Mass General Brigham

Bipolar disorder and psychosis in pregnancy

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Disclosures

No financial conflicts of interest

All medications discussed, when used in pregnancy, are off label and not FDA approved for use in pregnancy

Objectives

To provide an overview of the epidemiology of Bipolar Affective Disorder in women

To discuss epidemiology, evaluation, and risks for postpartum psychosis

To discuss the clinical presentation and general approach to the management of BPAD in women during the perinatal period

Bipolar disorder

Bipolar Affective Disorder- Type I

Mania

- Abnormally and persistently elevated mood & energy >1 week
- Can present as mixed state
- 3 additional symptoms
  - inflated self esteem
  - decreased need for sleep
  - pressured speech
  - flight of ideas
  - distractibility
  - increased goal directed activity
  - excessive engagement in activities with high potential of negative consequences

MUST cause impairment in function

Depression

5 or more symptoms for at least 2 weeks

- Depressed mood nearly daily
- Diminished interest or pleasure
- Significant weight loss
- Changes in sleep
- Psychomotor retardation or agitation
- Fatigue/loss of energy
- Feeling worthless or excessive guilt
- Poor concentration
- Recurrent thoughts of death

DSM-V

Bipolar Affective Disorder- Type 2

Hypomania

- Abnormally and persistently elevated mood & energy 4+ days
- 3 additional symptoms
  - inflated self esteem
  - decreased need for sleep
  - pressured speech
  - flight of ideas
  - distractibility
  - increased goal directed activity
  - excessive engagement in activities with high potential of negative consequences

Clear, uncharacteristic change in mood and behavior, observable to others, but not causing marked impairment

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- Poor concentration
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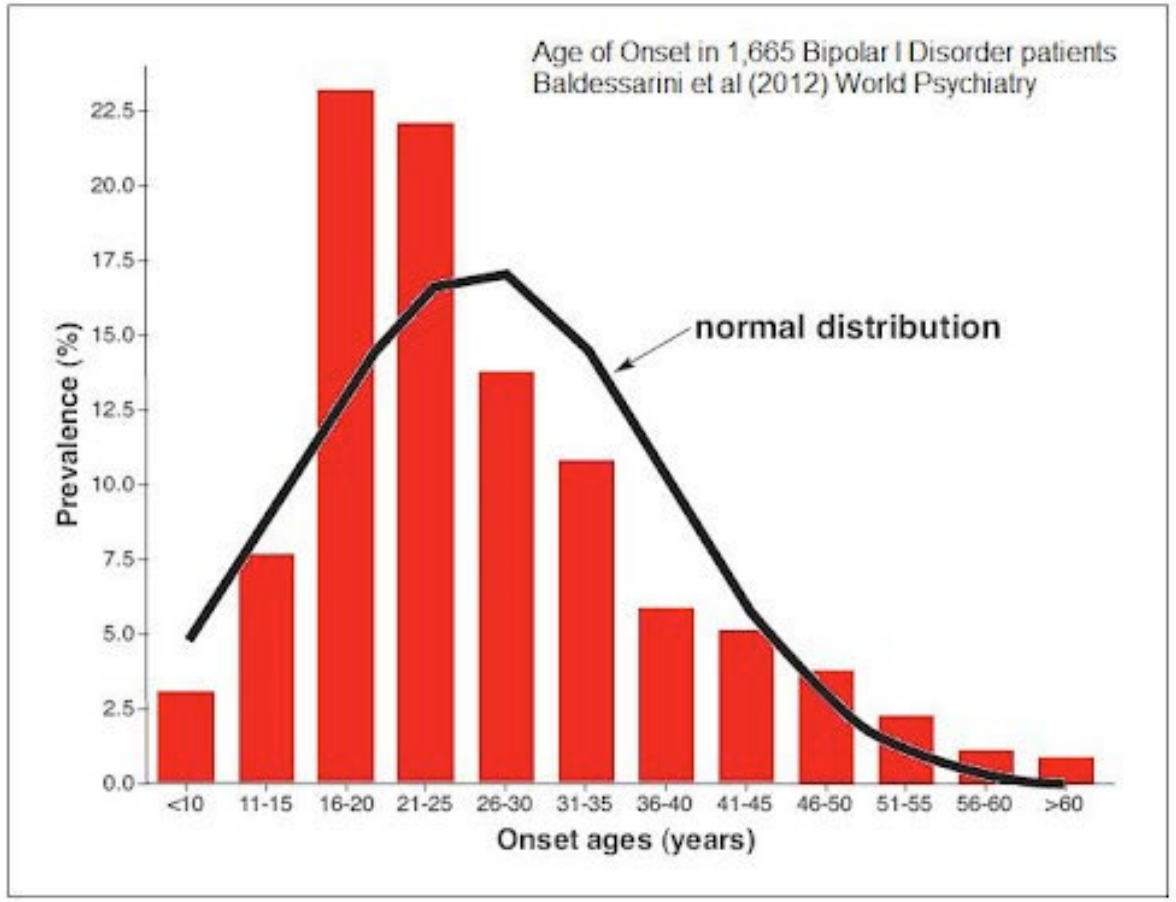
DSM-V

