Bipolar Disorders in Women

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Disclosure Statement

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Questions to Keep in Mind:

- Does she have a bipolar spectrum disorder?
- Might this patient become pregnant during her treatment?
- What are the risks of the mood stabilizer(s) to a baby (in utero, breastfeeding)?
- What are the implications of reproductive events – pregnancy, postpartum, menstrual cycle, perimenopause?

Does She Have a Bipolar Disorder?

- Bipolar disorder is often a missed diagnosis
- Women often present with bipolar depression – need to take careful history to assess for bipolar disorder
- Hypomania may be easy to overlook

Bipolar Disorders Across the Female Reproductive Lifespan

- General Considerations
- Menstrual cycle
- Pregnancy
- Postpartum
- Menopause

Bipolar Disorder:
Sex Differences

Bipolar Disorders in Women

- Women experience more rapid-cycling
- More mixed episodes
- More depressive symptoms
- Later age of onset
- More bipolar II
- More medical and psychiatric comorbidity
- Higher rates of obesity

Leibenluft, 1996 & 1997; Goodwin & Jamison, 1990; Angst et al., 1978; Roy-Burne et al., 1995; McElroy et al., 1995; Diflorio and Jones, 2010; Baldassano et al., 2005; Baskaran et al., 2014; Erol et al., 2015

Menstrual cycle

- May be exacerbation of symptoms premenstrually or menstrually for some women
- Case reports, retrospective data (Teatero et al, 2014)
- Up to 66% reported regularly occurring exacerbations (Blehar et al., 1998)
- 25% reported premenstrual depressive syndrome, increased anxiety (Roy-Byrne et al., 1985)
- Prospective studies – inconsistent findings (Leibenluft et al., 1999; Rasgon 2003; Shivakumar et al., 2008)
- Meds for PMDD may precipitate mania – mood stabilize first (Smith and Frey, 2016)
- Poorer outcomes in women with prospectively documented PMDD based on DSM5 criteria and bipolar disorder (Slyepchenko et al., 2017)

Mood Stabilizers and Menstrual Cycles

- Disruptions in menstrual cycles:
  - Valproic Acid
    - Associated with polycystic ovarian syndrome (PCOS)
  - Hyperprolactinemia
    - Galactorrhea, irregular menses/amenorrhea, infertility, sexual dysfunction
      - Associated most commonly with first generation antipsychotics and risperidone

Pacchiarotti et al., 2015; Gotlib et al., 2017

Pregnancy and Postpartum

Treating Women of Childbearing Potential

- 49% of pregnancies in U.S. are unintended[1]
- 80% of teen pregnancies unintended[1]
- 82% of U.S. women have had a child by age 40[2]

[1]Centers for Disease Control and Prevention. Unintended Pregnancy Prevention. http://www.cdc.gov/reproductivehealth/UnintendedPregnancy/index.htm. Accessed June 19, 2013;
[2]Martinez G et al. Centers for Disease Control and Prevention. National Health Statistics Reports. Number 51. April 12, 2012.

Context for Assessing Risk

- Rate of major malformations: 3-4%
- Rate of premature delivery: 11-12%
- Rate of gestational diabetes: 2-7%
- Untreated psychiatric disorders carry risks for woman and baby
- Alcohol and tobacco use prevalent in patients with untreated psychiatric disorders
- Obesity increases obstetrical risks

March of Dimes website, CDC website; Nonacs R, Cohen LS. *J Clin Psychiatry*. 2002;63 Suppl 7:24-30; King JC, Fabro S. *Clin Obstet Gynecol*. 1983;26(2):437-448.

Risks of Untreated Bipolar Disorder During Pregnancy

- >330,000 women; included comparisons of women with bipolar disorder, with and without treatment
  - Bipolar disorder increases risk of:
    - C-section
    - Small for gestational age
    - Prematurity
  - Congenital Malformations:
    - Without bipolar disorder: 2.0%; untreated 1.9%
    - 3.4% treated with a mood stabilizer (lithium or anticonvulsant)

Boden et al, BMJ, 2012

Breastfeeding

- …The experience of breastfeeding is special for so many reasons – the joyful bonding with your baby, the cost savings, and the health benefits for both mother and baby…
  - http://www.womenshealth.gov/breastfeeding/why-breastfeeding-is-important/index.html
- …Time to declare an end to the breastfeeding dictatorship that is drowning women in guilt and worry just when they most need support...

