MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Postpartum Mood and Anxiety Disorders

Marlene P. Freeman, M.D.
Professor of Psychiatry, Harvard Medical School
Associate Director, Center for Women's Mental Health
Medical Director, CTNI
Massachusetts General Hospital

Disclosure Statement

Investigator Initiated Trials /Research: JayMac, Sage; Advisory boards;
Independent Data Safety and Monitoring Committee: Janssen (Johnson& Johnson), Novartis; Steering Committee for Educational Activities: Medscape; eduational activities: WebMD.
Advisory Boards: Eliem, Sage
Dr. Freeman is an employee of Massachusetts General Hospital, and works with the MGH National Pregnancy Registry. MGH National Pregnancy Registry: Current Sponsors: Alkermes, Inc. (2016-Present); Aurobindo Pharma (2020-Present); AuroMedics Pharma LLC (2021-present); Johnson & Johnson/Janssen Pharmaceuticals, Inc (2019-Present); Otsuka America Pharmaceutical, Inc. (2008-Present); Sage Therapeutics (2019-Present); Sunovion Pharmaceuticals, Inc. (2011-Present); Supernus Pharmaceuticals (2021-Present); Teva Pharmaceutical Industries Ltd. (2018-Present).Past Sponsors: Forest/Actavis/Allergan (2016-2018, declined to sponsor: 2018-Present), AstraZeneca Pharmaceuticals (2009-2014, declined to sponsor: 2014-Present); Ortho-McNeil-Janssen Pharmaceuticals, Inc (2009-2014, declined to sponsor: 2015-Present); Pfizer, Inc. (2009-2011, declined to sponsor: 2012-Present). As an employee of MGH, Dr. Freeman works with the MGH CTNI, which has had research funding from multiple pharmaceutical companies and NIMH.
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Learning Objectives

- Describe and apply the risks/benefits safety of psychiatric medication during the postpartum and breastfeeding context
- Identify strategies for screening and treatment of postpartum depression
- Define the presentation and treatment of postpartum psychosis;
- Describe and assess the vulnerability for mood episodes in women with bipolar disorder and acute treatment and preventative strategies

Postpartum Mood and Anxiety Disorders

Postpartum Blues

Postpartum Depression (PPD)

- DSM5: Peripartum onset specifier
- Onset within 4 weeks of delivery

Postpartum Psychosis

Postpartum Episodes of Bipolar Disorder

Postpartum Anxiety Disorders or Symptoms

Postpartum Depression

- 10-15% of women experience major depressive episodes after delivery (25-40% of women with histories of MDD
- Symptoms similar to non-puerperal major depressive episodes
  - Depressed mood, insomnia, fatigue, anhedonia, suicidal ideation
  - Anxiety is prominent, often marked obsessions, hypochondriasis are present
- Impairment of functioning

Negative Effects of Maternal Depression on the Child

- Insecure attachment
- Behavioral problems
- Cognitive function
- Increased risk of abuse, neglect
- Childhood psychiatric diagnoses & symptoms
- Compliance with preventative measures
- Thoughts of harming infant

Civic & Holt, 2000; Cicchetti et al., 1988; Feldman et al., 1999; Murray et al., 1999; Murray et al., 1996; Sharp et al., 1995; Kotch et al., 1999; Cadzow et al., 1999; Jennings et al., 1999; McLennan & Kotelchuck, 2000; Weissman et al., 2006.

Postpartum Depression: Obsessions and Compulsions

- Obsessions are often present
- Obsessions more common than compulsions/rituals
- Obsessions more common in PPD (57%) than in non-puerperal MDD (36%)
- OCD in 9-11% of postpartum women
- 37.5% report subsyndromal OCD
- Aggressive obsessions > contamination > checking rituals

Miller et al., J Women's Health 2015; Wisner et al. *J Clin Psychiatry* 1999; Zambaldi et al. *Compr Psychiatry* 2009; Arnold *Prim Care Companion J Clin Psychiatry* 1999.