Onset of BPAD peaks during reproductive years in women



Average age of BAPD onset= 25 years old

Average age of first delivery= 27 years old

The perinatal period is a high risk time period for BAPD presentation

If no psychiatric history pre-pregnancy, 2.6% had first ever episode perinatally

If hx of unipolar depression diagnosed pre-pregnancy, 6.5% 'converted' to a bipolar disorder diagnosis perinatally

Masters GA, Hugunin J, Xu L, Ulbricht CM, Moore Simas TA, Ko JY, Byatt N. Prevalence of Bipolar Disorder in Perinatal Women: A Systematic Review and Meta-Analysis. J Clin Psychiatry. 2022 Jul 13;83(5):21r14045. doi: 10.4088/JCP.21r14045. PMID: 35830616; PMCID: PMC10849873.

Sharma V, Xie B, Campbell MK, et al. A prospective study of diagnostic conversion of major depressive disorder to bipolar disorder in pregnancy and postpartum. Bipolar Disord. 2014;16(1):16–21

Screening

Bipolar Disorder: A Common Screening Gap

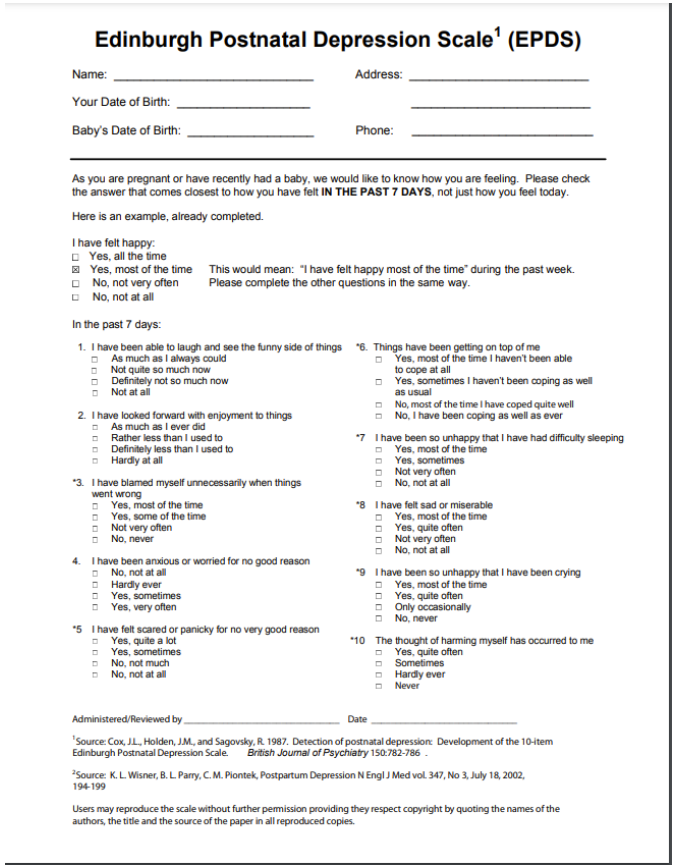
Peripartum depression screening is common but bipolar disorder screening is not as common

Depression

- Edinburgh Postnatal Depression Scale (EPDS)
  - 10 item self report
  - Validated in multiple languages
  - Focuses on cognitive symptoms

~20-30% of positive EPDS screens are not ultimately unipolar depression, they are bipolar depression

Must follow up a positive EPDS with bipolar disorder screening prior to treating!



Edinburgh Postnatal Depression Scale[1] (EPDS)

Name: _____ Address: _____

Your Date of Birth: _____ _____

Baby's Date of Birth: _____ Phone: _____

As you are pregnant or have recently had a baby, we would like to know how you are feeling. Please check the answer that comes closest to how you have felt **IN THE PAST 7 DAYS**, not just how you feel today.

Here is an example, already completed.

I have felt happy:
☐ Yes, all the time
☒ Yes, most of the time — This would mean: "I have felt happy most of the time" during the past week.
☐ No, not very often — Please complete the other questions in the same way.
☐ No, not at all

In the past 7 days:

1. I have been able to laugh and see the funny side of things
   ☐ As much as I always could
   ☐ Not quite so much now
   ☐ Definitely not so much now
   ☐ Not at all
2. I have looked forward with enjoyment to things
   ☐ As much as I ever did
   ☐ Rather less than I used to
   ☐ Definitely less than I used to
   ☐ Hardly at all

*3. I have blamed myself unnecessarily when things went wrong
   ☐ Yes, most of the time
   ☐ Yes, some of the time
   ☐ Not very often
   ☐ No, never

4. I have been anxious or worried for no good reason
   ☐ No, not at all
   ☐ Hardly ever
   ☐ Yes, sometimes
   ☐ Yes, very often

*5 I have felt scared or panicky for no very good reason
   ☐ Yes, quite a lot
   ☐ Yes, sometimes
   ☐ No, not much
   ☐ No, not at all

