Advanced Perinatal Pharmacology

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Disclosures

• Legal consultant to Astra Zeneca, Eli Lilly, Johnson and Johnson
• 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 mood stabilizing medications that should be avoided during pregnancy
  • Quantify the risk of Eptean’s anomaly in lithium-exposed infants
  • Name one risk associated with in utero antipsychotic exposure in infants

Talk Overview

• General Rules for Medication Management during Pregnancy
• Mood Stabilizers and Other Medications
• Breastfeeding
• Prevention and Treatment of Postpartum Psychosis
General Rules for Medication Plans During Pregnancy

- Assume all women of reproductive age will get pregnant!
- Consider Exposure to Psychiatric Illness In Utero an Exposure for the Baby
- Limit the number of exposures for the baby
- Use medications that we know more about
- Every case is different!
- It’s a Team Sport

Category B is NOT necessarily safer than Categories C and D!

Category B

- 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
The Rules: OOPS

- See or talk to the patient ASAP
- Don’t stop all meds immediately—most psychiatric meds can be continued
- Taper meds when possible
- Consider the risks of stopping teratogenic meds and educate everybody
- Try to minimize the number of meds
- If the patient is ill, make a plan that includes treating the illness.

Mood Stabilizers

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 (Epstein’s Anomaly) based on retrospective reporting
  - Absolute risk now thought to be 1 out of 1000 (<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 hypothyroidism, nephrogenic diabetes insipidus
  - 5 year follow-up of babies exposed in utero showed no sequela
Managing Lithium at Delivery

- Hold lithium at the first signs of labor
- Liberal hydration
- Check a lithium level after delivery
- Restart lithium at pre-pregnancy level the night after delivery

Pregnancy and Mood Stabilizers

- Lamotrigine
  - Pooled risk of major fetal anomalies after 1st trimester exposure: 2.6% (3-4% in general population)
  - Metabolic clearance may increase during pregnancy
  - 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
  - Use folic acid (4mg) if use AED during pregnancy

Blood Levels and Mood Stabilizers

- Blood levels tend to drop across the course of pregnancy
- It is useful to get a level just prior to or early in pregnancy
- There are no studies re: prophylactic increases in mood stabilizers based on blood levels
- Consider increasing based on blood levels during pregnancy and returning to pre-pregnancy doses post delivery

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 haloperidol and penfluridol found a higher rate of preterm births and a lower median birth weight

Atypical Antipsychotics and Pregnancy

- More evidence for older atypicals (Risperdal, olanzapine)
- One study of 713 women treated with Risperdal showed no teratogenicity
- Recommend monitoring for metabolic effects and excessive weight gain
- One study found mild developmental delays in exposed infants at 6 months that resolved by 12 months

Bipolar Disorder and Pregnancy: Summary

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

- Use folic acid supplementation if using AED (4mg)

Breastfeeding
Breastfeeding

- All psychiatric medications enter breast milk
- When starting a medication postpartum must consider whether or not to expose the baby

Lithium and Breastfeeding

- Lithium levels in the baby are half the serum levels of the mother
- Cautions:
  - Febrile illness
  - Any illness that compromises kidney function
  - Any illness that leads to dehydration
  - Lithium levels, kidney function and TSH should be monitored in the infant
- No long-term studies

Valproate and Breastfeeding

- Serum levels in the exposed infant are at most 40% of the mother's level
- Generally in the range of 4-6%
- No adverse effects have been reported
- Should monitor VPA level, CBC and hepatic function in the infant
- No long-term studies

Carbamazapine and Breastfeeding

- Serum levels in the infant are 6-65% of the mother’s level
- Serum levels, hepatic panel and CBC should be followed in the infant
- No long-term studies
Lamotrigine and Breastfeeding
- Serum levels are about 30% of the mother's level
- Serum levels should be followed in the infant
- To date, no reports of rash
- No long-term studies

