# Speaker:

## Elizabeth Fitelson, M.D.

Associate Professor of Psychiatry at CUIMC
Director, The Women's Program
Columbia University Department of Psychiatry

Contact:
eem36@cumc.columbia.edu

# Managing Bipolar Disorder in the Perinatal Period:

## Balancing Risks

# Disclosures

No relevant disclosures

# Outline:

- Bipolar Disorder and the female reproductive life cycle
- Risks of Bipolar Illness in Pregnancy and Postpartum
- Postpartum Psychosis: A Psychiatric Emergency
- Overview of Mood Stabilizers in Pregnancy
- Managing the Postpartum Bipolar Patient

# Poll 1: What is your experience or confidence caring for patients with Bipolar Disorder in pregnancy? (select all that apply)

- I've managed many patients with BD through pregnancy
- I have managed some patients with BD in my practice
- I have never managed a patient with BD through the perinatal period
- I am confident discussing and managing the risks of mood stabilizers in pregnancy
- I have seen at least one case of postpartum psychosis
- I have the supports I need to feel confident managing BD pts in pregnancy

# Bipolar Disorder and the female reproductive life cycle

Course in women

Hormonal interactions

Course in pregnancy

# BD in Women

- Higher rates of mixed episodes
- Higher rates of rapid cycling
- More depressive episodes at presentation
- >Suicide attempts
- Medical Comorbidities: thyroid, migraine, chronic pain, metabolic
- Psychiatric Comorbidities: GAD, PTSD (anxiety associated with higher suicide risk), substance, eating disorders

Regier et al, 1993; Grant et al, 2005; Leibenluft, 1996

# BD and the Menstrual Cycle

- Mood fluctuations across the menstrual cycle
  - 60% experience changes at some point during the cycle
  - Luteal phase highest risk
  - Not a predictable pattern

Payne et al, 2007, Blehar et al, 1998; Rasgon et al, 2003.

Poll 2: A 31yo married female patient you have been treating for several years has been stable on lamotrigine 300mg for the last 12 months and doing well. She presents at her monthly appointment with complaints of new onset cognitive dysfunction, including memory lapses and wordfinding difficulties. There are no focal neurologic signs concerning for stroke, and she denies depressive symptoms. What is the next most helpful question?

A. Have you started using THC for sleep?
B. Have you recently started hormonal contraception?
C. Have you recently stopped hormonal contraception?
D. Are you pregnant?

# 50% of Pregnancies are Unplanned!

- Likely higher in bipolar patients
- Mood stabilizers have important interactions with hormonal birth control
- Bipolar disorder has high morbidity in the perinatal period for mom, fetus, and family

# Interactions Between Mood Stabilizers and Reproductive Health

| Drug | Menstrual/Hormonal Interactions | Pregnancy |
|---|---|---|
| Valproic Acid (Depakote) | Can cause PCOS<br>OCP's lower VPA levels | Teratogenic in every trimester<br>*should not be 1st line in reproductive age women!* |
| Lamotrigine | OCP's lower LMG levels 50% | No clear teratogenicity |
| Antipsychotics | Can elevate prolactin levels (impact on menses, fertility, bone health) | No clear teratogenicity; weight gain and metabolic monitoring; neonatal EPS (rare) |
| Carbamazepine/Oxcarbazepine | Lowers OCP effectiveness | First trimester NTD's, craniofacial abnormalities, low VitK |
| Lithium | None | Cardiac defects (slt), polyhydramnios, neonatal effects |
| Topiramate | Lowers OCP effectiveness | Some signal of teratogenic risk >200mg |

# Psychiatric Risks of BD and Pregnancy

- Poor self-care, poor nutrition, prenatal care, risks of substance use, poor judgment, fetal injury
- Effects on family system
- Postpartum psychosis
- Suicide (suicidal ideation 5-14%)

