The Management of Mood Disorders During Pregnancy

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Disclosures

- No financial interests
- Research support from NIH, Brain and Behavior Foundation, Wharton Foundation
- Off label uses of medications will be discussed throughout this presentation

Objectives

- Participants will be able to:
  - Define the potential risks and benefits of psychiatric medication use during pregnancy
  - Define the potential risks of no treatment for psychiatric illness during and after pregnancy
  - Identify 2 or more treatment alternatives to psychiatric medication during and after pregnancy

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
- Antidepressants: PPHN and Poor Neonatal Adaptation Syndrome
- Mood Stabilizers and Other Medications
- Breastfeeding
- Alternatives to Medications

Rate of MDD in Women is Double the Rate in Men during the Reproductive Life Cycle

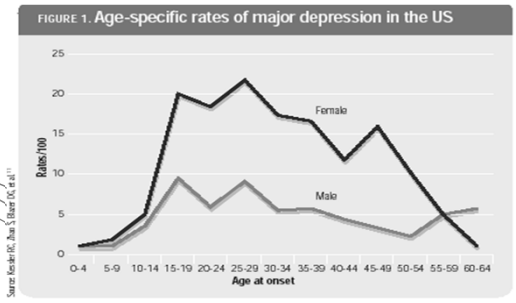


Chart shows the steep rise in risk for major depressive disorder just as females enter the fertile period of their lives.

Pregnancy and Mood Disorders

Depression During Pregnancy

- There is No Evidence that the risk of Major Depression increases during pregnancy
- 2002 National Epidemiologic Survey on Alcohol and Related Conditions (Vesga-Lopez, O. et al. Arch Gen Psychiatry 2008;65:805-815).
  - 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

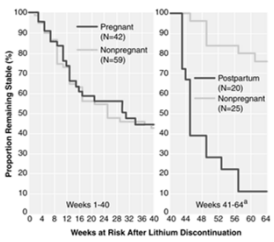
Table 3. Relapse of Major Depression During Pregnancy

		Medication Status			
Relapse Status	All Women	Maintained	Increased	Decreased	Discontinued
No relapse	115 (57.2)	61 (74.4)	11 (55.0)	22 (64.7)	21 (32.3)
Relapse by trimester					
All	86 (42.8)	21 (25.6)	9 (45.0)	12 (35.3)	44 (67.7)
First	44 (51.2)	11 (52.4)	7 (77.8)	5 (41.7)	21 (47.7)
Second	31 (36.0)	9 (42.9)	2 (22.2)	3 (25.0)	19 (43.2)
Third	11 (12.8)	1 (4.8)	0 (0.0)	4 (33.3)	4 (9.1)

Cohen, L. S. et al. JAMA 2006;295:499-507.

Pregnant Women with Bipolar Disorder

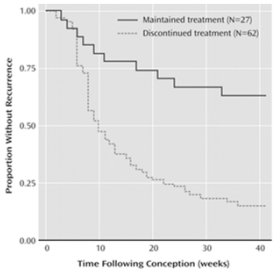
- The relapse rate off of lithium was no different during pregnancy than at other times for women with Bipolar Disorder
- In contrast, the relapse rate was 2.9 times more common postpartum than in nonpregnant females



Viguera et al, AJP 2000

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

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
- This indicates a need for treatment during pregnancy for many women…

Why treat depression during pregnancy?

- Depression during pregnancy is associated with….
  - Preterm delivery (OR ~ 1.5)
  - Low birth weight (OR ~ 2)
  - 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
    - See recent reviews: Davalos et al, Archives Women's Ment Health, 2012; Jarde et al. J*AMA Psychiatry*. 2016;73(8):826-837

Fetal programming

- The fetus is well protected from toxic effects of everyday maternal stress…
  - Maternal HPA axis has reduced baseline activity and reduced responsiveness during pregnancy
  - A placental enzyme (11βHSD2) inactivates some of the circulating maternal glucocorticoids
- But with severe, prolonged stress or depression…
  - Maternal cortisol level can rise enough to overwhelm these defenses (enzyme less effective)
  - This increases methylation at promoter regions of fetal genes that affect glucocorticoid receptors
  - The child's stress response system can become hypersensitive
  - This can lead to enduring behavioral changes

HPA = hypothalamic pituitary adrenal
11βHSD2 = 11β-hydroxysteroid dehydrogenase 2

Depression During Pregnancy

- 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

Risk For 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

Grace et al. Arch Women's Ment Health 2003;6:263–274. Dunkel Schetter et al. Current Opinion in Psychiatry 2012:25:141-148.

