Evidence-Based Approaches to Psychiatric Care during Pregnancy in the Age of Sensationalized Media

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- Research Support from NIMH, Stanley Medical Research Foundation, SAGE
- Off label uses of medications will be discussed throughout this presentation

Objectives
- Participants will be able to:
  - Identify two risks of untreated psychiatric illness during pregnancy.
  - Define the term “confounded by indication.”
  - Quantify the risk of persistent pulmonary hypertension in antidepressant exposed newborns

Talk Overview
- How Common are Mood Disorders During and After Pregnancy?
- Why treat mood disorders during pregnancy?
- General Rules for Medication Management During Pregnancy and Breastfeeding
- Confounding by Indication
- Focus on Persistent Pulmonary Hypertension
- Why Psychiatric Medication Use during Pregnancy is So Controversial
- The Future: A test for Postpartum Depression
Pregnancy and Mood Disorders

Take Home Point: There is an increased risk for a Major Depressive Episode Postpartum

Pregnancy is “risk-neutral”

Take Home Point: In Women with Mood Disorders who Stop Meds for Pregnancy, the Relapse Rate is High (but probably not different from stopping meds outside of pregnancy)

Depression During Pregnancy

- There is No Evidence that the risk of Major Depression increases during pregnancy
  - 14,549 women with a pregnancy in the past year
  - No increased risk for MDD during pregnancy compared to nonpregnant female population
  - Postpartum risk was elevated with an odds ratio of 1.52 (Vesga-Lopez et al, 2008)
Pregnant Women with Major Depression

- Women with history of Major Depression at greatest risk
- 60-70% of women who stop their antidepressants will relapse into Depression

<table>
<thead>
<tr>
<th>Table 2. Relapse of Major Depression During Pregnancy</th>
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<tr>
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<td>----------------------</td>
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<tr>
<td>No relapse</td>
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<tr>
<td>Relapse by trimester</td>
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<td>First</td>
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<td>Second</td>
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Pregnant Women with Bipolar Disorder

- The relapse rate off of lithium was no different during pregnancy than at other times for women with Bipolar Disorder
- In contrast, the relapse rate was 2.9 times more common postpartum than in nonpregnant females

Viguera et al, AJP 2000

Postpartum Depression: Who is at Risk?

- 10-15% of women in general population
- 25-50% of women with a pre-existing mood disorder
- 70-80% of women with a pre-existing mood disorder who stop their meds for pregnancy
- Genetics play a role
- Environment plays a role

Viguera et al, AJP 2007

Pregnant Women with Bipolar Disorder

- Discontinuation of mood stabilizers during pregnancy increases the risk of relapse:
  - 85.5% women who discontinued meds relapsed
  - 37% of women who continued meds relapsed

Viguera et al, AJP 2007
Myth: Women Should Tolerate Being Depressed During Pregnancy for the Sake of the Baby

Truth: Depression During Pregnancy Leads to Poor Outcomes for Mom and Baby

Why Treat Depression during Pregnancy?

- Depression during pregnancy is associated with:
  - Premature delivery
  - Low birth weight
  - Decreased motor tone and activity in the baby
  - Higher cortisol levels in the baby
  - Poor reflexes in the baby
  - ADHD and behavioral problems, particularly in boys

Maternal Suicide

- Suicide is a major cause of maternal death in pregnancy and accounts for up to 20% of all postpartum deaths (Shadigian & Bauer, 2005)
- Psychiatric disorders in general are the leading cause of indirect maternal deaths (Oates, 2003)
- Overall though, suicide is a rare event during pregnancy and is lower than the rate in the general population

Depression During Pregnancy and Postpartum Depression

- Depression during pregnancy is one of the biggest risk factors for PPD
- PPD is associated with the following in exposed children:
  - Lower IQ
  - Slower language development
  - ADHD
  - Behavioral problems
  - Psychiatric illness
(Postpartum) Depressed Moms are:

- More likely to smoke, use substances
- Less likely to talk to their babies
- Less likely to give their kids vitamins
- Less likely to put their kids in car seats
- Less likely to talk to their babies
- Less likely to get their kids vaccinated or go to checkups
- More likely to use the ER

Mood Disorders During and After Pregnancy: Summary

- Even though pregnancy is “risk neutral” for both MDD and BP disorder for new mood episodes, discontinuation of medications is associated with a high relapse rate
- Postpartum is clearly a period of elevated risk for both Major Depression and Bipolar Disorder
- Mood disorders during and after pregnancy are associated with poor infant outcomes
- This indicates a need for treatment during pregnancy for many women...