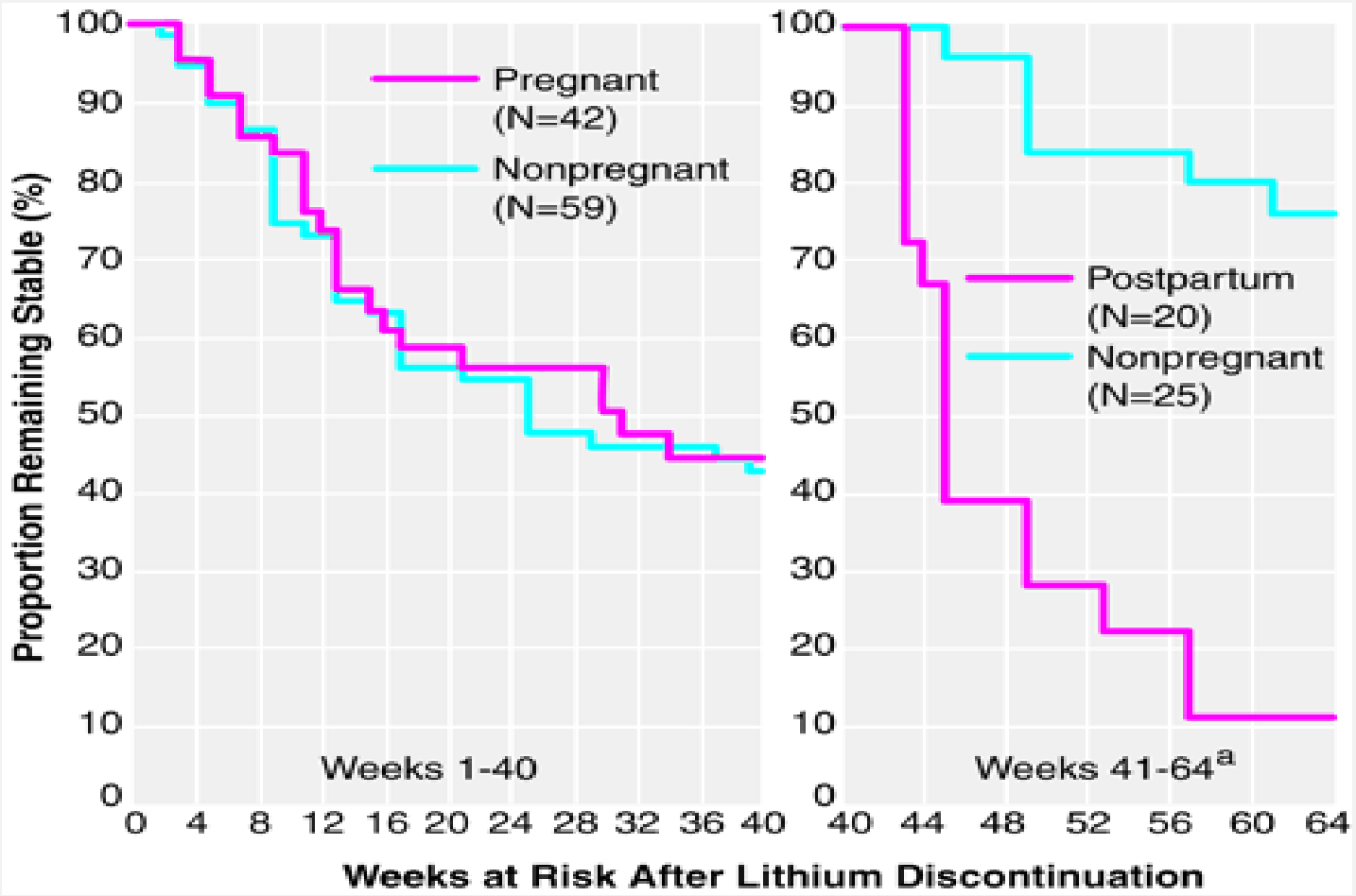
Wadhwa, 1993; Kurki 2000; Jablensky 2005, Vichi 2021

# Obstetric/Neonatal Risks of BD in Pregnancy

- Adverse effects on fetal growth (LGA and SGA both identified)
- Preterm birth
- Pre-eclampsia
- Higher rates of C/S
- PP hemorrhage
- Smaller head circumference