General Rules for Medication Plans During Pregnancy

Medication Treatment of Depression 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 2: Consider Exposure to Psychiatric Illness In Utero an Exposure for the Baby

Pregnancy: 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 medication changes before pregnancy and make sure that Mom is stable before getting pregnant

Pregnancy: Rule Number 4

- Use medications that we know more about
  - Older=Better (generally)
  - Epilepsy literature increases samples sizes
  - Old FDA categories not very useful
  - New pregnancy and lactation labeling rule is very helpful – but you have to read it!

Pregnancy: Rule Number 5

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

The Team Approach: Rule Number 6

Psychiatric Medication Use in Pregnancy

Studies of Birth Outcomes of Psychiatric Medications are Complicated By…

- Multiple medications used during pregnancy
- Substance use/abuse during pregnancy
- Social stressors
- Diagnosis of mood disorders is complicated
- Effects of psychiatric illness on eating, sleep
- Effects of psychiatric illness on outcomes
- Co-morbid medical illness in the psychiatric population (eg diabetes, obesity)
- Other behaviors associated with psychiatric disorders

Medications In Pregnancy

- There are NO studies of any medications on the efficacy of treating mood disorders during pregnancy
- Several studies indicate that discontinuation of medications increases risk of mood episodes in pregnancy
- There are NO safety studies and NO long-term (>5years) safety studies on exposed infants

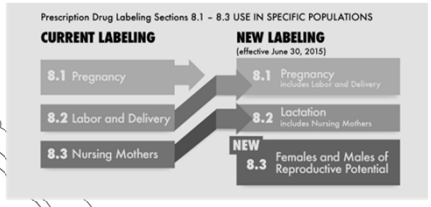
FDA Categories

FDA Category	Description	Problems
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.	
B	Animal studies have revealed no evidence of harm to the fetus, however, there are no adequate and well-controlled studies in pregnant women. 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.	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.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.	Not all drugs in this category have the same level of risk.
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.	
X	Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnancy	Some drugs are placed in this category because there is no reason to use them during pregnancy, not because of evidence of fetal abnormalities. Example: Oral Contraceptives

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; before 2001 NOT required
- "Pregnancy," "Lactation" and "Females and Males of Reproductive Potential" sections
- Will include all currently available information
- Gets rid of categorical system – categories MUST be removed from labels by June 2018

FDA's New Rule



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

Psychiatric Medications as Markers

- 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

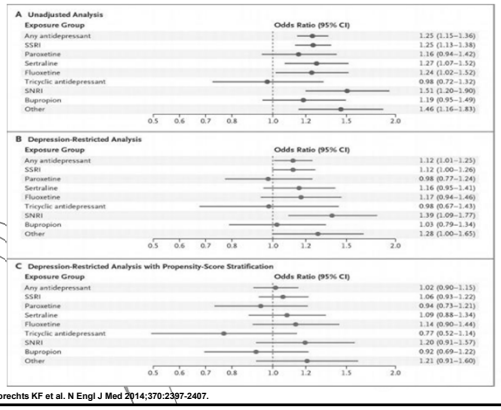
Antidepressants in Pregnancy: *Risks That Have Been Studied*

- Spontaneous Abortion
- Preterm Birth and Birth Weight
- Heart Defects
- Persistent Pulmonary Hypertension
- Poor Neonatal Adaptation Syndrome
- Autism

Heart Defects

- Multiple studies- some positive, some negative
- Most recent and largest: **Huybrechts KF**
  - *(N Engl J Med 2014;370:2397-2407)*
- Over 900K sample
- Controlled for MDD and severity of MDD
- No association with heart defects in the adjusted analyses

Risk of Cardiac Malformation in Infants, According to Maternal Exposure to Antidepressants.

