Brigham and Women's Hospital
Founding Member, Mass General Brigham

Management of BPAD in pregnancy and postpartum

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HARVARD MEDICAL SCHOOL
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MAGNET RECOGNIZED
AMERICAN NURSES CREDENTIALING CENTER

DISCLOSURES

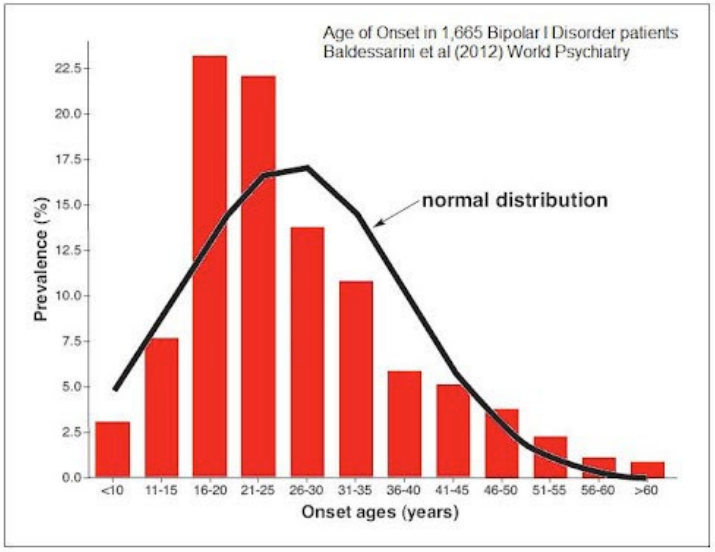
No financial conflicts

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

Objectives:

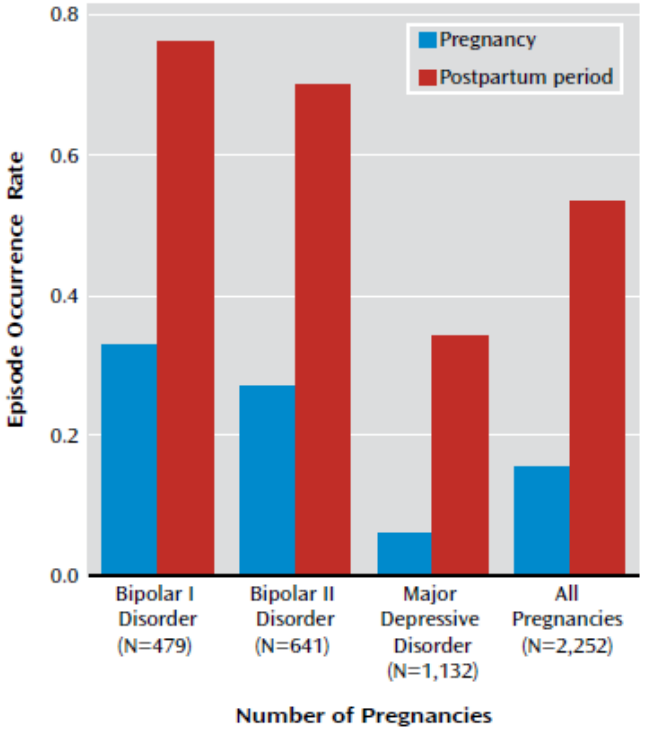
- To provide an overview of the epidemiology of Bipolar Affective Disorder in women
- To discuss the clinical presentation and general approach to the management of BPAD in women during the perinatal period