Wadhwa, 1993; Kurki 2000; Jablensky 2005, Wisner 2019

# Bipolar Disorder and Pregnancy




Viguera et al, 2000

# Postpartum Period is Particularly High Risk for Women with Bipolar Illness

- Lack of sleep
- Family stressors, role transition
- Sudden change in hormone levels
- Breastfeeding
- Immunological factors
- Circadian disruption
- Infant temperament




*Gordon-Smith K, Perry A, Di Florio A, Forty L, Fraser C, Casanova Dias M, et al. Symptom profile of postpartum and non-postpartum manic episodes in bipolar I disorder: a within-subjects study. Psychiatry Res. 2020;284: 112748.*

# Postpartum Psychosis

*A Psychiatric Emergency*




16

Poll 3: A 26yo G1P1 s/p C/S presents for 2 week PP visit. She is alert and oriented but appears a little down. Family reports she has been expressing odd concerns about the baby (ie that it is not really hers, or that someone has poisoned her breast milk), and at times appears to be confused or disoriented, and at other times energetic or even laughing to herself. When you speak with her, she reports she is convinced that the baby was switched by someone, and becomes guarded when you probe about why she believes that and refuses to answer more questions. The next most appropriate step in management is:

A. Send her to the emergency room for immediate psychiatric and medical evaluation
B. Screen with EPDS and MDQ and if positive refer to social work
C. Provide a referral for psychotherapy
D. Provide information about postpartum depression to patient and family

# Postpartum Psychosis

- Women with BD have highest risk for PPP
  - Baseline rate 1-2/1000
  - Bipolar women significantly higher risk (up to 20%)
  - 72-88% women with PPP have dx BD
- Onset 2 days to 4 weeks, waxing/waning course
- Paranoid, grandiose, or bizarre delusions,
- Mood swings, grossly disorganized behavior, confusion, cognitive disruption
- Risk for suicide, infanticide

Sit et al 2006; Chaudron 2003; Osborne 2019

# Postpartum Psychosis (cont'd)

- Distinguish from pre-existing stable psychotic disorder
- Patient needs immediate psychiatric evaluation and cannot be alone with the infant (usually needs psych ER)
- If in doubt, call Project TEACH
- Medical workup: look for other causes of delirium, intoxication, immune dysfunction
  - CBC, LFTs, TFTs, BMP, B12, Folate, Utox
  - Consider imaging if focal findings

# Brief Overview of Mood Stabilizers in Pregnancy

# Poll 4:

- 24yo recently married woman presented to transfer her care after moving from another city. She had a history of Bipolar 1 Disorder, and had been hospitalized twice for mania with psychosis. She was stabilized on valproate and olanzapine. Tapered off of both after one year with her psychiatrist, but within 2 months became acutely agitated and paranoid. Stabilized on lithium and olanzapine. Olanzapine was tapered off after several months due to weight gain. Became depressed, and citalopram was added. At the time of presentation she had been stable for 3 years on the combination of lithium 1200mg daily and citalopram 20mg daily. She and her husband planned to start a family within the next year.

# Poll 4 (cont'd) "Are my medications safe in pregnancy?"

- What do you tell this patient?
- A. You will have to stop lithium before you get pregnant, but citalopram is safe
- B. You should try to stop all medications before trying to conceive
- C. You should switch to lamotrigine, as that is safer in pregnancy
- D. It's complicated