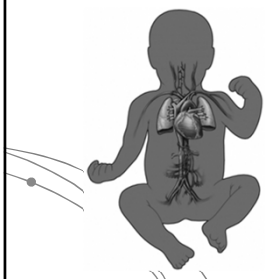


Huybrechts KF et al. N Engl J Med 2014;370:2397-2407.

Meta-analysis

- Included population based cohort studies of SSRI's during pregnancy
- 4 cohort studies: 1,996,519 participants
- Compared women with MDD who took SSRIs to women with MDD who did not take antidepressants *(i.e. controlled for MDD)*
- OR 1.06 (0.94-1.18)-Not significant
  - Wang et al, *J Amer Heart Assoc,* 2013

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, postmarturity, C-section, sepsis, others
- Leads to substantial infant mortality (10-20%) and morbidity

SSRIs and PPHN

- Seven studies to date
- 3 studies retrospectively examined risk factors in infants with PPHN
  - Chambers et al, 2006: **6 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**
  - Kieler et al, 2011: **2.5 fold increased risk**

Huybrechts 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 (hypertension, preexisting diabetes, gestational diabetes, epilepsy, renal disease, asthma, obesity)
- Other psychotropic medication use (anticonvulsants, antipsychotics, anxiolytics, benzodiazepines, other hypnotics, barbiturates, lithium),
- Other medications: antidiabetic, antihypertensive and asthma medications, and nonsteroidal anti-inflammatory drugs.
- Number of distinct prescription drugs excluding antidepressants dispensed,
- 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) <u>even when those women did not take antidepressants during pregnancy</u>
- The combination of a previous psychiatric admission plus antidepressant exposure tripled the risk of PPHN (Odds ratio 3.1)
- This indicates that it may be other factors associated with psychiatric illness that increase the risk for PPHN

Perspective on PPHN

- Some risk factors associated with PPHN are also associated with MDD/psychiatric illness
  - Smoking
  - High Body Mass Index
  - Diabetes
  - C-section

  All of the studies but one (Wilson et al.) did not control for mode of delivery, which is a known risk factor for PPHN

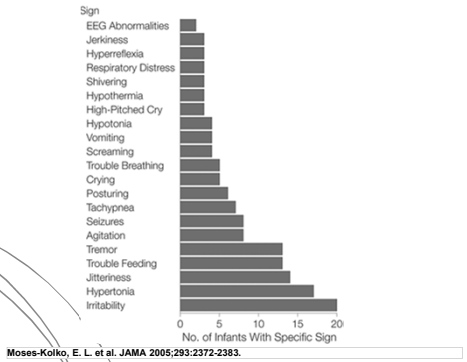
Perspective on PPHN

- 1-2 infants per 1000 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

Poor Neonatal Adaptation Syndrome

- Cluster of symptoms seen in infants exposed to SSRIs during the 3rd trimester
- Also seen in infants exposed to tricyclics, other meds and no meds
- Unclear if due to "withdrawal" or toxicity
- Symptoms include: respiratory distress, temperature changes, feeding difficulty, jitteriness, irritability, fits, difficulty settling, floppiness, rigidity, hypoglycemia, and jaundice
- No blinded studies conducted to date examining whether these symptoms are more common in SSRI (or other AD) exposed infants or not

Frequencies of Specific Signs Reported to the FDA Adverse Events Reporting System30



Moses-Kolko, E. L. et al. JAMA 2005;293:2372-2383.

JAMA

Poor Neonatal Adaptation Syndrome: Issues to be Explored

- Clear definition
- Measurement
- Blinded studies in both exposed and unexposed infants, including maternal psychiatric illness as a variable
- Does tapering of SSRI in 3rd trimester decrease the rate? Does this increase the risk of PPD?
- Does breastfeeding affect severity or rate? Recent study suggested formula feeding increases the risk
- Are there long-term repercussions of the syndrome?

Do antidepressants cause long-term developmental changes in offspring?

- Prospective studies find no IQ reductions and no increased risk of behavior problems in children up to age 7 exposed in utero to tricyclics, SSRIs or venlafaxine[1-3]
- Delayed language maturation associated with maternal depressive symptoms; not with SSRIs[4]

1. Nulman I et al: New Eng J Med 336:258-62, 1997; 2. Nulman I et al: Am J Psychiatry 159:1889-95, 2002; 3. Nulman I et al: Am J Psychiatry 169:1165-74, 2012; 4. Weikum WM et al: PNAS May 2012;

Do SSRIs cause Autism??