Antipsychotics and Breastfeeding
- No need for therapeutic blood monitoring
- Monitor for sedation, EPS
- Unknown risks re: metabolic parameters
- No long-term studies

Mood Stabilizers
- Valproic Acid and Carbamazepine are considered safe in breastfeeding
- Lithium can be used but requires a vigilant mother for possible toxicity
- Lamotrigine is safe in breastfeeding
- Studies on antipsychotic medications are limited but reassuring

Summary: Breastfeeding
- All of the "classic" mood stabilizers require blood draws in the infant
  - Lamotrigine requires the least
- Antipsychotics do not require blood draws but have unclear long-term risks re: EPS, Metabolic parameters
- NO LONG-TERM STUDIES
- Communicate with the pediatrician!
- Don't forget to discuss birth control
What is Postpartum Psychosis?

Characterized by:
- Confusion with disorganized speech and behavior
- Mood lability
- Psychosis, often with mood incongruent delusions
- Manic symptoms including decreased sleep and increased activity/energy
- May resemble a Mixed state
- Catatonic symptoms
- Strongly Associated with Bipolar Disorder

74% of women who went on to develop PPP recall onset of symptoms by day 3
52% recalled feeling excited, elated or high
48% recalled not needing to or being able to sleep
37% recalled feeling active or energetic
31% recalled feeling talkative or chatty
Prodrome of hypomania?

Postpartum Psychosis

How Common is Postpartum Psychosis?

- Occurs in 1-2 out of every 1000 deliveries in the general population
- At least 20-30% of women with Bipolar I disorder experience PPP, with some estimates as high as 70% in women who stop their medications for pregnancy
- In women with bipolar disorder and a first degree relative with PPP, 74% develop PPP
- Women with known schizophrenia have about a 25% risk of PPP

Postpartum Psychosis: Early Symptoms
(Heron et al, 2007)

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- Prodrome of hypomania?
Suicide and Postpartum Psychosis

- Suicide risk increases 70 fold in the first year after childbirth (CEMD, 2001)
- Suicide is the leading cause of maternal death up to one year post-delivery (CEMD, 2001)
- 2 out of every 1000 women with PPP commit suicide, usually by violent means (CEMD, 2001)
- The majority of maternal deaths in the year after delivery occur in women with PPP (Jones and Craddock, 2005)

Infanticide

- 28-35% of women hospitalized for PPP express delusions about their infants
- 9% have thoughts of harming their infants
- Disorganization may result in neglect or unsafe practices with the infant
- 4% of women with Postpartum Psychosis commit infanticide (Parry, 1995)

Guidelines for the Prevention and Treatment of Postpartum Psychosis

- Starts PRIOR to pregnancy if at all possible
- Include information about Bipolar Disorder, Postpartum Psychosis and Suicidal Thoughts
- Educate the patient and everybody else associated with the patient (husband, mother, etc)
- Look for early hypomanic symptoms
- Make sure that the primary support team (e.g. significant other) has a good idea of symptoms look for and a way to contact you in an emergency

Prevention Rule 1: Educate, Educate, Educate
Prevention Rule Number 2: Medication

- Highest risk in women off of medications
- Decreased risk with use of medications during pregnancy
- If the patient is off of medications, should restart immediately postpartum

Prevention of PPP: Medication Use

- Cohen et al, 1995
  - 1 of 14 women with BPI disorder who were taking mood stabilizers/antipsychotics postpartum relapsed with a mood episode within 3 months postpartum
  - 8 of 13 women with BPI disorder who were not taking psychiatric medications postpartum relapsed with a mood episode within 3 months postpartum

Prevention of PPP: Mood Stabilizers

- Several very small studies
- NO double-blind, placebo controlled studies in either the prevention of or treatment of PPP in subjects with BP (+/- hx of PPP)
- Austin et al, 1992
  - 2/9 on lithium either during or after pregnancy relapsed
  - 6/8 on no meds relapsed
- Cohen et al, 1995
  - 1/14 subjects who restarted lithium, CBZ, or combo within 48 hours relapsed
  - 8/13 subjects not restarting meds relapsed