*6. Things have been getting on top of me
   ☐ Yes, most of the time I haven't been able to cope at all
   ☐ Yes, sometimes I haven't been coping as well as usual
   ☐ No, most of the time I have coped quite well
   ☐ No, I have been coping as well as ever

*7 I have been so unhappy that I have had difficulty sleeping
   ☐ Yes, most of the time
   ☐ Yes, sometimes
   ☐ Not very often
   ☐ No, not at all

*8 I have felt sad or miserable
   ☐ Yes, most of the time
   ☐ Yes, quite often
   ☐ Not very often
   ☐ No, not at all

*9 I have been so unhappy that I have been crying
   ☐ Yes, most of the time
   ☐ Yes, quite often
   ☐ Only occasionally
   ☐ No, never

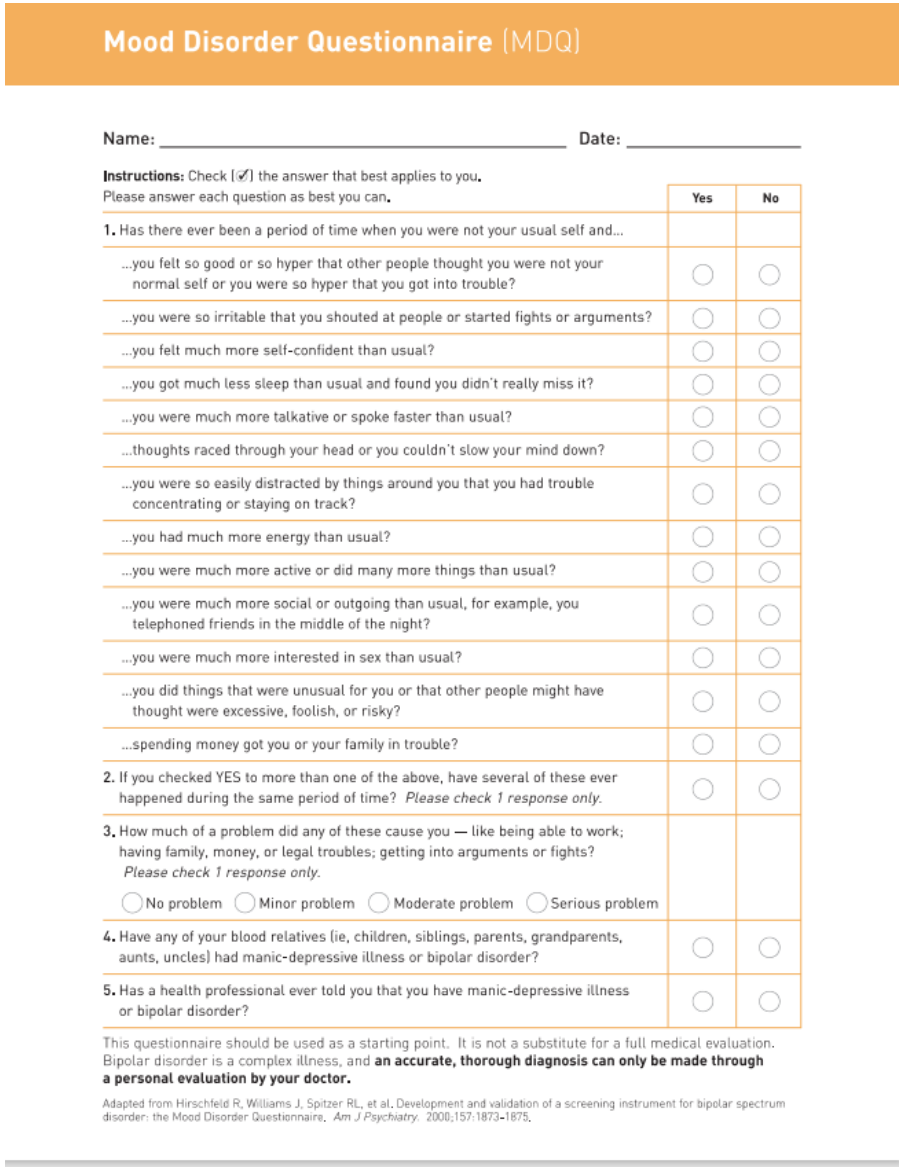
*10 The thought of harming myself has occurred to me
   ☐ Yes, quite often
   ☐ Sometimes
   ☐ Hardly ever
   ☐ Never

Administered/Reviewed by _____ Date _____

[1]Source: Cox, J.L., Holden, J.M., and Sagovsky, R. 1987. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry* 150:782-786 .

[2]Source: K. L. Wisner, B. L. Parry, C. M. Piontek, Postpartum Depression N Engl J Med vol. 347, No 3, July 18, 2002, 194-199

Bipolar Disorder Screening



Mood Disorder Questionnaire (MDQ)

Name: _____ Date: _____

Instructions: Check (✓) the answer that best applies to you.
Please answer each question as best you can.

