Anxiety in Pregnancy

- Spontaneous abortions
- Premature or prolonged labor
- Preterm delivery
- Fetal distress
- Forceps deliveries

Schizophrenia in Pregnancy

- Placental abnormalities
- Antenatal hemorrhage
- Fetal distress/death
- LBW ≤ 10%
- Congenital anomalies 6%
- Feticide (delusional content)
Risk Categories

• Pregnancy loss, miscarriage
• Major birth defects (@ 3% in general population)
• Growth effects, timing of delivery
• Neonatal syndrome
• Neurobehavioral effects, impact on development

These domains are impacted by BOTH psychiatric disorders AND antidepressants.
## Perinatal Antidepressant Use

<table>
<thead>
<tr>
<th>SSRI’s</th>
<th>TCA’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No loss, miscarriage</td>
<td>• No loss, miscarriage</td>
</tr>
<tr>
<td>• Low birth weight</td>
<td>• No major malformations</td>
</tr>
<tr>
<td>• Shorter gestation</td>
<td>• + anticholinergic effects</td>
</tr>
<tr>
<td>• Paroxetine</td>
<td>• Nortriptyline favored in pregnancy</td>
</tr>
<tr>
<td>• PPHN */Autism</td>
<td>• No Neurobehavioral sequelae</td>
</tr>
<tr>
<td>• NAS **</td>
<td></td>
</tr>
<tr>
<td>• No Neurobehavioral sequelae</td>
<td></td>
</tr>
</tbody>
</table>

* Persistent Pulmonary Hypertension

** Neonatal Adaptability Syndrome

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Chambers et al N Eng J Medicine 2006; 354: 579-587

Bengt et al Pharmacoepid 2008; 17 (8): 801-806

Prospective Studies Antidepressants and Major Malformations

![Bar chart showing number of outcomes first trimester exposure]
Antidepressants

- SSRI’s: Fluoxetine, citalopram, sertraline (escitalopram)
- TCA’s: Nortriptyline, desipramine
- Bupropirion
- Mirtazapine
All Psychotropics Cross Placenta

N=303  umbilical/maternal plasma

SSRI’s  ESC > FLV > CIT@FLU > PAR@SER
  Lexapro  Luvox  Celexa  Prozac  Paxil  Zoloft

TCA’s  Nort > Clom
  Pamelor  Anafranil

Other  Ven ↑ > Bupr
  Effexor XR  Wellbutrin

All are present in Amniotic Fluid

Case reports amniotic fluid/maternal serum

Ven>, Par,Ser <

Kim J Br J Pharmacol 2006;61(2)15-163
Psychotropic medications and Breastfeeding

- All meds enter human breast milk
- Measuring serum blood levels in breast fed infants not recommended
- Meds with fewer metabolites favorable
- Shorter T ½ (half life) favorable
- Newborns ability to clear metabolically
Lactation Safety Classification and Resources

American Academy of Pediatrics

Thomas Hale Medications and Mother’s Milk Laleche
Bipolar Disorder in Pregnancy
Treatment Planning

- Prepregnancy gradual discontinuation (gauge relapse)
- Resumption clinical judgment
- Benzodiazepines
- Risk of Postpartum Psychosis
Bipolar Illness History

• Prior response to meds
• Illness severity
• Time to relapse after discontinuation
• Time to recovery when reintroduced
Bipolar I

- Lithium responsive, no Li during pregnancy and well, protective until last 5 weeks
- Postpartum Psychosis risk
- Lithium Prophylaxis prior to delivery (36 weeks no later than 48 hrs postpartum)
Psychiatric Hospitalization For Women During Postpartum Years

Pharmacotherapy for Bipolar Disorder

• Mood stabilizers are essential

• If patient wishes to avoid 1st trim Li, typical antipsychotics preferred. May use benzos prn, Lorazepam preferred

• Additional medications OFTEN needed even with prophylaxis both during and after pregnancy

• ECT with medications

• SLEEP and support may attenuate mood swings
Antiepileptic Drugs (AEDS)

Valproate

Carbamazepine
  Can breastfeed with infant monitoring

Gabapentin

Topiramate

Lithium

Lamotrigine

Neural tube defects major and minor malformations

Minimal data

Oral clefts

Preferred over AEDS

Holds Promise
Bipolar treatment in pregnancy

• **Yonkers** (psychosis)

If infant already exposed to atypical, patient tolerating and derives benefit continuing is preferable rather than switching to a typical which may not be beneficial, patient may not tolerate or derive benefit and then you have exposed the fetus to two drugs

• **Cohen**

In severe bipolar, Lithium alone or in combination with an antipsychotic may be a safe alternative to valproate. For Lithium nonresponders consider lamotrigine monotherapy or treatment with lamotrigine and typical antipsychotic.