General Rules for Medication Plans During Pregnancy

Rule Number 1

- Assume all women of reproductive age will get pregnant!
- Discuss potential complications for the baby with the medication that you’re prescribing
- Discuss what form of birth control they are using or will in the future
- Emphasize the need for a planned pregnancy regarding psychiatric medications
Rule Number 2
- Consider Exposure to Psychiatric Illness In Utero an Exposure for the Baby

Rule Number 3
- Limit the number of exposures for the baby
  - Exposure to psychiatric illness counts- thus goal is to keep Mom well during pregnancy to eliminate this exposure
  - Maintain Mom on as few medications as possible
  - Try to make medications changes before pregnancy and make sure that Mom is stable before getting pregnant

Rule Number 4
- Use medications that we know more about
  - Older=Better (generally)
  - Epilepsy literature increases samples sizes
  - FDA categories not very useful

### FDA Categories

<table>
<thead>
<tr>
<th>FDA Category</th>
<th>Description</th>
<th>Problems</th>
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<tbody>
<tr>
<td>A</td>
<td>Animal studies have demonstrated no adverse effect on the fetus. However, there is a lack of adequate and well-controlled studies in pregnant women.</td>
<td>Not all drugs in this category have the same level of investigation. For example, bupropion was originally classified in this category because of one small sample of women. It has since been reclassified at Category C based on animal studies. Medications without a lot of human data are placed here. For example, Lurasidone is category B.</td>
</tr>
<tr>
<td>B</td>
<td>Animal studies have shown an adverse effect on the fetus, and there is no adequate and well-controlled study in pregnant women.</td>
<td>Not all drugs in this category have the same level of risk.</td>
</tr>
<tr>
<td>C</td>
<td>No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.</td>
<td>Not all drugs in this category have the same level of risk.</td>
</tr>
<tr>
<td>D</td>
<td>Studies, adequate and wel-controlled or laboratory studies, have demonstrated no risk to the fetus.</td>
<td>Not all drugs in this category have the same level of risk.</td>
</tr>
<tr>
<td>X</td>
<td>Categories of drugs that have not been studied or are highly contraindicated.</td>
<td>Not all drugs in this category have the same level of risk.</td>
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Category B is NOT necessarily safer than Categories C and D!

- Animal studies have revealed no evidence of harm to the fetus, however, there are no adequate and well-controlled studies in pregnant women OR
- Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
- New meds typically are rated Category B

FDA’s New Rule
- The “Pregnancy and Lactation Labeling Rule” went into effect on June 30, 2015
- All new products will have the new label and old products will be phased in
- “Pregnancy,” “Lactation” and “Females and Males of Reproductive Potential” sections
- Will include all currently available information
- Gets rid of categorical system
Rule Number 5

- Every case is different!
- IE There are no rules…

The Team Approach: Rule Number 6

Myth: Antidepressants During Pregnancy are Associated with Poor Infant Outcomes

Truth: Well-Controlled Studies Do NOT Find Associations with Adverse Long-Term Infant Outcomes
Problems with the Literature

- Most studies don’t control for:
  - The underlying psychiatric illness
  - Severity of psychiatric illness
  - Risk factors that are found in a higher rate in the psychiatric population
    - Diabetes, Smoking, Substance Use, Obesity etc
  - Whether or not the mother was psychiatrically ill during pregnancy
  - Multiple medications

Confounding Variables

Confounding Variable

It’s a rather interesting phenomenon. Every time I press the lever, that post-epidural student breathes a sigh of relief.

Confounding by Indication

Beware of Confounding Variables

- The object of an experiment is to prove that A causes B.
- A confounding variable is anything that could cause change in B, that is not A.
- Lifestyle and family history may also affect the heart.
In other words psychiatric medication use during pregnancy is a **marker** for a population of women, different from the general population of women, with attendant risk factors and behaviors that can affect birth outcomes.