	Yes	No
1. Has there ever been a period of time when you were not your usual self and...		
...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?	◯	◯
...you were so irritable that you shouted at people or started fights or arguments?	◯	◯
...you felt much more self-confident than usual?	◯	◯
...you got much less sleep than usual and found you didn't really miss it?	◯	◯
...you were much more talkative or spoke faster than usual?	◯	◯
...thoughts raced through your head or you couldn't slow your mind down?	◯	◯
...you were so easily distracted by things around you that you had trouble concentrating or staying on track?	◯	◯
...you had much more energy than usual?	◯	◯
...you were much more active or did many more things than usual?	◯	◯
...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?	◯	◯
...you were much more interested in sex than usual?	◯	◯
...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?	◯	◯
...spending money got you or your family in trouble?	◯	◯
2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time? *Please check 1 response only.*	◯	◯
3. How much of a problem did any of these cause you — like being able to work; having family, money, or legal troubles; getting into arguments or fights? *Please check 1 response only.* ◯ No problem ◯ Minor problem ◯ Moderate problem ◯ Serious problem		
4. Have any of your blood relatives (ie, children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder?	◯	◯
5. Has a health professional ever told you that you have manic-depressive illness or bipolar disorder?	◯	◯

This questionnaire should be used as a starting point. It is not a substitute for a full medical evaluation. Bipolar disorder is a complex illness, and **an accurate, thorough diagnosis can only be made through a personal evaluation by your doctor.**

Adapted from Hirschfeld R, Williams J, Spitzer RL, et al. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. *Am J Psychiatry.* 2000;157:1873-1875.

Mood Disorder Questionnaire (MDQ)
Positive screen requires 7 of 13 positive symptoms
And impairment in function

MDQ also asks about family history of bipolar disorder– a major risk factor for diagnostic change from MDD to BAPD type II in the peripartum (11x higher rates)

Antidepressants including SSRIs may precipitate hypomania or mania in a patient with bipolar depression

Treatment approach

Risk vs. Risk Discussions

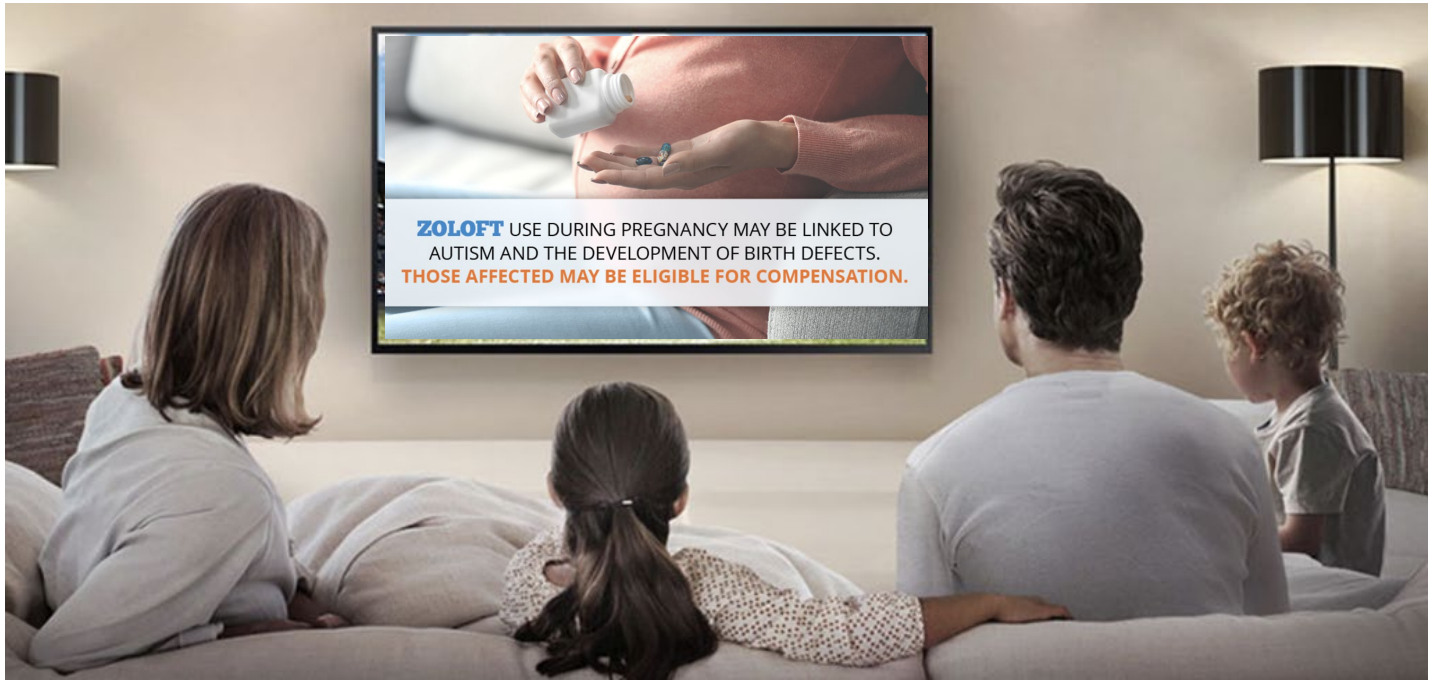
- Evidence based/gold standard treatment for bipolar disorder involves medication
- Pregnant patients may overestimate teratogenic risks of medications in general (Csajka 2014), and even more so for psychiatric medications (Bonari 2005)
- Important to a comprehensive discussion with patient about ‘risk vs. risk’– risk of medication compared to risk of untreated illness