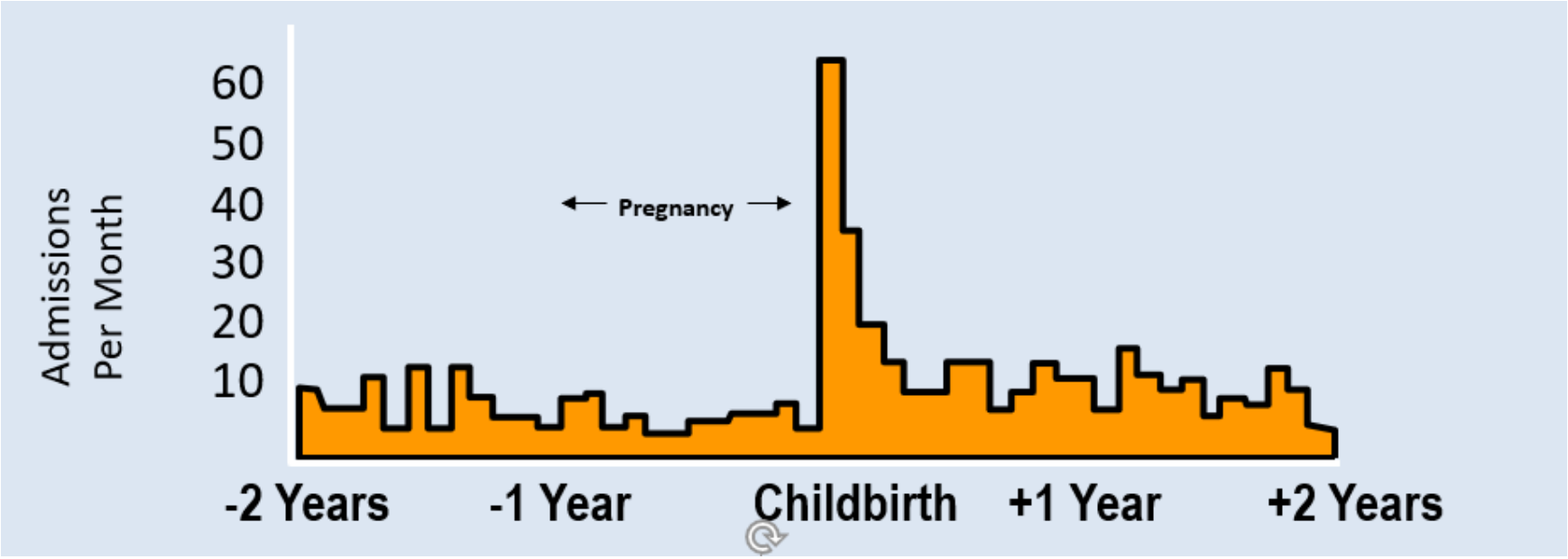
Gayle Tzemach Lemmon, **Breastfeeding is a Choice, Let's Treat it that Way**
Posted: 05/11/2012 http://www.huffingtonpost.com/gayle-tzemach/breastfeeding_b_1509658.html

Pregnancy and Postpartum: Risks of Discontinuing Medication

- Retrospective and prospective data show mean rates of relapse during pregnancy between 55% to 70%
- Women who discontinue medication more likely to experience recurrences (85.5% vs. 37%) and spend more time ill
- Particularly high rate of mood episodes postpartum (70%)
- Recurrence risk greater after rapid discontinuation (≤2 wks) than gradual (2 to 4 weeks)
- Unplanned pregnancy associated with greater risk of recurrence

Viguera AC et al. *Am J Psychiatry*. 2000;157(2):179-184; Viguera AC et al. *Am J Psychiatry*. 2007;164(12):1817-1824.

Risk of Psychiatric Hospitalization During Pregnancy and Postpartum



Highest risk of hospitalization for new mothers is 10 to 19 days postpartum, increased outpatient contacts first three months

Kendell et al. *Br J Psychiatry*. 1987;150:662; Munk-Olsen et al., *JAMA*. 2006;296(21):2582-2589.

Postpartum Psychosis

Postpartum Psychosis

- 1 to 2 per 1,000 pregnancies
- Rapid, dramatic onset within first 2 weeks
- **High risk of harm to self and infant**
- **Suspect bipolar disorder**
  - Underlying diagnosis: affective psychosis (bipolar disorder or schizoaffective disorder)
  - Family and genetic studies, index episode follow-up

Nonacs R, Cohen LS. *J Clin Psychiatry*. 1998;59(Suppl 2):34-40; Jones I, Craddock N. *Ann Med*. 2001;33(4):248-256; Spinelli MG. *Am J Psychiatry*. 2009;166(4):405-408.

