Medication Use During Pregnancy & Lactation

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Disclosures

- None
Goal of Treatment

Wellness for mom that then translates into health for her child.

“... it is not possible to talk about an infant without at the same time talking about infant-care and the mother.”

D.W. Winnicott, M.D. 1965
Questions About Medication Use in Pregnancy

- What do we know about safety?
- Are some antidepressants safer than others?
- Does it make sense to avoid use of antidepressants during certain stages of pregnancy?
- Is keeping the dosage as low as possible important?
- What are the risks if antidepressants are not prescribed?
- Are there alternative treatments?
- What about patients with bipolar depression?
Studies Looking at Safety of Medications

- Most are retrospective case-control designs using large birth registry information or managed health care databases.
- Prospective case-control data review studies.
- Few small, prospective observational studies.
- Meta-analyses of above.
- Recent studies compare exposure to antidepressants with exposure to depression, look at biomarkers for stress and the complexity of genes and environment.
2008 ACOG Opinion on Psychiatric Medication Use During Pregnancy

- “The potential risk of SSRI use throughout pregnancy must be considered in the context of the risk of relapse of depression if maintenance treatment is discontinued.”
- Avoid paroxetine due to concerns about heart defects, but do not discontinue abruptly.
- Association of SSRI use and PPHN is “unconfirmed”.
- Recent studies have not shown a link between prenatal exposure to TCAs and perinatal problems.

Obstetrics and Gynecology 2008;111 (4):1001
Identifies the risks of untreated depression in pregnancy/postpartum period:

- Poor nutrition, poor prenatal care, tobacco, alcohol and drug use, risk of suicide.
- Adverse obstetric complications (pre-eclampsia, PTD, LBW, miscarriage, SGA, low Apgars, neonatal complications).
- Postpartum: diminished maternal-infant interactions leading to negative infant development, infant mortality, neglect, abuse, homicide, domestic violence.
AHRQ report contd.

- Poses 3 questions regarding treatment:
  - What are the comparative **benefits** of medications and nonpharmacological txs?
  - What are the comparative **harms**?
  - What patient characteristics (eg: SES, BMI, comorbidities), intervention characteristics and provider characteristics predict positive response to treatments?
AHRQ Findings

- Very few studies show direct evidence for outcomes of antidepressants.
- Studies using indirect evidence compare outcomes for women taking ADs for any reason with women not on ADs where presence of depressive symptoms are rarely reported and not analyzed.
- RCT studies meeting criteria for efficacy have drawbacks (exclude pts with co-morbidities, lack health outcomes, lack comprehensive assessment of adverse events, are short in duration and small.)
- Studies of non-pharmacologic treatments have a “lack of detail” regarding the characteristics of the treatment.
AHRQ Conclusions

- Pharmacologic treatment for pregnant women “may offer benefits.”
- Regarding harms:
  - There is direct evidence that SSRIs are associated with respiratory distress, and are not associated with neonatal convulsions.
  - 5 quality, indirect studies (low bias, systemized classification of malformation, controlled for 3 out of 4 major confounders) found no evidence for association of SSRIs and cardiac malformations.
No direct evidence for Neonatal Abstinence Syndrome, but 5 small cohort studies with medium risk for bias show evidence for NAS.

Encourage concurrent breastfeeding with SSRIs
- Negligible amounts get through breast milk
- No evidence of adverse events in children
Respiratory Distress & PPHN

- **Respiratory Distress**
  - Infants require supportive measures like O2 due to apneic spells (non-life threatening and transient)

- **PPHN** rare, heterogeneous failure of neonatal lung circulation to dilate. Incidence of 2/1000.
  - 6 indirect studies with conflicting findings: 3 find association but have conflicting timing for exposure risk and 3 find no association.
  - 50 neonates w/ PPHN/25,000 exposed to SSRI (2/1000 incidence equivalent to population statistics.)

1Ochiogrosso, M, 2012
Depression and Anxiety as Physical Stress

**Depression**
- 6.7% 12-month incidence in U.S.¹

**Anxiety**
- 18.1%
  - GAD 3.1%
  - OCD 1%
  - Panic D/O 2.7%
  - Social Anxiety 6.8%

**Stress Response**
- Hypothalamic-Pituitary Axis Dysregulation (eg: ↑ cortisol)
- Alterations in Immune Response
- Constricted Bloodflow

¹Kessler et al, 2005.
Does Maternal Mental Distress Harm the Fetus?

- Depressive Symptoms 18%\(^1\)
- MDD 10%\(^1\)
- Anxiety 13%\(^2\)
  - OCD 2% (PP 2.4%)\(^3\)

Stress Response

Perinatal/Infant Outcome
Fetal Origins of Adult Disease

\(^1\) Marcus, SM 2009
\(^2\) Heron J, 2004
\(^3\) Russell, FJ 2013
Does Medication for Maternal Emotional Distress Harm or Protect the Fetus?

Antidepressant 8.1%¹

Depression

Stress Response

Anxiety

¹Alwan, S, 2011

Perinatal/Infant Outcome
Fetal Origins of Adult Disease
What Exposure Poses More Risk to Fetus?

Depression

Antidepressant

Atypical Uterine Environment (ie: uterine blood flow, maternal corticosteroid & other hormones)

Fetal Development (ie: overall growth, heart rate variability, glucocorticoid receptor expression)

Anxiety

Perinatal/Infant Outcome

Adult Disease (FOAD)

¹Monk, C, 2011
Fetal Origins of Adult Disease

- Dutch Famine during WWII led to a marked increase in schizophrenia & CNS abnormalities in offspring.
  - malnutrition & maternal stress as causes?
- ALSPAC study: cohort of families from pregnancy to teens in the UK:
  - mothers with high levels of anxiety during late pregnancy produced a higher rate of children with behavioral & emotional problems at ages 4 & 7.