Inadequate response to typicals consider atypical antipsychotic monotherapy or atypical with Lithium or lamotrigine
Clinical Considerations
Perinatal Lithium Use

1. Gradual taper prior to conception
2. Taper before conception; reinstitute after organogenesis
3. Continue through gestation; counsel
4. Fetal assessment with fetal echocardiography

Viguera A et al  Am J Psychiatry 2007; 164 : 342-345
Lithium Use in Pregnancy

- Teratogenicity / Exposure
  - Ebstein’s Anomaly 1:1000
    - Fetal Goiter
    - Lethargy
    - Floppy baby syndrome
- Neurobehavioral Sequelae
  - None known

Cohen et al  JAMA 1994; 271: 146 – 50
Shoum  Actapsychiatr Scand 1976; 54: 193 - 7
Lithium Use in Pregnancy
Late Exposure

1. Complete placental passage

2. Higher concentrations at delivery $\rightarrow$ ↑ adverse perinatal outcomes

3. Brief withholding (24 – 48hrs) prior to delivery does not compromise therapeutic outcome

*Newport et al. Am J Psychiatry 2005; 162: 2162-2170*
Perinatal use of Lamotrigine

1. Lamotrigine (Lamictal) inhibits folate formation
2. Potential maintenance therapy in pregnancy
3. Midline facial clefts (doses > 200)
4. Pregnancy increases clearance > 50%
5. Plasma concentration increases first 2 wks postpartum
6. Infants with slow elimination
7. Breastfeeding ???

Dolk H et al Neurology 2008 Sept vol 77
Tran T et al Neurology 2002 July 23; 59 (2): 251 – 5
Tennis P Epilepsia 2002 Oct; 43 (10): 1161 – 7
Antipsychotics

- First generation, typicals, high potency over low potency favored: Haloperidol, perphenazine, trifluoperazine
- Second Generation, atypicals, older drugs more data favored: Olanzapine, quetiapine
Atypical Antipsychotics in Pregnancy

Olanzapine, Risperidone, Quetiapine, Clozapine

N=151 + registries

No increase in rate of major malformations, spontaneous abortions or birth weight

Ziprasidone, Aripiprazole no data

Quetiapine

Least likely to elevate Prolactin and less placental passage

www.womansmentalhealth.org
Placental Passage Antipsychotics

Newport et al Am J Psychiatry 2007; 164: 1214 - 1220
Antipsychotics in Breastfeeding Guidelines

- Not recommended due to minimal data
- If a woman chooses to breastfeed
  - Avoid polypharmacy
  - Use lowest possible dose
  - Monitor infant for side effects
  - Coordinate with pediatrician
## Perinatal Anxiety Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAD, Panic</td>
<td>Premature delivery, Preeclampsia, Postpartum panic within 12 wks</td>
</tr>
<tr>
<td>OCD</td>
<td>SCARY; intrusive thoughts &amp; images of harm, sexual abuse, suicide; 39% new onset in pregnancy</td>
</tr>
<tr>
<td>PTSD</td>
<td>Chronic, multiple traumas, infertility, pregnancy loss, birth trauma</td>
</tr>
</tbody>
</table>

Abramowitz J. Anxiety Dis 2003; 17: 461 – 478
Loveland et al. Obstet and Gynecol 2004; 103 (4): 710 - 714
### Benzodiazepines in Pregnancy

**Category D = Bad Wrap**

<table>
<thead>
<tr>
<th>C-Section</th>
<th>Induction of Labor</th>
<th>Premature Labor</th>
<th>Anxiety Disorders</th>
<th>Surgery</th>
<th>Placental Abruption</th>
</tr>
</thead>
</table>

- Studies > 30 years – no increased risk of major malformations
- Case-control studies – increased risk for cleft palate (Diazepam)
- Occasional neonatal withdrawal symptoms minimized by slow tapering
- Long term studies show no adverse effects
- Very useful in pregnancy, postpartum, lactation

**Lorazepam**

*Dolovich LR et al. BMJ 1998; 317: 839 - 843*
Nontraditional Treatments

- Light Therapy
- Massage
- Acupuncture
- Omega 3 fatty acids
- Mindfulness Based Stress Reduction
- Exercise
- Nutrition / Sleep
- rTMS
- Religiosity / Spirituality
"We never forget you have a choice."
Questions

Renee M. Bruno, MD, Presenter