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
  - May not be distressed by thoughts
  - May not show avoidant behaviors
  - Not common disorder
  - High risk of harm to baby

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

Breastfeeding

- Public health initiatives vs. individual situations
- Baby friendly hospital initiative
- What is it: education around breastfeeding, rooming in 24 hours/day, no use of infant nursery, emphasis on exclusive breastfeeding on demand, no bottles or pacifiers
- Overemphasis over maternal wellbeing may increase risk of postpartum depression and anxiety
- Data do not support 24 hr/day rooming in and breastfeeding success

Diez-Sampedro et al., 2019; Jaafar et al., Cochrane Database Syst Review 2012 & 2016; babyfriendlyusa.org

Postpartum Depression: Etiology and Risk Factors

Risk for Postpartum Depression: Hormonal Variables

- Inconsistent findings: no one hormone has been implicated in the cause of PPD
- Thyroid dysfunction is common- either hypo- or hyperthyroidism (hypothyroidism more common; thyroiditis with acute hyperthyroidism may occur)
- Behavioral sensitivity to gonadal steroids in women with PPD has been demonstrated
  - Models of hormone withdrawal to simulate postpartum hormonal decreases in estrogen and progesterone can reproduce depressive symptoms in small studies of women with histories of PPD *(Bloch* Am J Psychiatry *2000)*

Postpartum Depression Predictors Inventory

Stronger Predictors:

- History of depression
- Depression in pregnancy
- Anxiety in pregnancy
- Stressful life events
- Marital dissatisfaction
- Child care stress
- Inadequate social supports
- Difficult infant temperament
- Low self-esteem
- Family History of Postpartum Depression – heritability 44-54% (from twin and sibling studies

Weaker Predictors:

- Unwanted or unplanned pregnancy
- Lower socioeconomic status
- Being single
- Postpartum blues

Risk for Postpartum Illness: History of Psychiatric Illness

- Depression during pregnancy is a robust predictor of postpartum illness
- History of PPD or PP psychosis: 50-70% risk of recurrence
- History of bipolar disorder: 30-50% risk of PP illness
- History of recurrent MDD: Up to 30% risk of PPD

Cohen et al. *Psychiatr Clin North Am.* 2010; Pearlstein et al. *Am J Obstet Gynecol* 2009.

Screening for Postpartum Depression

Postpartum Psychiatric Illness: Detection

- PPD is frequently missed
- Overlap with "normal" postpartum experience: decreased sleep, fatigue, overwhelmed, anxiety ("normal" or not)
- Multiple contacts with health care providers provides opportunity for detection
- Edinburgh Postnatal Depression Scale (EPDS): frequently used, 10-item, self-rated

Cox et al. *Br J Psychiatry.* 150:782-786.

Screening for Depression in Adults
US Preventive Services Task Force Recommendation Statement

DESCRIPTION Update of the 2009 US Preventive Services Task Force (USPSTF) recommendation on screening for depression in adults.

METHODS The USPSTF reviewed the evidence on the benefits and harms of screening for depression in adult populations, including older adults and pregnant and postpartum women; the accuracy of depression screening instruments; and the benefits and harms of depression treatment in these populations.

POPULATION This recommendation applies to adults 18 years and older.

RECOMMENDATION The USPSTF recommends screening for depression in the general adult population, including pregnant and postpartum women. Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up. (B recommendation)

JAMA. 2016;315(4):380-387. doi:10.1001/jama.2015.18392

Pitfalls: Risks of Screening Without a Net

Screening itself does not lead to better outcomes

- Several studies indicate that screening in obstetric setting has not yielded higher rates of treatment engagement
- Women receiving care often receive suboptimal treatment
- Low rates of follow-up on referrals, especially if mental health treatment is offsite
- Recent review: No evidence from any well designed studies that screening leads to better depression outcomes
- 22% rate of treatment engagement after screening (review, Byatt et al., 2015)
- Increased with health care provider education and provision of interventions

Screening must be accompanied by:

- Adequate numbers of well-trained treaters to provide assessments and care to women who screen positive for PPD
- Care needs to be available and delivered in a timely fashion
- Treatment options must reflect heterogeneity of depression detected and patient preferences

Yonkers et al. *Psychiatric Serv* 2009; Flynn et al. *J Womens Health* 2006; Smith et al. *Gen Hosp Psychiatry* 2010; Nelson et al. *J Matern Fetal Neonatal Med.* 2013. Thombs et al., J Psychosom Res. 2014.; Byatt et al., Obstet & Gynecol 2015

Postpartum Depression: Treatment

Treatment Recommendations: Postpartum Depression

- Moderate to severe depression
  - Consider role of antidepressants; discuss risks and benefits with mother
- Use lowest effective doses
- Consultation with perinatal/reproductive psychiatry specialists as needed
- Maximize non-medication alternatives

Postpartum Depression: Non-Pharmacologic Strategies

- Maximize social supports
- Psychoeducation of patient and family members
- Group therapy and support groups
- Interpersonal therapy (IPT)
- Cognitive-behavioral therapy (CBT)
  - CBT is the best studied psychotherapy for PPD
  - Similar results: fluoxetine vs. 6 sessions CBT

Cohen et al. *Psychiatr Clin North Am.* 2010; Perlstein et al. *Am J Obstet Gynecol* 2009; Appleby et al., 1997; Branquinho et al., J Affect Disorders 2021.