Postpartum Psychosis (cont'd)

- Psychiatric emergency
- Estimated that 4% of women with postpartum psychosis commit infanticide
  - Actual rates of infanticide are difficult to estimate, as infanticide may be underreported

Spinelli MG. *Am J Psychiatry.* 2004;161:1548–1557; Spinelli MG. *Am J Psychiatry*. 2009;166(4):405-408.

Risk Factors for Postpartum Psychosis

Risk factor	**% that developed postpartum psychosis**
Hospitalization for psychotic episode **during** the pregnancy	44%
Hospitalization for a psychotic episode **prior** to the pregnancy	14.5%
Any previous psychiatric hospitalization	9.2%
Previous hospitalization for bipolar mood episode	2.0%
Baseline population risk	0.07%

Harlow BL. *Arch Gen Psychiatry*. 2007;64:42-48.

Acute Treatment

- Inpatient psychiatric hospitalization
- Rule out medical conditions
- Length of stay depends on clinical condition
- Many women will need to stop breastfeeding
- Primary pharmacotherapy: mood stabilizer and an antipsychotic, with medications for anxiety, insomnia, and agitation as needed
  - Sequential use of benzodiazepines, antipsychotics, lithium and ECT proposed

Sit et al., J Women's Health, 2006; Bergink et al., AJP 2015

Acute Treatment

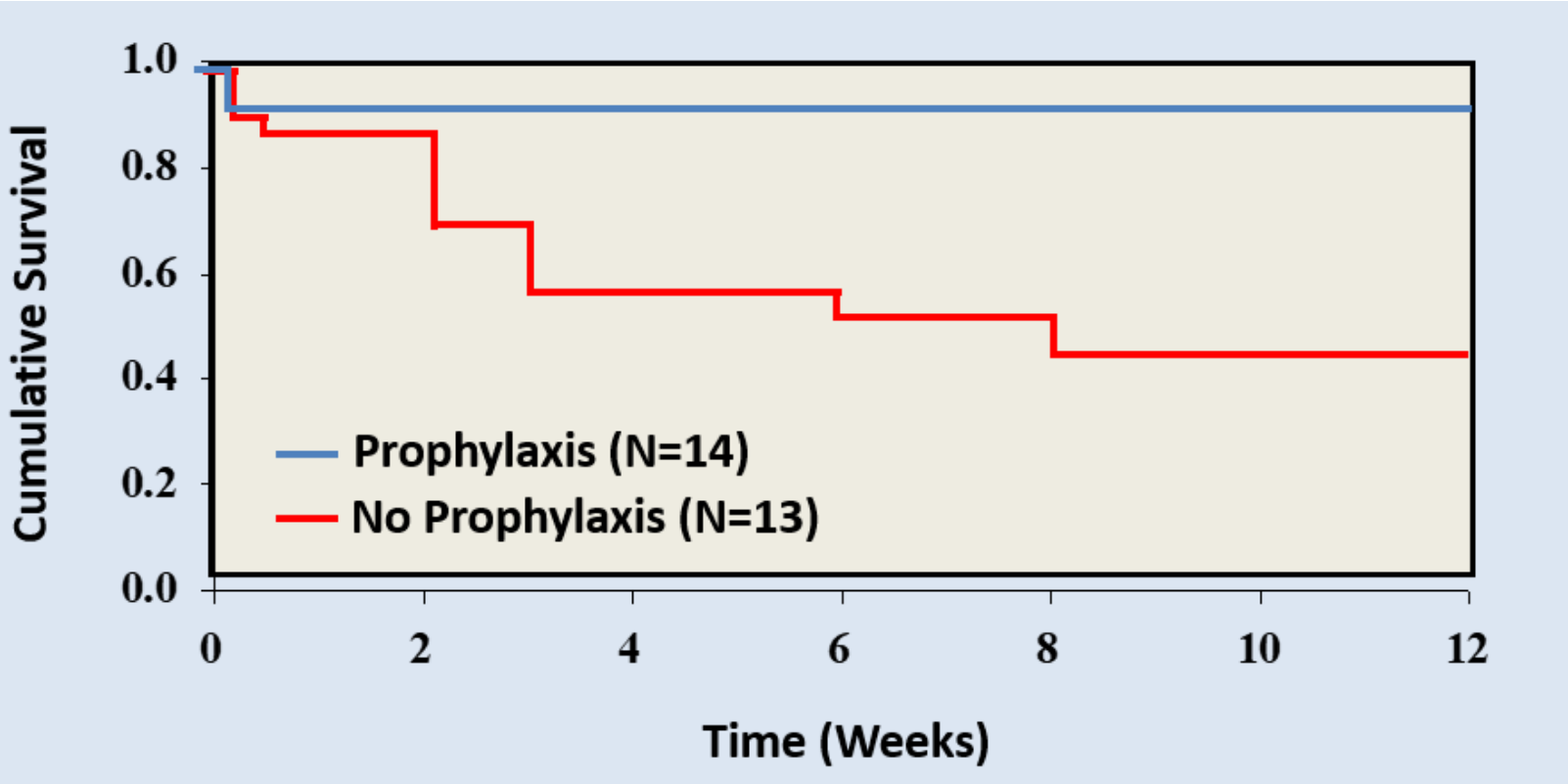
- Inpatient Protocol: Sequential use: N=64
  - Step 1: Benzodiazepine (lorazepam), 3 days - 6% remitted (N=4)
  - Step 2: Antipsychotic: haloperidol or atypical – 19% remitted (N=12)
  - Step 3: lithium – 73% remitted (N=48)
  - Step 4: ECT – none underwent
  - Total of 98% remission; only 1 patient did not fully remit
    - Most women responded to by addition of lithium
  - Sustained remission at 9 months postpartum in 80%
    - Affective diagnosis more associated with remission than non-affective
    - Relapse rates higher with antipsychotics than with lithium