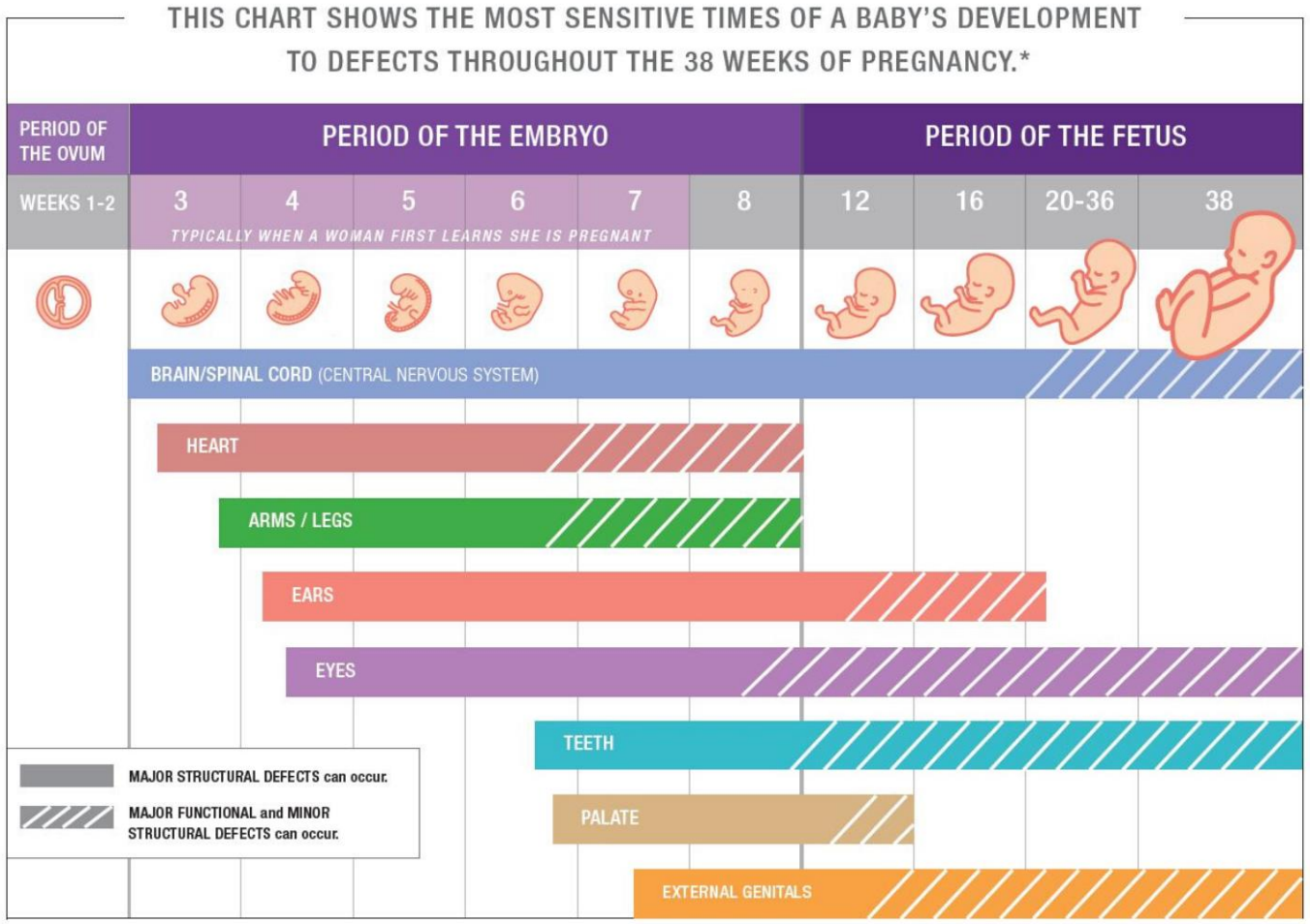
# Treatment Principals for Prescribing Psychotropics in Pregnancy


1. Know what you are treating
2. There are no risk-free decisions. Where there is illness, there is risk.
3. Cases by case, “risk of no/under treatment vs risks of treatment”
4. Maximize non-medication therapeutic options even when meds indicated
5. The best medication is usually the one that works for the patient
6. Avoid polypharmacy when possible
7. Use the lowest EFFECTIVE dose of medications
8. Re-screen, monitor effectiveness, changes across puerperium
9. Involve family/partner when possible, consider family system in risk
10. Communication and education with patient, supports, treatment team