1 O’Connor, TG et al 2003
Fetal Origins of Adult Disease

- Prospective, longitudinal study of 35 pregnant women assessed for anxiety at 19, 25 and 31 weeks. MRIs of their children done at 6-9 y.
  - Anxiety at 19 weeks GA associated with ↓ gray matter volume, esp. in prefrontal cortex.\(^1\) No association with anxiety at 25 and 31 weeks GA.
  - Psychobiological markers of maternal stress associated with disrupted emotional regulation & impaired cognitive development in offspring.\(^2\)

\(^1\)Sandman CA et al, 2010
\(^2\)Sandman CA et al, 2011
Fetal Origins of Adult Disease

- ALSPAC (n: 3,442)\(^1\)
  - Pregnant women & partners (to control for intrauterine effects vs. general environment in home) tested for anxiety during pregnancy.
  - Positive association between antenatal maternal depression & anxiety with attention and behavioral problems in 3-4 year old children.
  - Confounders such as smoking, SES & postnatal depression also factors in severity of child difficulties.

\(^1\)Van Batenburg-Eddes et al, 2013
Factors Supporting Wellness

- Sleep
- Nutrition
- Exercise
- Social Support
- Contemplative Practice
- Medication
Sometimes Medication is Key to Recovery

- Medication
- Sleep (Sense of Social Support)
- Diet (Mindfulness, Exercise)
Current FDA Safety Categories Are Not Helpful

- Teratogens have historically been identified not through animal studies but through astute clinicians noting patterns of malformations (examples: Fetal Alcohol Syndrome, Thalidomide, Retinoic Acid).
- Studies currently used to identify risk are indirect and prone to bias.
- Priveleges medications with less data.
- Do not help clinicians weigh the strength of the data.
New FDA Categories are coming!

- 2008, FDA announced a new system with 3 sections
  
  1. “Fetal Risk Summary” – conclusion as to risk of fetus based on quality & quantity of studies
  2. “Clinical Considerations” – compares risks to mother and fetus of exposure to illness vs. exposure to medication
  3. “Data” – what Fetal Risk Summary is based upon

1FDA News Release, May 28, 2008
Benzodiazepines

- Reports of increased risk of oral clefts, though extent of risk remains controversial\(^1\)

- Perinatal dependence syndrome of low Apgar scores, hypotonia, and hypothermia\(^2\)

- Perinatal withdrawal syndrome of hypertonia, hyperreflexia, restlessness, irritability, seizures, bradycardia, abdominal distention, and unconsolable crying\(^3\)

- Neurobehavioral teratogenicity data limited
  - Some studies suggest developmental delays\(^4,5\), while others do not\(^6\)

Epidemiology of Bipolar Disorder

- Common illness (~1-2% lifetime prevalence)
- Early onset (Peak onset: 15-24 years)
- Recurrent in >90%
- Long average duration of mood episodes
  - depression: 19 weeks
  - mania: 10 weeks
  - mixed: 36 weeks
- High comorbidity
- High suicide risk (10-15% completion rate)

Kessler RC, et al. *Arch Gen Psychiatry* 1994;51:8-19
Bipolar Disorder

Recurrence Risk During Pregnancy

- Pregnancy does not consistently protect against recurrence of mania or depression
  - 45-50% of women may have an exacerbation of illness during pregnancy\(^1,2\)

- Factors associated with higher risk of relapse during pregnancy include\(^3,4\):
  - abrupt discontinuation of mood stabilizers
  - a history of 4 or more prior mood episodes
  - prior intrapartum mood episode(s)

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Bipolar Disorder

Recurrence Risk During Postpartum Period

- 60-80% recurrence rates in the first three to six months postpartum\(^1-3\)

- 10-20% risk of postpartum psychosis (compared to 0.1-0.2% in general population)\(^4-6\)
  - Risk of recurrent postpartum psychosis in subsequent pregnancy may be as high as 90%\(^7,8\)

General Guidelines for the Management of Medication During Pregnancy

- Planning prenatally is optimal

- If unplanned pregnancy occurs while on meds:
  - Don’t panic
  - Avoid abrupt medication change
  - Discuss benefits v. risks of stopping meds
    - Highest risk period may have already passed
  - If discontinuing medication, taper slowly
  - Create timeline from LMP to delivery that documents medication exposures, Etoh/drug use, PNV use, and Obstetric visits

Summary

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Case Discussion #1

28 year G0 woman with a history of anxiety and depression treated successfully with sertraline seeks preconception counseling.
Case Discussion #2

- 35 year old G1P0 at 20 weeks gestation whose mother died suddenly a month ago, struggling with insomnia, low energy, inability to enjoy herself, difficulty concentrating at work and preoccupied with negative outcome with the pregnancy.
Case Discussion #3

- 22 year old G1P1 at 2\textsuperscript{nd} day postpartum feels like something is very wrong with her mood and can’t sleep even when infant is sleeping.
Case Discussion #4

- 38 year old G1P1 at 3 months postpartum who keeps presenting to pediatrician with concerns about the health and development of her baby.
Family member calls concerned about odd behavior of a 30 year old 3-week postpartum mom exhibiting paranoia about anyone but her caring for the baby.