Bergink et al., AJP 2015

Treatment After Discharge

- Little data to inform length of care
  - 6-12 months of pharmacotherapy
  - psychotherapy and close monitoring
- Treatment planning for adequate sleep, support, help in meeting the needs of caring for a baby
- Close monitoring is required for safety
  - Psychoeducation of family and friends

Postpartum Prophylaxis of Bipolar Disorder



Cohen LS, Sichel DA, et al. *Am J Psychiatry*. 1995.

Prevention of Postpartum Bipolar Episodes and Postpartum Psychosis

Group	During Pregnancy	With postpartum prophylaxis	Did not start postpartum prophylaxis	
Women with histories of **psychosis in the postpartum only**	**All (29/29) remained stable** off of medication during pregnancy	Started Postpartum Prophylaxis: No relapses (N=20)	Did not start Postpartum Prophylaxis: 44% relapse (N=9)	
Women with bipolar disorder	**24.4% relapse:** 75.6% on maintenance meds Relapse rates: 19.4% on meds 40% off meds	Of those who stayed well during pregnancy: postpartum relapse rate 7.7% on prophylaxis	Of those who stayed well during pregnancy: 20% relapse rate not on prophylaxis	**60% postpartum relapse among those who experienced mood episodes during pregnancy**

Main points

- **History of isolated postpartum psychosis**
  - High risk for recurrence **postpartum**
  - Prophylaxis may be deferred to immediately postpartum if mother well throughout pregnancy
- Bipolar disorder
  - **High risk for recurrence throughout pregnancy and the postpartum**, particularly with medication discontinuation
  - High risk postpartum relapse, postpartum prophylaxis decreases risk
  - Clinical picture during pregnancy greatly factors into postpartum prognosis – do not delay treatment

Postpartum Treatment

- **Prescribe Sleep!**
  - Sleep deprivation – similar to antidepressants regarding risk of induction of mania/hypomania (10%)
- **Prescribe Support!**
  - Good social support associated with quicker recovery, less symptomatic; better prophylaxis against episodes

Colombo, et al. 1999; Johnson, et al. 1999; Stefos, et al. 1996

Differentiating OCD and Psychosis

Postpartum OCD

- Thoughts are ego-dystonic
- Disturbed by thoughts
- Avoid objects or being with their newborn
- Very common disorder
- Low risk of harm to baby

Postpartum psychosis

- Thoughts are ego-syntonic
- Rarely distressed by thoughts
- Do not have avoidant behaviors
- Not common disorder
- High risk of harm to baby

OCD, obsessive-compulsive disorder

Brandes M et al. *Arch Womens Ment Health*. 2004;7(2):99-110.