# Non-pharmacologic approaches

- Psychotherapy (IPSRT, CBT, supportive, etc)
- ECT, TMS
- Bright Light Therapy
- Support groups, peer support, telephone
- Acupuncture, yoga, meditation
- Exercise
- Sleep regulation
- Postpartum: Focus on practical and emotional supports

# Use of Mood Stabilizers in Pregnancy




*All mood stabilizers cross the placenta; folate supplementation (5 mg/day) pre-conception and throughout pregnancy

*motherstobaby.org; Adapted from Moore 1993, and the National Organization of Fetal Alcohol Syndrome (NOFAS) 2009

# Lithium

- First line for treatment of bipolar 1: reduces rates of suicide and postpartum psychosis
- MFM consult/monitoring indicated for women on lithium in pregnancy
- Teratogenicity
  - Ebstein's anomaly: abnormalities of tricuspid valve and right ventricle; risk increased from 1:20,000 to 1:2,000
  - Prevalence cardiac defects increased from ~1% -> 2%
  - Risk ratio proportional to dose (3x>900 mg)

Patorno 2017

# Lithium

- Obstetric Complications
  - Hypothyroidism
  - Polyhydramnios
  - Nephrogenic diabetes insipidus
- Neonatal complications
  - Apnea, cyanosis
  - Hyperbilirubinemia
  - Muscle flaccidity and hypotonia
  - Hypothyroidism/hypoglycemia
  - Cardiac rhythm abnormalities
  - Seizures
- Neurodevelopmental outcomes
  - Data are limited but 3 small studies have **not** demonstrated negative outcomes

Jacobson 1992, Schou 1976, Forsberg 2018, Menon 2008

# Lithium Management in Pregnancy

- Obtain preconception level and monthly in pregnancy
- Lithium levels *will decrease* in 2nd/3rd trimester (blood volume, renal metabolism)
- Close management with psychiatrist for mood monitoring
- Monitor fluid levels after 24 weeks
- Check more frequently in women at risk for dehydration, ie hyperemesis gravidarum
- No NSAIDS
- Fetal echocardiogram and high resolution ultrasound at 18-20 weeks
- Maintain hydration

# Lithium

- Management postpartum (levels increase)
  - Decrease dose postpartum to preconception dose
  - Check level 24 hours postpartum and 1-2x weekly first 2 weeks postpartum
  - Consider higher target serum lithium level in first postpartum months
- Breastfeeding
  - Only recommended after careful consideration in certain reliable/adherent patients of fullt erm infants who are able to monitor their babies
  - Monitor infant TSH/BUN/Cr

# Lamotrigine

- FDA approved for maintenance of bipolar disorder but not effective for treatment of acute mania
  - 2008 study found that 30% of women taking lamotrigine had postpartum bipolar disorder relapses versus 100% of women not taking mood stabilizing medications
- Teratogenicity:
  - Single study found an increased risk of oral cleft defects (2.5/1000 births) but this has not been replicated in later larger studies
  - Rate orofacial clefts in general population ~0.7/1,000
- Pregnancy complications
  - No significant differences found in birthweight
- Neurodevelopmental outcomes
  - No significant differences found in IQ

Newport 2008, Dolk 2008

# Lamotrigine

- Management during pregnancy:
  - Consider preconception or early pregnancy level
  - Estradiol upregulates UGT1A4 which increases lamotrigine clearance
  - Levels fall 50% through pregnancy – consider dose increase 2nd trimester or breakthrough sx
- Management postpartum
  - Reduction at least 25% PPD 1
  - Lamotrigine clearance normal 4 weeks postpartum
  - Signs of toxicity: diplopia/ataxia/nausea/dizziness
- Breastfeeding
  - Infant serum levels reported 18- 50% maternal serum
  - No reports of neonatal Stevens Johnson Syndrome
  - No evidence of neurobehavioral toxicity

# First generation antipsychotics

- Teratogenicity
  - No evidence of teratogenic risk in high potency typical AP (Haldol/Fluphenazine)
  - Possible teratogenic risk in low potency typical AP (Chlorpromazine)
- Neonatal outcomes
  - Risk of neonatal EPS with late fetal exposure
- Neurodevelopmental outcomes
  - No known neurobehavioral effects
- Lactation
  - Low transmission
  - No adverse effects reported