No!

- Initial studies found increased risk[5,6]
- Subsequent studies which more carefully ruled out influence of confounds found no increased risk[7,8]
- Same level of risk for non-exposed siblings
- Two 2016 articles in JAMA – one a population-level study with 1.6 million births, the other with 35,000 – found no association with antidepressant use but an increased risk for mothers with depression[9,10]

5. Croen LA et al: Arch Gen Psychiatry 7/4/11 Epub; 6. Rai D et al: BMJ 346:f2059, 2013 Apr 19; 7. Hvid A et al: N Eng J Med 369(25):2406-15, 2013; 8. Sørensen MJ et al: Clin Epidemiol 2013 9 SujanAC,RickertME,ObergAS,etal. *JAMA*. doi:10.1001/jama.2017.3413 10 BrownHK,RayJG,WiltonAS,LunskyY,Gomes T, Vigod SN. *JAMA*. doi:10.1001 /jama.2017.3415

General Recommendations: Antidepressants

- SSRIs and SNRIs generally considered safe
- Consider tricyclics
- Of the SSRIs Zoloft and Prozac have the most evidence for safety
- Paxil has been associated with heart defects in some studies with exposure in the 1st trimester
- Less evidence for others including Wellbutrin which until recently was FDA category B
- Risk for Persistent Pulmonary Hypertension extremely small

Dosing during pregnancy

- Use a therapeutic dose
- For most antidepressants, pharmacokinetic changes reduce plasma concentrations by as much as 40-50%
- Most prescribers rely on clinical indications to decide whether dose needs to be increased – there are no guidelines!

1. Wisner KL et al. Am J Psychiatry. 1993;150(10):1541-1542; 2. Hostetter A et al. Depress Anxiety. 2000;11(2):51-57; 3. Freeman MP et al. J Clin Psychopharmacol. 2008;28(6):646-653

Pregnancy and Mood Stabilizers

- Valproate is a known teratogen
  - 7-10% risk of NTD
  - Cardiac Defects, Craniofacial abnormalities with 1st trimester exposure
  - Behavioral and Cognitive effects are associated
- Carbamazepine
  - 1% risk of spina bifida
  - Associated with Craniofacial anomalies and microcephaly

Use folic acid 4mg if use AED during pregnancy

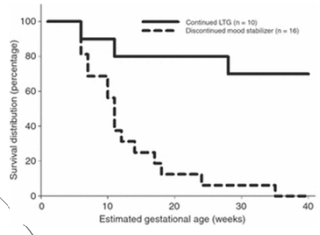
Pregnancy and Mood Stabilizers

- Lithium
  - Originally thought to have a high risk of cardiovascular malformations (Ebstein's Anomaly) based on retrospective reporting
  - Absolute risk now thought to be 1 out of 1000 (0.1%)
  - Advantage: Can monitor lithium level in both mom during pregnancy and in baby postpartum
  - Risks: Floppy baby syndrome with 3rd trimester exposure, rare neonatal hypothroidism, nephrogenic diabetes insipidus
  - 5 year follow-up of babies exposed in utero showed no sequelae

Pregnancy and Mood Stabilizers

- Lamotrigine
  - Pooled risk of major fetal anomalies after 1st trimester exposure: 2.6% (3-4% in general population)
  - Metabolic clearance increases during pregnancy
  - Ideally, measure a level when woman is stable and NOT pregnant – then adjust dosing during pregnancy to maintain that level
  - Recent study examined 10 women who continued Lamotrigine during pregnancy versus 16 who discontinued mood stabilizers
    - 30% on Lamotrigine relapsed
    - 100% who discontinued meds relapsed

Lamotrigine During Pregnancy



Newport et al, Bipolar Disorders 2008

Older Antipsychotics and Pregnancy

- >40 years of experience with older antipsychotics
- No significant teratogenic effect has been shown for chlorpromazine, haloperidol, and perphenazine
- One study of haldoperidol and penfluridol found a higher rate of preterm births and a lower median birth weight