Onset of BPAD peaks during reproductive years in women



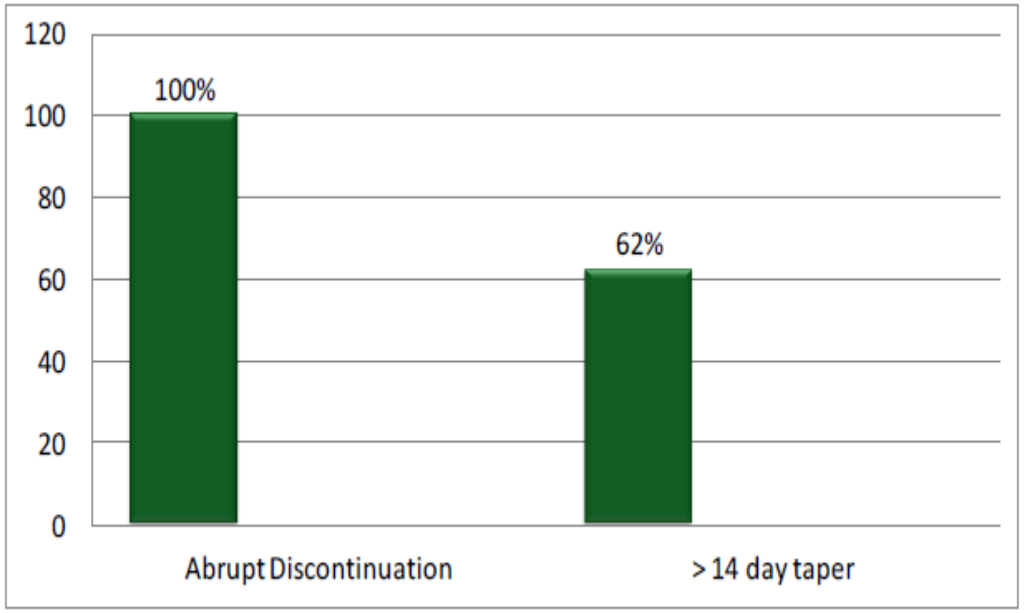
WHO, NIMH

FIGURE 1. Episode Occurrence Rates of Major Affective Episodes During Pregnancy and During the Postpartum Period in 1,162 Women With Bipolar I, Bipolar II, or Major Depressive Disorder[a]

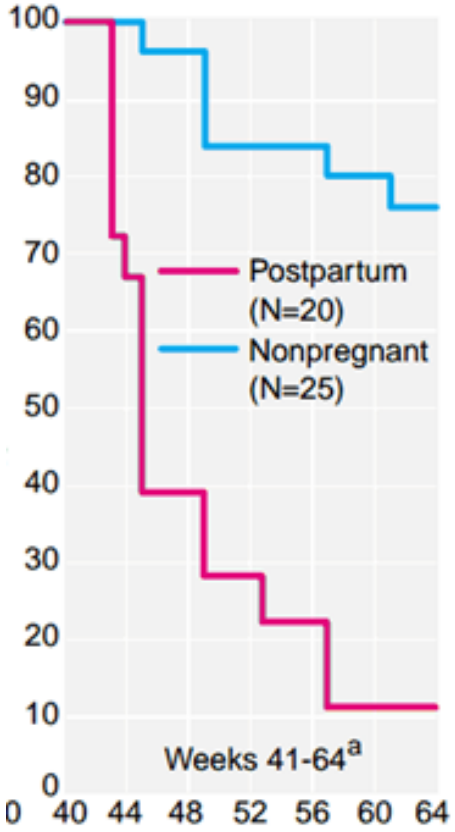


[a] Episode occurrence rates are reported as illness episodes per pregnancy per year.

During pregnancy and postpartum, medication discontinuation increases risk of recurrence of BPAD



Yonkers et al. AJP 2004



Viguera et al. AJP 2000

Bipolar Affective Disorder

(Manic Depression)

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

MUST cause impairment in function

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

DSM

Differential Diagnosis

- Personality Disorder
- Substance Use Disorder
- Complex trauma and trauma related disorders

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

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
- Rapid onset within days postpartum up to a few weeks
- Initial presentation often like delirium (confusion/agitation) followed by mood and psychotic symptoms, irritability
- Must rule out medical causes or AMS
- 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

Perinatal Psychiatric Hospitalizations

Swedish study looking at rates of postpartum psychiatric hospitalization in women with history of prior hospitalization or not:

- Rates of psychiatric admission for PPP or BPAD postpartum in patient with **no prior mental health history** was about **0.4%**
- For women with **history of psychiatric hospitalization** prior to delivery, rate was **9%**

Risk factors included: the recency of pre-pregnancy hospitalizations, number of previous hospitalizations, and length of most recent hospitalization.