Prevention of Postpartum Psychosis: Olanzapine

- Olanzapine was studied in 11 women either alone or in combination with other psychiatric meds compared to 14 women on either no meds or other psychiatric meds.
- Women had been previously diagnosed with either BPI or BPII, some had previous postpartum mood disorders
- 18% in the olanzapine group relapsed with a mood episode compared to 57% in the no olanzapine group
Prevention Rule Number 3: Support
- Protect Sleep
  - Recommendations include:
    - Longer hospital stay, private room
    - Rooming out of the infant
    - Use of stored breast milk or formula at night
    - Induction of labor for day-time delivery
    - Early intervention for insomnia
- Provide support - the more the better
- Close follow-up after discharge from the hospital

Treatment Rule Number 1: Err on the side of hospitalization
- True psychiatric emergency
- Establishes safety for the mother and child
- Labs and imaging should be completed to rule out an organic cause such as stroke, hemorrhage or other cause of delirium

Treatment Rule 2: Check for Suicidal Thoughts
- Risk for suicide deaths and attempts is lower during and after pregnancy than in the general population
- BUT suicide accounts for up to 20% of all postpartum deaths
- AND suicide represents one of the leading causes of peripartum mortality
- Make a safety plan

Treatment Rule 3: Check for Thoughts of Harming the Baby
- Directly ask, note that these thoughts are common
- Don’t morally condemn the thoughts
- 3 Kinds
  - Obsessive anxious thoughts or Obsessions
  - Actual thoughts of harm without intent
  - Thoughts of harm with intent
- Also assess for symptoms that would increase the likelihood of the woman acting on the thoughts
  - Psychotic symptoms
  - Suicidal thoughts
  - Poor social support/chaos
Treatment Rule 4: Think Lithium and Antipsychotics

- Bergink et al, 2015 presented a treatment algorithm: sequential benzodiazepines, antipsychotics, and lithium
- Those on lithium had a substantially lower rate of relapse

Treatment Rule 5: Close Follow-Up

- Monitor for suicidal thoughts
- Monitor for thoughts of harming the baby
- Monitor for emerging bipolar disorder symptoms
- Provide support and further education
- Weekly visits are best until it's clear that things are stabilizing

Treatment Rule 6: Find Support for the Patient

- Postpartum Support Groups
- Online Support Groups
- Play Groups for New Moms
- Parenting Skills classes
- Books on Postpartum Depression
- CBT, IPT
Treatment of PPP: ECT

- Most studies done in Postpartum Depression
- No evidence that ECT is ineffective in PPP
- Consent may be an issue
- Should be considered early in cases where there are prominent catatonic symptoms or refusal to eat or drink
- Medications will be needed after ECT

Case Studies

Remember: Every case is different and there are no absolute right or wrong answers!!

Case Study 1

- Nancy has a long history of Bipolar I disorder and has been stable for 3 years on lithium and clonazepam for sleep.
- Scene 1: She presents prior to pregnancy for recommendations.
- Scene 2: She just found out she’s pregnant

Case 2

- Shirley has a long history of Bipolar I disorder that has been difficult to manage.
- She’s taking Depakote, lithium and abilify.
- She has a history of violence and suicide attempts when off medications.
- She had unprotected sex multiple times last week.
Case 2 Version 2

- Shirley is successfully managed through pregnancy on lithium and Abilify.
- Should she breastfeed?

Case 3

- Lindsay has a long history of Bipolar I disorder that has been stable on Risperdal for several years.
- Upon discovering she was pregnant she was switched to lurasidone
- Version 1: She remains stable- should she be switched back?
- Version 2: She destabilizes

Case 4

- Amy, a 24 year old woman with no past psychiatric history, presents to the ER brought by her concerned husband for lack of sleep, agitation and “crazy talk” for 3 days beginning 4 days after delivering their first child.

Thank you!