Online and Group Resources

- Postpartum Support International
- Help finding local resources
- Online groups for postpartum depression and anxiety, loss

Postpartum Support International
www.postpartum.net
Helpline: 1-800-944-4773

Antidepressant Trials for the Treatment of PPD

Study	Design and Size	Medication studied, result
Appleby et al., 1997	Placebo-controlled, N=87 CBT studied in same trial	Fluoxetine - superior to placebo
Yonkers et al, 2008	placebo controlled, N=70	Paroxetine - not superior to placebo)
Wisner et al., 2006	RCT, Setraline vs. Nortriptyline, N=109	Sertraline vs. Nortriptyline - no significant difference
Hantsoo et al., 2013	Placebo-controlled RCT, N=36	Setraline- superior to placebo
Bloch et al., 2012	N=40, all received brief psychodynamic therapy, RCT to sertraline or placebo	Both groups improved – no significant difference for sertraline vs. placebo
Sharp et al., 2010	RCT, AD selected by general practitioner or counseling, N=254	Antidepressants- superior to placebo
Misri et al., 2012	Open trial, N=15	Citalopram – open study
Misri et al., 2004	N=35, all received parox, half randomized to CBT also	Paroxetine – no control group
Stowe et al., 1995	Open-label; N=21	Sertraline – open study
Cohen et al., 1997	Open-label; N=19	Venlafaxine- open study
Suri et al., 2001	Open-label; N=6	Fluvoxamine - open
Nonacs et al., 2005	Open-label; N=8	Bupropion- open

Antidepressant Treatment During Breastfeeding

Most studies of infant exposure to antidepressants show low levels of drug in breast milk and infant serum

Weissman et al., 2004; Burt et al., 2001

Breastfeeding and Antidepressants

Fluoxetine	Due to long half life, may be more likely to be found at detectable levels in infant serum, especially at higher doses; Reasonable for use if a woman has had a good previous response to it and if used during pregnancy.
Sertraline	• Consistent reports of low levels of exposure, relatively large amount of study
Citalopram, escitalopram	• Less systematic study of mom-baby pairs compared with sertraline and paroxetine, observed low levels of exposure to infant via breastfeeding
Paroxetine	• Consistent reports of low levels of exposure, relatively large amount of study • Use limited by tolerability
Bupropion	• Paucity of systematic study; a few case reports in older infants that demonstrate low levels of exposure via breastfeeding; May be advantageous in smokers; Reasonable for use if women have had good previous response; One case report of possible infant seizure
Venlafaxine, Desmethyl venlafaxine	• Higher levels of desmethylvenlafaxine found in breastmilk than venlafaxine • No adverse events reported
Tricyclic Antidepressants	• Considered reasonable for breastfeeding if use clinically warranted; few adverse affects in babies and generally low levels of exposure reported
Newer antidepressants, MAOIs	• Systematic human lacking in the context of breastfeeding for MAOIs, most newer antidepressants • Case series for vortioxetine (N=3) showing low levels of exposure, duloxetine (N=1)

Brexanolone (SAGE-547)
Allopregnanolone/Neurosteroids

- FDA approval in 2019
- IV delivered analogue of allopregnanolone
- Allosteric modulator of GABA receptors
- Two positive, controlled trials in postpartum depression (onset during late pregnancy or postpartum, presented within six months postpartum with MDD)
- Rapid onset of benefit, durable efficacy to 30 days
- Implementation challenges: cost, in hospital

Meltzer-Brody et al., Lancet 2018

Zuranolone: Neuroactive steroid in phase 3 studies

- Oral neurosteroid GABA allosteric modulator
- In phase 3 trials for PPD
- Recent study demonstrated benefit in placebo-controlled trial
- Administered orally for 2 weeks
- N=150 randomized patients, significant improvement on HAM-D observed from day 3, at primary endpoint (day 15), through day 45
- Improvements on anxiety also demonstrated
- Under study for MDD in men and women