Mood Stabilizers in Pregnancy

- **Lithium: First-trimester risk of cardiovascular malformations**[1]
  - Ebstein's anomaly: 0.1% to 0.2% (risk ratio 10 to 20)
  - Risk ratio for cardiac malformations is 1.2 to 7.7 and the risk for Ebstein's anomaly rises from 1/20,000 to 1/1000
- **Lithium**
  - Complicated by maternal glomerular filtration rate (GFR) changes during pregnancy. Excreted more rapidly—may need to increase dose[2]
  - After delivery, GFR decreases rapidly, should follow lithium levels during labor and delivery, adjust dose as needed[2]

[1]Yonkers KA et al. *Am J Psychiatry*. 2004;161:608-620; [2]Newport DJ et al. *Am J Psychiatry.* 2005;162:2162–2170.

Valproic Acid

- **Worst Teratogen Known Among Psychotropics**
- Rate of major malformations: ≥ 10%
  - Neural tube defects, craniofacial, cardiovascular, and others
  - Risk of defects is substantial in very early pregnancy
- Associated with increased risk for adverse cognitive and neurodevelopmental effects
  - Long-term follow-up (up to 3 years) suggests fetal exposure to valproate associated with lower IQ scores (not observed with lamotrigine)

Yonkers KA, et al. *Am J Psychiatry*. 2004;161(4):608-620. Newport DJ, et al. *Am J Psychiatry*. 2005;162(11):2162-2170. Meador KJ, et al. *Epilepsy Behav*. 2009;15(3):339-343.

IQ Scores of Children at 3 Years of Age According to In Utero Exposure to Antiepileptic Drugs

Variable	Carbamazepine (N=73)	Lamotrigine (N=84)	Phenytoin (N=48)	Valproate (N=53)
Mean IQ (95% CI)†	98 (95–102)	101 (98–104)	99 (94–104)	92 (88–97)
Mean difference in IQ from valproate group (95% CI)‡	6 (0.6–12.0)	9 (3.1–14.6)	7 (0.2–14.0)	
P value§	0.04	0.009	0.04	

* The results are based on regression models for the intention-to-treat population (309 children). See Table 1 in the Supplementary Appendix for full results of the regression models. IQ at 3 years of age was imputed for 77 of the original 309 children born alive who were not assessed at that age (1 of these children died from severe heart malformation, 6 were enrolled in the NEAD study from the United Kingdom study after they had reached 3 years of age, 31 withdrew before 3 years of age, and 39 did not present for testing).

† Least-squares means from the primary analysis are given after adjustment for maternal IQ and age, antiepileptic-drug dose, infant's gestational age at birth, and maternal preconception use of folate.

‡ Although the confidence intervals for carbamazepine and phenytoin overlap with the confidence interval for valproate, the confidence intervals for the differences between carbamazepine and valproate and between phenytoin and valproate do not include zero.

§ P values are for the comparison with the valproate group. P values from tests of the null hypothesis of no difference from the valproate-group mean were adjusted for multiple comparisons.[23]

Meador KJ et al. *N Engl J Med*. 2009;360(16):1597–1605.

Lamotrigine in Pregnancy

- No increased risk of major malformations
- Association with oral clefting NOT seen with larger numbers
  - Early data suggested it might be when numbers were smaller
  - Recent large study of registries did not find any association between oral clefts and lamotrigine
- Pregnancy increases lamotrigine clearance by > 50%
  - Returns to baseline after delivery

Myllynen PK, et al. *Eur J Clin Pharmacol*. 2003;58(10):677-682. Tran TA, et al. *Neurology*. 2002;59(2):251-255. Dolk H, et al. *Neurology*. 2008;71(10):714-722.

Atypical Antipsychotics in Pregnancy

- Large administrative Medicaid database
  - Nationwide sample of N= 1 360 101 pregnant women
  - After confounding adjustment, the RR was reduced to 1.05 (95% CI, 0.96-1.16) for atypical APs and 0.90 (95% CI, 0.62-1.31) for typical APs. The findings for cardiac malformations were similar
  - For the individual agents examined, a small increased risk in overall malformations (RR, 1.26; 95% CI, 1.02-1.56) and cardiac malformations (RR, 1.26; 95% CI, 0.88-1.81) was found for risperidone that was independent of measured confounders
- Pooled odds ratios of prospective studies
  - Antipsychotic exposure associated with slightly increased risk of major malformations , heart defects), preterm delivery , small-for-gestational-age births , decreased birth weight
  - There was no significant difference in the risk of major malformations differences between typical (and atypical antipsychotic medications.