More than 40% of women hospitalized during the prenatal period for a bipolar or a psychotic condition were hospitalized again during the postpartum period.

Approximately 90% of all postpartum psychotic and bipolar episodes occurred within the first 4 weeks after delivery.

Harlow, B. et al 2007

Risk of harm to baby when mother has thoughts of harm

OCD/anxiety/depression	Postpartum Psychosis
• Good insight • Thoughts are intrusive and scary • No psychotic symptoms • Thoughts cause anxiety	• Poor insight • Psychotic symptoms • Delusional beliefs or distorted reality present
↓	↓
Low risk	**High risk**

Screening and Monitoring

- Depression
  - Edinburgh Postnatal Depression Scale (EPDS)
    - 10 item self report
    - Validated in multiple languages
    - Focuses on cognitive symptoms
  - Patient Health Questionnaire (PHQ-9)
    - 9 items
    - More focused on physical symptoms
- Mania
  - Mood Disorder Questionnaire (MDQ)
    - Positive screen requires 7 of 13 positive symptoms
    - And impairment in function

Depression Screening

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

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use "✓" to indicate your answer)	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____
=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

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.

Preconception planning is essential

- Balance discussion regarding risks and benefits of medication treatment versus the risks and benefits of untreated illness
- There are NO risk free options
- Discuss pregnancy prevention as well
  - topiramate and oxcarbazepine lower efficacy of OCP

Preconception counseling and relapse prevention

- Evaluation of medication plan
- Birth plan
- Creating advanced directive
- Collaboration with family, OB, pediatrics
- Plan for breastfeeding
- Education regarding protection of sleep
- Plan for maternal-infant bonding
- **Close monitoring**

Preconception planning:
Same general principles apply

- Consider what has been proven to work in the past
- Use lowest **EFFECTIVE** dose
- Minimize switching
- Minimize polypharmacy
- May need to adjust does as pregnancy progresses and then at delivery
- Consideration of current trimester and fetal development
- Considerations regarding breastfeeding goals
- Folic Acid 4 mg daily