Studies which compare pregnant women with depression taking meds and pregnant women with depression not taking meds do **not** find associations between antidepressants and:
- Heart Defects
- Persistent Pulmonary Hypertension
- Autism

### Persistent Pulmonary Hypertension (PPHN)

- PPHN – failure of pulmonary vascular resistance to decrease at birth
- 1-2 per 1000 live births
- Associated with: Maternal smoking, maternal diabetes, meconium aspiration, postmaturity, C-section, sepsis, others
- Leads to substantial infant mortality (10-20%) and morbidity

### SSRI's and PPHN

- Seven studies to date
- 3 studies retrospectively examined risk factors in infants with PPHN:
  - Chambers et al, 2006: 5 fold increased risk
  - Källén et al, 2008: 2-3 fold increased risk
  - Wilson et al, 2011: No association
- 3 studies retrospectively examined rates of PPHN in infants exposed to antidepressants:
  - Andrade et al, 2009: No association
  - Wichman et al, 2009: No association
  - Keler et al, 2011: 2.5 fold increased risk
Huybrecht’s et al, 2015

- Most recent study
- Largest to date- 3.8 million pregnancies
- 128 thousand took an antidepressant
- Unadjusted analysis: OR 1.51 (1.35-1.69)
- Adjusted analysis: OR 1.10 (0.94-1.29)
  
  NOT SIGNIFICANT
- Propensity score adjustments for confounders

Confounds Considered

- Year of delivery, age, race, multiple gestation, antidepressant indications
- Proxies for depression severity (number of outpatient and inpatient depression diagnoses),
- Other chronic maternal illness
- Other psychotropic medication use
- Other medications
- Number of physician outpatient visits and number of hospital days were used as a general marker of comorbidity.

Perspective on PPHN

- Kieler et al, 2011 also found that a history of a psychiatric admission increased the risk of PPHN (Odds ratio 1.3) even when those women did not take antidepressants during pregnancy
- This indicates that it may be other factors associated with psychiatric illness that increase the risk for PPHN

Perspective on PPHN

- 1-2 infants in the general population normally develop PPHN
- If the odds ratio is 6… (the highest found)
- 6-12 infants per 1000 exposed to SSRIs in late pregnancy will develop PPHN
- Approximately 99% of infants exposed will NOT develop PPHN
Why the Negative Media?

Hype: Google Search- October 2015
- Search of "Antidepressants, Pregnancy"
  - 901,000 results
- Added "Harm"
  - 9,160,000 results
- Deleted "Harm," added "Safe"
  - 529,000 results

A Scary Story is a Popular Story

The Devil is in the Details

AD use during the second and/or third trimester of pregnancy was statistically significantly associated with an 87% increased risk of ASD, after taking all potential confounders into account. N=31, increased risk from 0.7% to 1.3%

The effect was persistent even after taking into account maternal history of depression (adjusted hazard ratio, 1.75; 95% CI, 1.03-2.97). Note: close to 1

In sensitivity analysis restricted to children with a diagnosis of ASD confirmed by specialists (psychiatrists and/or neurologists), the findings were consistent with those of the main analyses, increasing the validity of these results. But these results were not statistically significant.

Results: Berard et al (JAMA Pediatrics)
Stigma

What if We Had a Test for Postpartum Depression?

Epigenetics Defined
- Heritable changes in gene activity which are not caused by changes in DNA sequence
- DNA methylation and histone modification alter how genes are expressed
- Why differentiated cells in a multicellular organism only express the genes they need
- Environmental exposures can induce epigenetic changes and change gene expression

Estrogen and the Brain...
- Numerous animal studies have demonstrated that estrogen has anxiolytic and antidepressant effects specifically within the hippocampus
- Estrogen administration results in increased synaptic plasticity and dendritic spine density in the hippocampus
- Estrogen withdrawal results in decreased hippocampus BDNF expression
- Hypothesis: Increased levels of estrogen during pregnancy lead to epigenetic changes in the hippocampus that result in a depressive episode
First…the Mouse

- Screened for genetic loci responsive to high doses of estrogen (to model pregnancy) in the mouse hippocampus
- Identified loci were cross-referenced with DNA methylation differences identified in blood taken during pregnancy in women with mood disorders who did and did not develop PPD

Epigenetic Changes Associated with PPD

- Used linear discriminant models
- We identified two biomarker loci at the HP1BP3 and the TTC9B genes that predicted PPD with approximately 87% accuracy
- We have since replicated these findings in three samples collected by other researchers
- We are currently working to replicate this work in a larger sample of women

HP1BP3 and TTC9B

- Exact functions are unknown
- HP1BP3 has been shown to associate with the β estrogen receptor
- HP1BP3 has recently been shown to influence maternal care behavior in mice
- TTC9B has been shown to be responsive to gonadal hormones
- TTC9B may be linked to hippocampal synaptic plasticity

The Way Forward

- Will having a test for PPD decrease the negative media attention surrounding treatment during and after pregnancy?
- Stay tuned…
Thank You!!

- Our patients and research subjects
- Tessa Ring, Samantha Meilman, Molly O'Rourke
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