Discontinuing medications doesn't protect you from lawsuits

There's also no true 'no risk' option for you as the clinician

Fight against omission bias

For mom, fetus, and clinician: the best approach is an **informed discussion of potential risks and benefits of treatment options**



(Friedman and Hall, 2021)

Risk vs. Risk Discussions

- Baseline risk of complications in pregnancy
  - Congenital malformation rate is 3-5%
- Relevant comparisons of potential risk
  - Discuss ‘confounding by indication’
- Relevant comparisons of potential benefit
- Exposure to fetus- relevant timeline of organogenesis
- Breastfeeding considerations
  - Most medications are compatible, but a broader discussion of goals and priorities can be helpful

BPAD recurrence risk is high in the perinatal period

Risk of decompensation

27% when maintaining medication

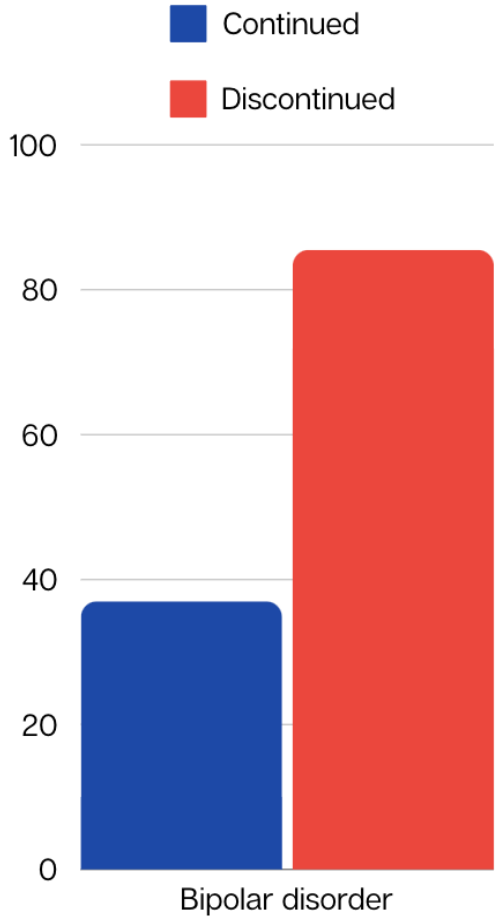
86% when discontinuing mood stabilizer

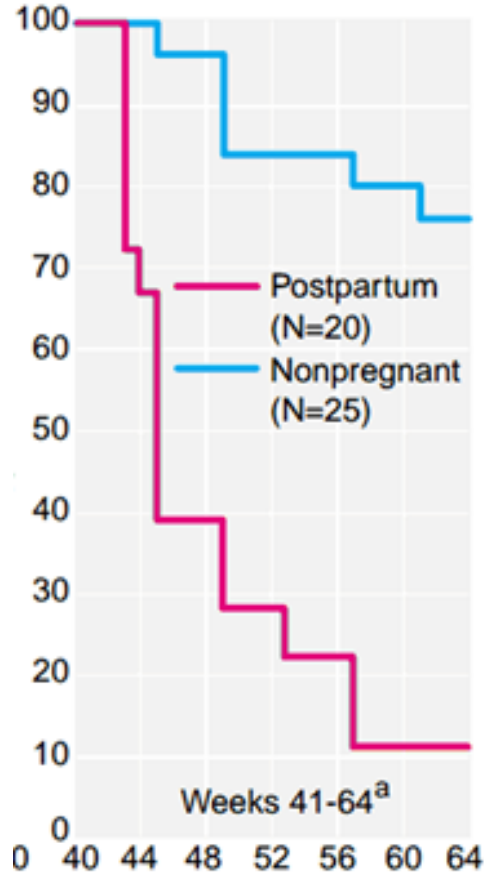
Discontinuing abruptly increases risk (50% likelihood of recurrence within 2 weeks)

If unmedicated, 40% of pregnancy spent in an illness episode

Postpartum, nearly all who remained well then decompensate

Only ~1 in 100 remain well at 4mo postpartum





Viguera AJP 2007
Viguera AJP 2000

BPAD episodes in the perinatal period

During pregnancy

Recurrence is most commonly a depressive episode

Effects on fetal development, obstetric complications, and risky behaviors

During postpartum

Mixed episodes common

Increased risk of psychosis

Psychiatric admission risk is high (37x baseline), and even higher if admitted during pregnancy (~40%)

Insufficiently managed BPAD in pregnancy is associated with negative outcomes

Effects on fetal development

- Low birth weight
- Prematurity
- Small for gestational age
- Intellectual/cognitive delays