Hubrechts et al., 2016; Coughlin et al., 2016.

National Pregnancy Registry for Atypical Antipsychotics

Research Study at the Massachusetts General Hospital Center for Women's Mental Health

To determine the safety of atypical antipsychotics in pregnancy for women and their babies

Participation will involve 3 brief phone interviews over approximately 8 months

Call toll-free: 1-866-961-2388

National Pregnancy Registry for Atypical Antipsychotics

Now > 2000 participants enrolled

Aggregate Risk Analyses: As of Dec 2014, N=487 enrolled, N=303 eligible for analyses; 89 controls:

- Rates of major malformations in the two groups similar:
  - 1.4% (3/214 live births) in exposed group ; 1.1% (1/89) in control group
  - Odds ratio comparing exposed with unexposed infants was 1.25 (95% CI=0.13-12.19) – not statistically significant

Quetiapine: N=152 exposure to quetiapine compared with 205 controls

- 2/155 malformations were confirmed (1.3%), compared with 3/210 (1.4%) in control group
- Odds ratio for major malformations between infants with and without quetiapine exposure was 0.90 (95% CI=0.15, 5.46), which is consistent with the pooled estimate of the available controlled data on fetal exposure to quetiapine

Cohen et al., Am J Psychiatry 2016: Cohen et al., Am J Psychiatry 2018

Benzodiazepines and Pregnancy

- 1st trimester exposure: previously inconsistent findings of association with cleft palate or other congenital abnormalities
  - Recent studies do not suggest teratogenicity
- Recent study suggested association with c-section, low birth weight, use of ventilator support for newborn
- Timing of exposure likely makes difference in obstetrical outcomes
- May contribute to poor neonatal adaptation syndrome when used with antidepressants
- Possible longer-term impact on language development
- Difficult to disentangle confounding variables, disease state, concomitant medications

Kanto JH. Drugs 1982;23:354-380. Hanley and Mintzes. BMC Pregnancy Childbirth 2014. Ornoy A, et al. Reprod Toxicol 1998;12:511-515. Eros E, et al. Eur J Obstet Gynecol Reprod Biol 2002. Whitelaw AG, et al. Br Med J (Clin Res Ed) 1981. Mazzi E. Am J Obstet Gynecol 1977. Iqbal MM. et al. Del Med J 2002. Askaa et al., Obstet Gynecol Int 2014. Wikner and Kallen. J Clin Psychopharmacol 2011. Yonkers et al., JAMA Psychiatry, 2017; Salisbury et al., AJP 2016; Odsbu et al., Eur J Clin Pharmacol 2015

Mood Stabilizers and Breastfeeding

Lithium

- Toxicity reported in cases with infant serum levels at 0.1 to 0.5 times the maternal level
- Contraindicated at one time by the American Academy of Pediatrics[1]
- Revised to classification "Drugs That Have Been Associated With Significant Effects on Some Nursing Infants and Should Be Given to Nursing Mothers With Caution"

American Academy of Pediatrics Committee on Drugs. *Pediatrics*. 2001;108(3):776-789.

Mood Stabilizers and Breastfeeding (cont'd)

Lithium and Breastfeeding

- N=10 mother-baby pairs
- Mothers stable, lithium monotherapy 600 to 1,200 mg/day
- Babies' serum levels 0.09 to 0.3 meq/L (average 0.16)
- Transient increases in elevated infant TSH, BUN, Cr

Recommendations

Consider lithium when:

- Bipolar disorder in mother who is stable
- Lithium monotherapy (or simple regimen)
- Adherence to infant monitoring (lithium level, TSH, BUN, Cr immediately postpartum, 4 to 6 weeks of age, and then every 8 to 12 weeks)
- Healthy infant
- Collaborative pediatrician

BUN, blood urea nitrogen; Cr, creatinine; TSH, thyroid-stimulating hormone.

Viguera AC et al. *Am J Psychiatry*. 2007;164(2):342-345.

Menopause

- Very sparse data
- There may be mood worsening associated with the menopausal transition, particularly depressive episodes and symptoms

Blehar et al., 1998; Marsh et al., 2015; Marsh et al., 2012; Freeman et al., 2002

Thank you!

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