Atypical Antipsychotics and Pregnancy

- Mainly case reports
- More evidence for older atypicals (Risperdal, olanzapine)
- One study of 713 women treated with Risperdal showed no teratogenicity, but recent large population study (Huybrechts) showed possible risk of cardiac defects for Risperdal only
- Recommend monitoring for metabolic effects
- Recent summary of 700 cases in registry data – no risks

Huybrechts JAMA Psychiatry. doi:10.1001/jamapsychiatry.2016.1520
Cohen AJP 173: 3, 263-270

Bipolar Disorder and Pregnancy: Summary

- Avoid Valproate and Carbamazepine
- Options to consider:
  - Lithium
  - Lamotrigine
  - Antipsychotics

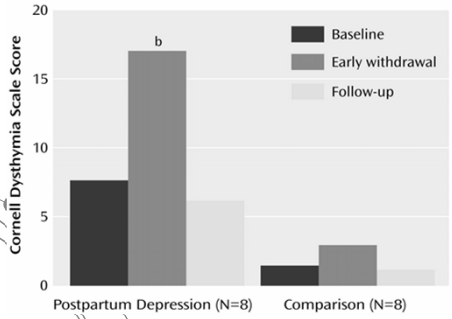
Use folic acid supplementation if using AED (4mg)

Treatment of Anxiety in Pregnancy

- Benzodiazepines
  - Early evidence for association with cleft palate, recent studies do not support this
  - Associated with preterm birth, low birth weight
  - Floppy baby syndrome and withdrawal if large doses used in 3rd trimester
- Gabapentin
  - Early animal studies showed growth impairment and developmental delay
  - Limited evidence in humans shows no risk
  - Use folic acid 4 mg!

Postpartum/Breastfeeding

PPD Sensitivity to Hormonal Change



Breast Feeding: Rule Number 1

- All psychiatric medications enter breast milk
- BUT – almost all safe to use
- American Academy of Pediatrics <10%

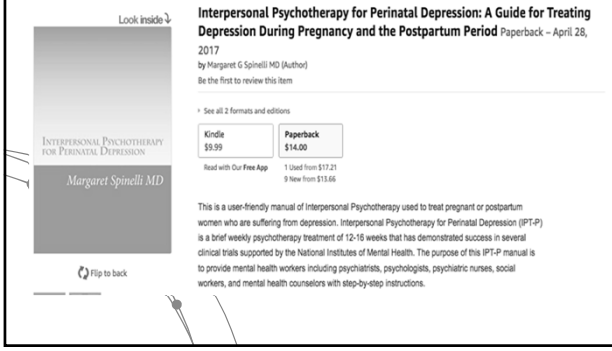
Breast Feeding Rule Number 2

- If the baby was exposed in utero there is usually no reason to not continue the medication during breast feeding
  - Exceptions: clozaril or if baby seems to be sedated or having particular side effects
  - Lithium toxicity has occurred in infants- monitor blood levels, TSH and kidney function
  - Large doses of long-acting benzos likely to result in sedation

Are there Alternatives to Medications?

Psychotherapy

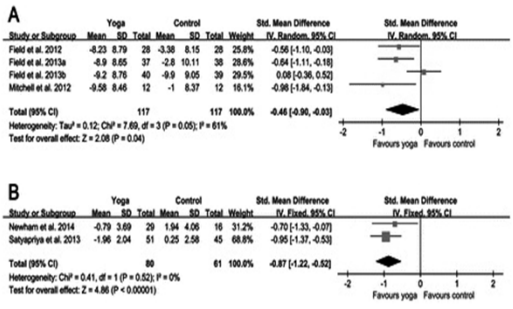
- There have been a number of studies of various types of psychotherapy for depression during and after pregnancy
- Interpersonal Therapy best studied
- Cognitive Behavioral Therapy also shows promise
- Mindfulness Based CBT also shows promise
- Need more well-designed, randomized trials



Exercise

- Exercise was equally effective as Zoloft in reducing depressive symptoms in two separate studies. (Blumenthal et al, *Arch Intern Med*. 1999 and *Psychosom Med*. 2007).
- A meta-analysis confirmed the efficacy of exercise as both as stand-alone and as adjunctive to medication in MDD. (Saeed et al, *Amer Fam Phys*. 2010)
- There has been one study of aerobic exercise during pregnancy that showed reduced depressive symptoms in women without a psychiatric history. (Robledo-Colonia et al, *J. Physiother*. 2012;58(1):9-15).
- No studies in pregnant women with mood disorders.