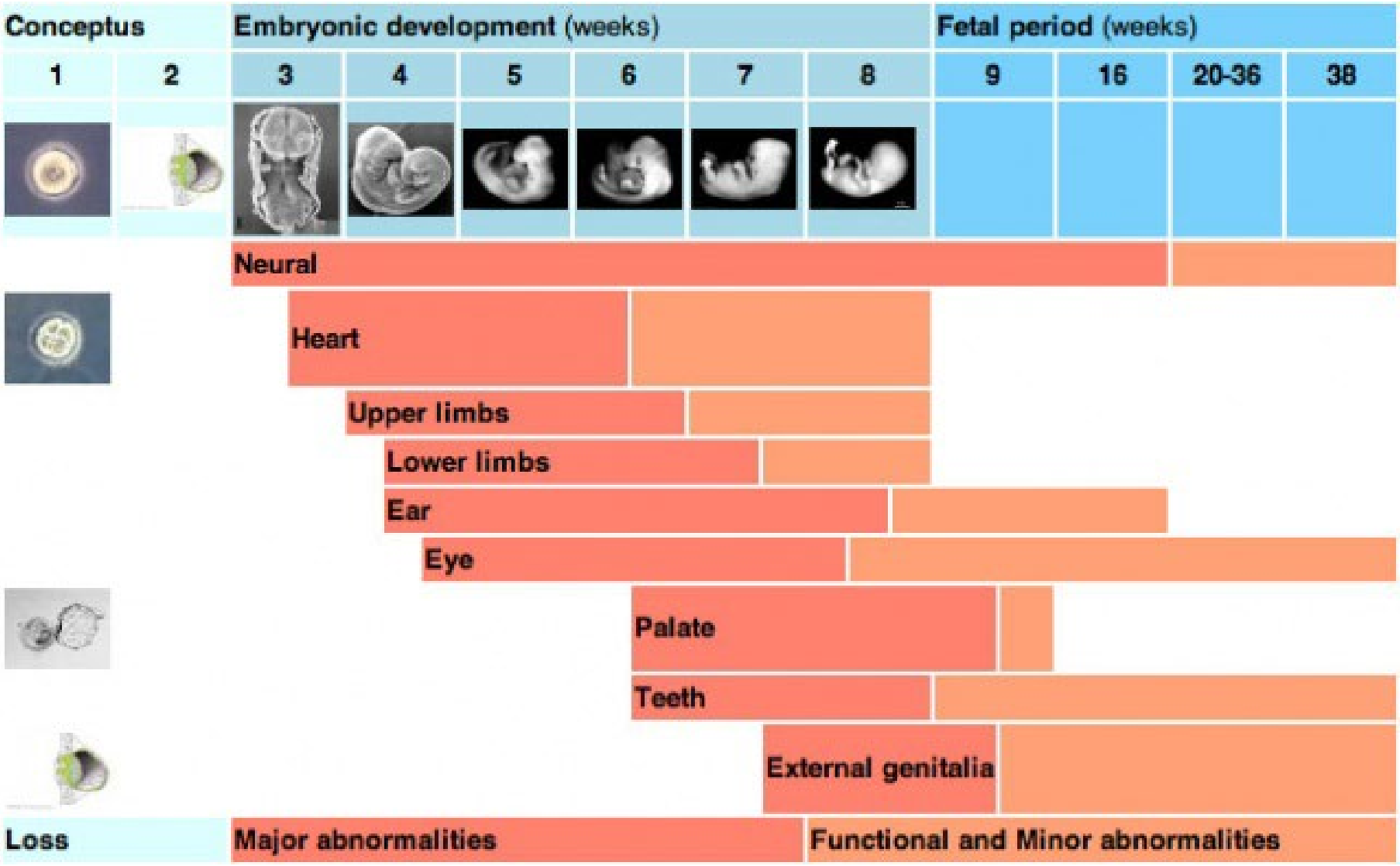
When considering medication alternatives:

- Risk of birth defects
- Impact on growth
- Impact on neurocognitive development
- Neonatal adaptation syndrome

Treatment

- When in pregnancy is the patient
  - 1st trimester—physical teratogenicity
  - 2nd & 3rd –behavioral, altered mental functioning. Altered pharmacokinetics
  - End—neonatal side effects, growth, timing of labor, withdrawal, breastfeeding plans
- Med management
  - What has worked in the past?
  - Monotherapy when possible
  - Minimize switching
  - Lowest EFFECTIVE dose
  - FDA categories are misleading and should not be used

McAllister-Williams et al J Psychopharm 2017


Conceptus
Embryonic development (weeks)
Fetal period (weeks)
1
2
3
4
5
6
7
8
9
16
20-36
38
Neural
Heart
Upper limbs
Lower limbs
Ear
Eye
Palate
Teeth
External genitalia
Loss
Major abnormalities
Functional and Minor abnormalities