Deligiannidis et al., JAMA Psychiatry 2021

Perinatal Depression

Non-medication treatments

- **Psychotherapy**[1,2,3]
- Electroconvulsive therapy[4]
- Complementary and Alternative Medicine (CAM treatments) (Integrative Medicine)

[1]Spinelli MG. *Am J Psychiatry*. 1997;154(7):1028-1030; [2]Dennis CL. *J Clin Psychiatry*. 2004;65(9):1252-1265; [3]Yonkers KA et al. *Obstet Gynecol*. 2009; 114(3):703-713; [4]Miller LJ. *Hosp Community Psychiatry*. 1994;45(5):444-450.

CAM/Integrative Treatments

- Omega-3 fatty acids—add-on
- Exercise—add-on
- Folate—add-on
- SAMe—?monotherapy (no specific study)
- St John's wort—similar to antidepressants but less known
- Acupuncture—monotherapy or add-on
- Bright light therapy—monotherapy or add-on
- Massage—add-on

SAMe, S-adenosylmethionine

Parker G et al. *Am J Psychiatry*. 2006;163(6):969-978; Freeman MP et al. *Acta Neuropsychiatrica*. 2006;18, 21-24; Su KP et al. *J Clin Psychiatry*. 2008;69(4):644-651; Nemets B et al. *Am J Psychiatry*. 2002;159(3):477-479; Deligiannidis KM, Freeman MP. *Psychiatr Clin North Am*. 2010;33(2):441-463.

RCTs of Antidepressants for Prevention of PPD in women at risk

Study	High Risk defined by…	Intervention	N	Findings
Wisner et al., 1994	Past h/o postpartum MDD	Open trial; monitoring alone vs. monitoring + a medication that had been effective for the previous episode or nortriptyline (pt selected monitoring vs. monitoring + med)	N=23; monitoring compared to medication +monitoring	Significantly greater proportion of the women who elected **monitoring alone (62.5 percent) suffered recurrence** compared to monitoring plus medication (6.7 percent) (p = .0086)
Wisner et al., 2001	Past h/o postpartum MDD	RCT: Nortriptyline vs. placebo (started immediately postpartum) x 20 wks	N=51 (N=26 Nortrip; N=25 placebo)	No significant differences between groups; **about 25% recurrences for both** (6/25 relapsed on placebo; 6/26 on nortrip)
Wisner et al., 2004	Past h/o postpartum MDD	RCT: Sertraline v. Placebo (started immediately postpartum) x 17 wks (followed for 20 wks)	N=22 (N=14 sert, N=8 placebo)	7% recurrence with sert; **50% recurrence with placebo** (significantly different)

Bipolar Disorder: Postpartum Considerations

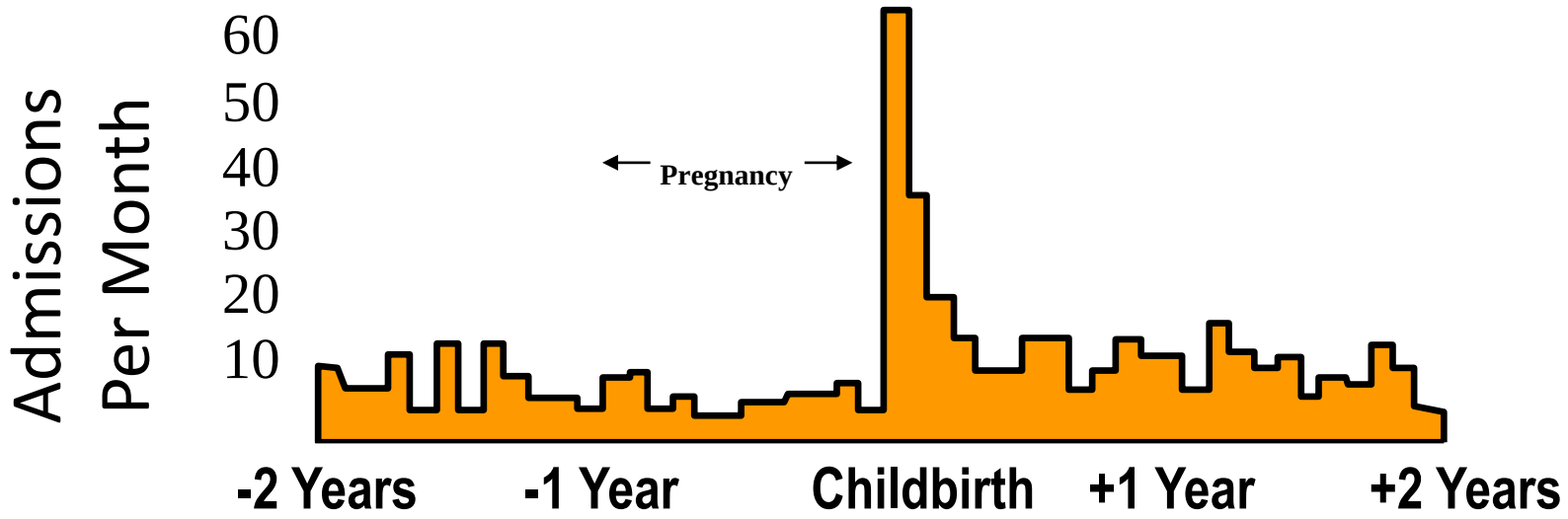
Pregnancy & Postpartum: Risks of Discontinuing Medication