Effects on pregnancy

- Increased c-section rate
- Less prenatal care
- Preterm labor
- Pre eclampsia

High risk behaviors

- Increased rates of substance use
- Hypersexuality
- Loss of supportive relationships
- Suicide
- Less engagement in prenatal care

Mei-Dan et al, AM J OB Gyn 2015, Boden Et al, BMJ 2012

BPAD increases risk of postpartum psychosis

1-2/1000 women

>70% have previous hx of BPAD or Schizoaffective DO

20% of women with BPAD type 1 experience PPP

Rapid onset within days postpartum up to a few weeks

90% occur within the first month postpartum

Initial presentation often like delirium (confusion/agitation) followed by mood and psychotic symptoms, irritability

Increased risk of suicide, 4% risk of infanticide

Psychiatric emergency

Wesseloo et al AJP 2016, Manic Depression Illness, Goodwin and Jamison, 2007 ; Harlow et al Arch Gen Psych 2007
Harlow, B. et al 2007
Perry et al Journal of Affective Disorders 2021

Other Risk Factors for PPP

- Personal hx of bipolar disorder or PPP
- Not currently treated with medications
- Family history of BPAD
- Older maternal age
- Sleep disruption
- First delivery

Symptoms of postpartum psychosis

Early symptoms

- Insomnia
- Mood fluctuation
- Irritability
- Depressive symptoms

Features to Evaluate

- Waxing and waning of symptoms
- Delusions and bizarre thoughts
- Disorganized, odd behavior
- Suicidal or homicidal thoughts

Intrusive Thoughts of Harm in OCD can mimic PPP

Postpartum psychosis	Postpartum OCD
• Ego-syntonic • Not always distressed by her thoughts • Content bizarre or unusual • Distorted reality • Psychotic symptoms • Desire to act on thoughts, or acceptance of necessity to act	• Ego-dystonic • Disturbed and distressed by thoughts, thoughts feel ‘scary’ • No desire to act on thoughts, avoidance behaviors to ensure she will not act • Can engage in compulsive behavior (checking, seeking reassurance) to ease distress
Higher risk	Lower risk

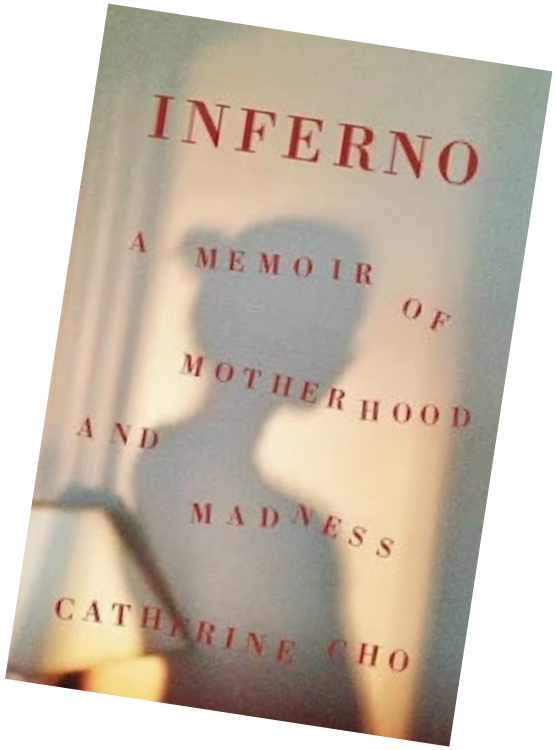
Pearls for the postpartum psychosis evaluation

Get all the **collateral information** you can obtain, especially from close contacts who have seen her behavior

When clarifying OCD vs. PPP, elicit **detail**

Timing is helpful factor but can't rule out PPP- 10% occurs 'later-onset'

For new onset psychosis, needs a full first break psychosis workup. Rule out other potential underlying causes of symptoms.



Treatment for BPAD in pregnancy/postpartum

Medication management

- Typically **mood stabilizer** and/or **antipsychotic** in regimen
- What has worked in the past?
- Monotherapy when possible
- Minimize switching
- Lowest EFFECTIVE dose
- May need to adjust dose during pregnancy
- FDA 'ABCDX' categories are misleading and should not be used for medication selection
- Genetic testing does not have evidence base for guiding medication selection

During pregnancy, mother is the patient

- 1st trimester—physical teratogenicity
- 2nd & 3rd –behavioral, altered mental functioning.
- End—neonatal side effects, growth, timing of labor, withdrawal, breastfeeding plans

McAllister-Williams et al J Psychopharm 2017

Lithium (in pregnancy)

Risk of fetal cardiovascular malformations:

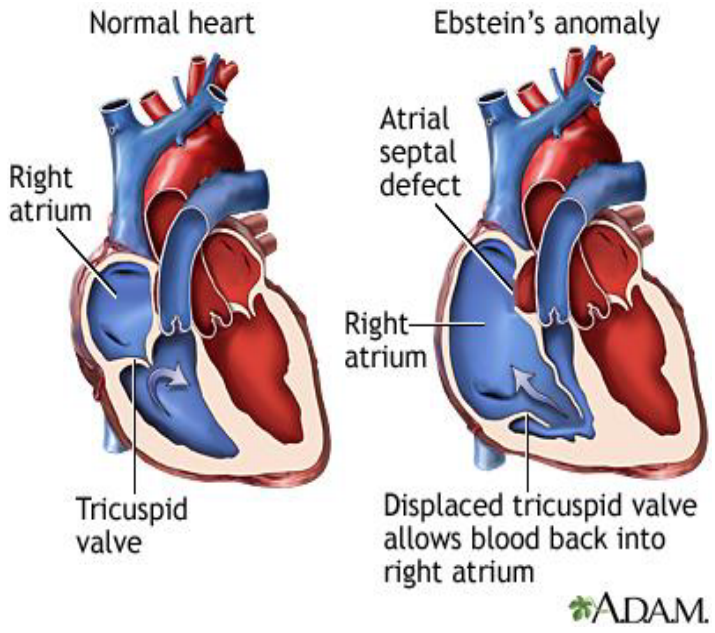
Absolute risk is low: 2 in 100 infants exposed to lithium (compared to 1 in 100 if not exposed)

Dose-related: significantly higher risk only with >900 mg daily

Exposures in **first trimester**

Other fetal considerations:

- Transient hypothyroidism of neonate, neonatal hypotonicity, lethargy, prematurity, large for gestational age
- No known developmental/cognitive effects
- Get anatomy scan ultrasound at 16-18wks



Deligiannidis et al. J Clin Psychopharm 2013,
Patorno et al., NEJM 2017

Lithium (in pregnancy)

- Dose adjustment may be required to stay in therapeutic range
  - Lithium is cleared by the kidnesy, GFR increases in pregnancy
  - Lithium clearance is increased by 20-50% by 3rd trimester and then returns to baseline after delivery)
- Conception- 34 weeks GA: lithium levels every 3 weeks
- 34wks GA – delivery: lithium level weekly
- Keep level in the therapeutic range

Deligiannidis et al. J Clin Psychopharm 2013
Wesseloo et al. Br J Psychiatry. 2017

Lithium (at delivery/postpartum)

At delivery

- Check level when admitting for delivery and 24 hrs postpartum
- Avoid NSAIDs in pain management plan- can increase lithium levels
- Check levels and monitor for toxicity daily while in hospital, keep level below 1 but in therapeutic range
- Should usually be back at pre-pregnancy dose by discharge (ie, ~72hrs)

Breastfeeding

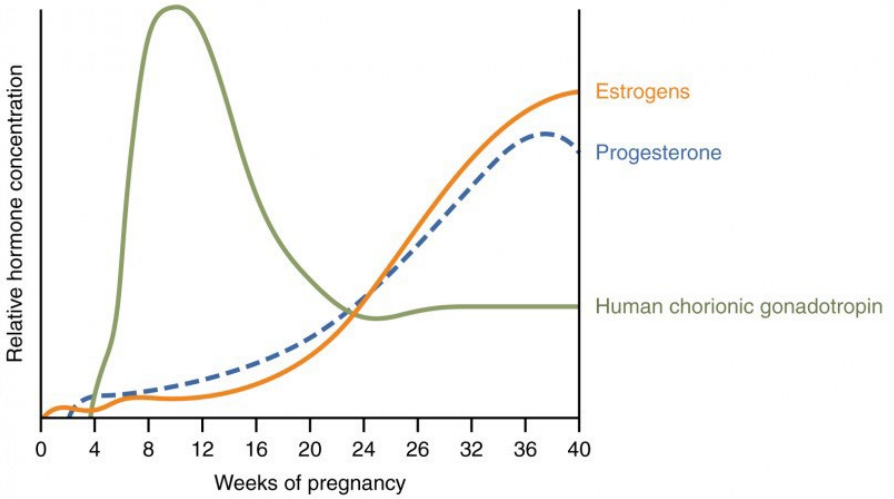
- Ensure sleep is being prioritized
- Excreted in breast milk at higher levels than many other medications, but not inherently incompatible with breastfeeding
- Ideal circumstances would be stable maternal mood and
  - Lithium monotherapy
  - Healthy full term infant
  - Pediatrician for collaboration-
    - Neonatal monitoring of TSH, BUN, Cr and lithium level needed

Deligiannidis et al. J Clin Psychopharm 2013

Lamotrigine

- Not associated with congenital malformations (including cleft palate)
- No evidence suggesting negative neurodevelopmental outcomes
- Take regular prenatal supplementation of folic acid
- Consider obtaining pre-pregnancy level, if possible
- May need dose increase and/or split dosing due to metabolism induction by estrogen & progesterone
- After delivery, return to pre-pregnancy dose by decreasing 25% every 3-4 days
- High transmission in breast milk (relative infant dose ~30%, but compatible with lactation.