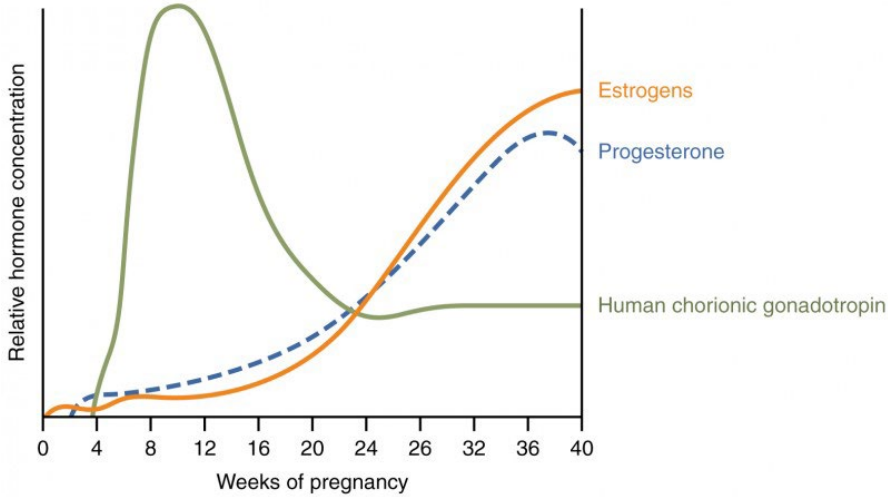
Lithium

- Weak CV teratogen (0.01-0.05%), nephrogenic DI (polyhydramnios)
- Transient hypothyroidism of neonate, neonatal hypotonicity, lethargy, prematurity, large for gestational age
- No known developmental/cognitive effects
- Dose adjustment maybe required (clearance increased by 30-50% in 3rd trimester and then drops post delivery)
- If breastfeeding, need to check infant levels, TSH, and renal function & coordinate with peds
- Level 2 US 16-18 weeks for neural tube defects, cardiac and facial malformations
- Avoid NSAIDS and nephrotoxins
- Check level when admitting for delivery and 24 hrs post partum

Deligiannidis et al. J Clin Psychopharm 2013

Lamotrigine

- GSK has registry
- Lower malformation rates, still need FA
- 1st trimester, increased risk of cleft lip & palate?
- Needs dose increase due to metabolism induction by estrogen & progesterone
- Consider obtaining pre-pregnancy level
- High transmission in breast milk



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

Deligiannidis et al. J Clin Psychopharm 2013

Haloperidol and Perphenazine

- Data since 1966, 1st used as antiemetic so data from non-mentally ill women
- No evidence of teratogenicity
- Small risk for transient EPS of neonate
- No evidence of long-term developmental effects

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

Atypical antipsychotics

- Quetiapine has lowest placental passage and lowest passage into breast milk. However, takes a long time to act
- Risperidone may be associated with cardiac malformation
- Risk of premature birth and low birth weight
- Increased risk of gestational diabetes and large for gestational age baby
- Aripiprazole may lower serum prolactin levels and thus impede lactation
- No data on long-term effects

AVOID

- Valproic Acid
  - Birth defects: spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, craniosynostosis
  - Neuro: average IQ 9 points lower, autism. Dose dependent
  - But ok in breastfeeding
- 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
  - Often used in pregnancy in epilepsy, but we have better options
  - But ok in breastfeeding
- The two together is synergistically worse

Marsh et al. Psych Annals 2012

Systemic Review of Neurodevelopmental outcomes of prenatal exposure to AED

Drug	Outcome
Valproic Acid Dose depended 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

Selection of mood stabilizer: during gestation

Typical Antipsychotics	Atypical Antipsychotics	Carbamazepine/ Oxcarbamazepine
Lamotrigine	Lithium	Valproic Acid

Selection of mood stabilizer: breastfeeding

Antidepressants	Carbamazepine	Lithium
Antipsychotics	Valproic Acid	
	Lamotrigine	

Suggested monitoring in infant during breastfeeding:

DRUG	INFANT MONITORING
Lithium	BUN, Cr, TSH, CBC
Lamotrigine	Level, liver enzymes, rash
Typical antipsychotics	CPK, stiffness
Atypical antipsychotics	Weight, blood sugar
Valproic Acid	Level, liver enzymes, platelets
Carbamazepine	Level, CBC, liver enzymes

http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

Summary:

- 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
- Screening for mood disorders is essential
- Consider the risks of untreated psychiatric illness when making treatment plan

REFRENCES:

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- Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Fetal growth restriction and birth defects with newer and older antiepileptic drugs during pregnancy. J Neurol. 2014 Mar;261(3):579-88.
- Alliance for Innovation of Maternal Health

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/**