Viguera, et al. 2000:

- Retrospective comparison of recurrence rates, pregnant (N=42) vs. nonpregnant women (N=59) with bipolar disorder
- Rates of recurrence after discontinuation of medication
  - Similar for pregnant and nonpregnant women, except more depressive episodes in pregnant women **(overall recurrence rate = 55%)**
  - **Women at increased risk of recurrence postpartum** (**70% vs. 24%**; 2.9 x more likely to have recurrence than nonpregnant women after same time course)
  - **Recurrence risk greater after rapid discontinuation** (≤2 wks) than gradual (2-4 wks)

Viguera, et al. 2000

Risk of Psychiatric Hospitalization During Pregnancy and Postpartum



Kendell et al. *Br J Psychiatry*. 1987;150:662.

Highest risk of hospitalization for new mothers 10-19 days postpartum, increased outpt contacts 1st three months

-*Munk-Olsen et al., JAMA, 2006*

Postpartum Psychosis

Postpartum Psychosis

- 1 to 2 per 1000 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 and Cohen, 1998; Jones & Craddock, 2001;
Spinelli, AJP, April 2009

Postpartum Psychosis

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

Spinelli, AJP 2004; Spinelli, AJP 2009

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 Relapse: Bipolar Disorder

- Pharmacotherapy strongly influences rate of relapse

Prevention of Postpartum Psychosis

- Are outcomes different in women who have only had postpartum psychotic episodes and no other mood episodes?
- When should medication prophylaxis be initiated?
  - Most using lithium
  - Advised to use lithium prophylaxis immediately after delivery

Bergink et al., AJP 2012

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

Mood Stabilizers & Breastfeeding

- **Lithium**
  - Toxicity reported in cases with infant serum levels at 0.1-0.5 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 2001

Mood Stabilizers & Breastfeeding

- **Lithium and Breastfeeding: Recent report**
  - N=10 mother-baby pairs;
    - Mother's stable, lithium monotherapy 600-1200 mg q day
    - Babies' serum levels 0.09-0.3 meq/L (average 0.16)
    - Transient increases in elevated infant TSH, BUN, Cr
  - **Recommendations** –consider when
    1) Bipolar disorder in mother that is stable
    2) Lithium monotherapy (or simple regimen)
    3) Adherence to infant monitoring

       Monitoring Li level, TSH, BUN, Cr immediately postpartum, 4-6 weeks of age, and then every 8-12 weeks
    4) Healthy infant
    5) Collaborative pediatrician

Viguera, et al. 2007 (Feb)

Avoiding Pregnancy

Ask About Birth Control Methods and Document

Interactions with Oral Contraceptives Pills (OCPs)

- <u>May Decrease Efficacy of OCPs:</u>
  - Carbamazepine
  - Oxcarbazepine
  - Topiramate
  - St John's Wort
  - Modafinil, armodafil
- Oral contraceptives may decrease lamotrigine levels

Take Home Points

- The postpartum is a vulnerable window of time for many women
- Women, children, and families are impacted
- Effective, safe, accessible, and acceptable treatments are needed
- Treatment considerations involve risks of medications, risks of the untreated disorder
- Unknowns
  - Warrant collaborative treatment decisions, prioritizing patient preferences

Thank you!

Marlene P. Freeman, MD

www.womensmentalhealth.org