Deligiannidis et al. J Clin Psychopharm 2013



https://courses.lumenlearning.com/ap2/chapter/maternal-changes-during-pregnancy-labor-and-birth/

Haloperidol

- Data since 1966, 1st used as anti-emetic so safety data exists from non-mentally ill women
- No evidence of teratogenicity
- Small risk for transient extrapyramidal symptoms (EPS) of neonate (abnormal muscle movements)
- No evidence of long-term developmental effects on fetus
- Flexible dose range, multiple routes of administration
- Relatively less sedating compared to some second generation antipsychotics
- Helpful for nausea!

Huybrechts et al Jama Psychiatry 2016; Boden et al Arch Gen Psychiatry 2012; Tosato et al J Clin Psychiatry 2017

Atypical antipsychotics

- Reassuring safety data regarding risk of congenital malformations due to fetal exposure
- Quetiapine has lowest placental passage and lowest passage into breast milk.
- Possible dose-dependent increased risk of gestational diabetes for quetiapine in particular
- Aripiprazole may lower serum prolactin levels and affect lactation
- Medication choice likely to be guided by clinical scenario (e.g., acute mania/psychosis vs. bipolar depression, need for specific/flexible delivery modes to maximize monotherapy)

Huybrechts et al Jama Psychiatry 2016; Boden et al Arch Gen Psychiatry 2012; Tosato et al J Clin Psychiatry 2017

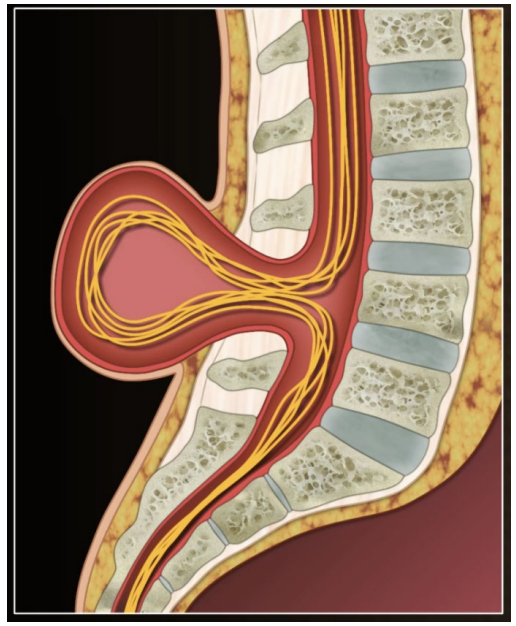
Medications to **AVOID**

Valproic Acid

- Birth defects: spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, craniosynostosis
- Valproic acid increases risk of neural tube defects >10-20x
- Neuro: average IQ 9 points lower, dose dependent
- Risks exist across all 3 trimesters
- In some countries, cannot be given to reproductive age women

Carbamazepine

- Birth defects: spina bifida, cleft lip/palate, urinary and cardiac anomalies, reduced head circumference, low weight
- Neuro: also lower IQ but by 1-3 pts



Spina bifida

Marsh et al. Psych Annals 2012

Systemic Review of Neurodevelopmental outcomes of prenatal exposure to AED

Drug	Outcome
Valproic Acid Dose dependent effect	2-4 increased risk of ASD 2-5 increased risk of intellectual disability 1.5 fold increased risk of ADHD 2-4 fold increased of emotional/behavioral disturbance Birth defects—spinal cord, hear, hypospadias
Carbamazepine	Higher prevalence of behavioral regulation problems
Topiramate	2 fold increase of ASD 3 fold increase in intellectual disability 2 fold increase in ADHD Bither birth defect rate
Lamotrigine	No relationship seen with adverse neurodevelopmental outcomes

Honybun E, et al 2024; Veiby et al 2014

Non-pharmacologic aspects of perinatal bipolar disorder treatment

- Support groups for perinatal individuals with bipolar disorder
- Ensure a block of sleep
  - Can be done while supporting breastfeeding goals
  - Plan ahead!
- Close follow-up postpartum
  - Monitor for mood, insomnia, unusual thoughts/behavior
- Engage social supports
  - Request ROI to communicate with family who can provide collateral

Summary/Key Points

- Maternal mental health affects the patient, her child, and family
- Roughly 30-50% of pregnancies in the USA are unplanned
- Assume that all women of reproductive age can become pregnant at any time in treatment
- When possible, discuss treatment plans pre-conception
- Screening for mood disorders is essential
- Screening =/= diagnosis, use screening as a launching point for diagnostic evaluation that considers a full differential
- Consider the risks of untreated psychiatric illness when making treatment plan- high BPAD recurrence risk and increased risk of PPP
- Fetal medication exposure concerns vary by medication and gestational age during exposure
- Medication choice will often be guided by case-specific factors, but should not include Valproic Acid

Resources

MCPAP for Moms Mcpapformoms.org
MGH Center for Women's Mental Health Womensmentalhealth.org
Reprotox Reprotox.org
Postpartum Support International Postpartum.net
Lactmed toxnet.nlm.nih.gov/newtoxnet/lactmed.htm
MotherToBaby https://mothertobaby.org/

Questions?