Gentile 2010, Yaeger 2006

# Second generation antipsychotics

- Teratogenicity
  - Data does not support increased risk of malformations)
- Pregnancy outcomes
  - Higher baseline weight, but not increased weight gain antepartum
  - Metabolic risks, both SGA and LGA reported, ?preterm birth
- Neurodevelopmental outcomes
  - Few studies
- Breastfeeding
  - Lactation: Seroquel preferred (lowest transmission)
  - Monitor for sedation

Huybrechts 2016, Sadowski 2013

# Second generation antipsychotics: Clozapine

- Cessation of clozapine more likely to result in severe relapses
- 2X risk of gestational diabetes
- Risks of neonatal seizures, agranulocytosis (theoretical), floppy baby syndrome
- Lactation: not recommended due to risk of agranulocytosis (monitoring required)

# Depakote

- Teratogenicity
  - Neural tube defects (1-9%)-dose-response relationship
  - Neural tube development begins in early weeks of gestation before many women know they are pregnant
  - Increased risks hypospadias, polydactyly, facial clefts, cardiac defects, abnormal facial features
- Neonatal outcomes
  - Irritability/low apgar/hypertonia/feeding problems/hepatotoxicity/hypoglycemia/low fibrinogen
- Neurodevelopmental outcomes
  - Low IQ (all trimesters)
  - Increased risk of autism (all trimesters)
- Breastfeeding: Low transfer to breastmilk so considered compatible. Pt should be on contraception

# Carbamazepine

- Teratogenicity
  - Risk of neural tube defects 0.5-1%
  - Risk of Craniofacial abnormalities, microcephaly, IUGR
- Neonatal abnormalities
  - Fetal vitamin K deficiency
  - Neonatal bleeding
  - Rec: 20mg/d oral vit K last month of pg, 1mg IM to neonate
- Neurodevelopmental outcomes
  - No association with cognitive dysfunction
- Breastfeeding
  - Case reports of transient hepatic dysfunction
  - OK with monitoring

# Supporting Bipolar Women through the Postpartum

# Patient and Family Support PP

- Frequent outreach
- Emphasize sleep: "Sleep is a mood stabilizer!"
- Discuss breastfeeding, bottle feeding, combination, in non-judgmental, supportive way
- Involve partner and all other support system
- Plan in advance for relapse: "plan for the worst, hope for the best"

# Patient and Family Support PP (cont'd)

- Most mental-health related maternal death occurs beyond the "fourth trimester"
- Linkage to ongoing psychiatric care is critical
- Pay attention to comorbidities (ie substances, medical)
- Support resources for families (ie NAMI)

# Some Helpful Reviews:


- Batt MM, Olsavsky AK, Dardar S, St John-Larkin C, Johnson RL, Sammel MD. *Course of Illness and Treatment Updates for Bipolar Disorder in the Perinatal Period*. Curr Psychiatry Rep. 2022 Feb;24(2):111-120. doi: 10.1007/s11920-022-01323-6
- Osborne LM. *Recognizing and Managing Postpartum Psychosis: A Clinical Guide for Obstetric Providers.* Obstet Gynecol Clin North Am. 2018 Sep;45(3):455-468. doi: 10.1016/j.ogc.2018.04.005.
- Fitelson E, McGibbon C. *Evaluation and Management of Behavioral Health Disorders in Women: An Overview of Major Depression, Bipolar Disorder, Anxiety Disorders, and Sleep in the Primary Care Setting.* Obstet Gynecol Clin North Am. 2016 Jun;43(2):231-46. doi: 10.1016/j.ogc.2016.02.001

# Staying Up to Date: Resources

- **Project TEACH**: https://projectteachny.org/
- Mothertobaby.org (free resources including fact sheets for patients)
- Reprotox.org (subscription site)
- Lactmed: https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm
- Postpartum Support International: www.postpartum.net
- MGH Center for Women's Mental Health www.womensmentalhealth.org