Yoga and Acupuncture

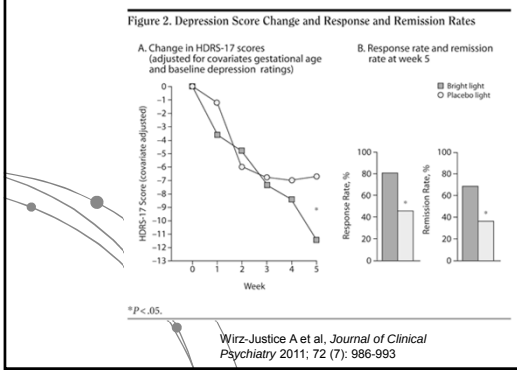


Gong et al. BMC Psychiatry. 2015; 15: 14.
Best Pract Res Clin Obstet Gynaecol. 2014 Jan; 28(1): 85–95.

Light Box Therapy

- Established therapy for Seasonal Affective Disorder
- Has also been shown to be helpful in nonseasonal depression
- Three studies have shown that LBT was effective in treating depression in pregnant women with MDD.
  - Oren DA et al, *American Journal of Psychiatry* 2002; 159: 666-669
  - Epperson CN et al, *Journal of Clinical Psychiatry* 2004; 65: 421-425
  - Wirz-Justice A et al, *Journal of Clinical Psychiatry* 2011; 72 (7): 986-993

Randomized Trial of LBT



Wirz-Justice A et al, *Journal of Clinical Psychiatry* 2011; 72 (7): 986-993

Repetitive Transcranial Magnetic Stimulation

- Approved by FDA for adults with MDD who have failed an antidepressant
- Open label study of 10 depressed pregnant women: 70% responded, 30% remitted (Kim, D. RJ *Womens Health* 2011; 20(2): 255-261).
- No adverse outcomes for the fetus but no long-term data
- No maintenance studies to date
- Recent review of 12 studies found good response rates (largest studies 40-70%, remission in 20-30%) and no adverse effects (Felipe & Ferrao, Trends Psych Psychother 2016;38(4):190-197)
- More work needs to be done!

Conclusions

- There is a high relapse rate for mood disorders in women who stop their medications for pregnancy
- Exposure to psychiatric illness in utero is associated with poor outcomes for both mother and child
- The use of psychiatric medications can be safely done but requires an individualized plan based on the woman's history and preferences.

Conclusions

- A number of studies have been done for alternative (to meds) treatments for a major depressive episode during pregnancy but data is still lacking
- Little to no work done looking at alternative treatments for maintenance of mood in women who are well on medications but want to discontinue them for pregnancy
- Stay tuned!

Goal: Healthy Mom, Healthy Baby!

Resources

- Women's Mood Disorders Center (East Baltimore): (410) 502-7449: Clinical and Research, MOST insurance http://www.hopkinsmedicine.org/psychiatry/specialty_areas/moods/patient_information/clinic_women.html
- Perinatal Mood Clinic (Bayview): (410) 550-0104: Clinical Only, BCBS http://www.hopkinsmedicine.org/psychiatry/bayview/medical_services/adult/perinatal_mood.html
- Reprotox: Summary of literature on all meds in pregnancy, subscription service https://reprotox.org/
- Lactmed: Summary of literature on all meds in lactation, free services http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm
- MothertoBaby: Patient-friendly fact sheets on meds: http://mothertobaby.org/
- MGH Center for Women's Mental Health: Best informational website: https://womensmentalhealth.org?doing_wp_cron=1452175286.3503780364990234375000
- Motherrisk: Canadian helpline: http://www.motherisk.org/
- Postpartum Support International: Support group and help finding local resources http://www.postpartum.net/
- MCPAP FOR MOMS, https://www.mcpapformoms.org/