



Mass General Brigham

Pharmacologic Considerations in Pregnancy

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MEDICAL SCHOOL

TEACHING AFFILIATE

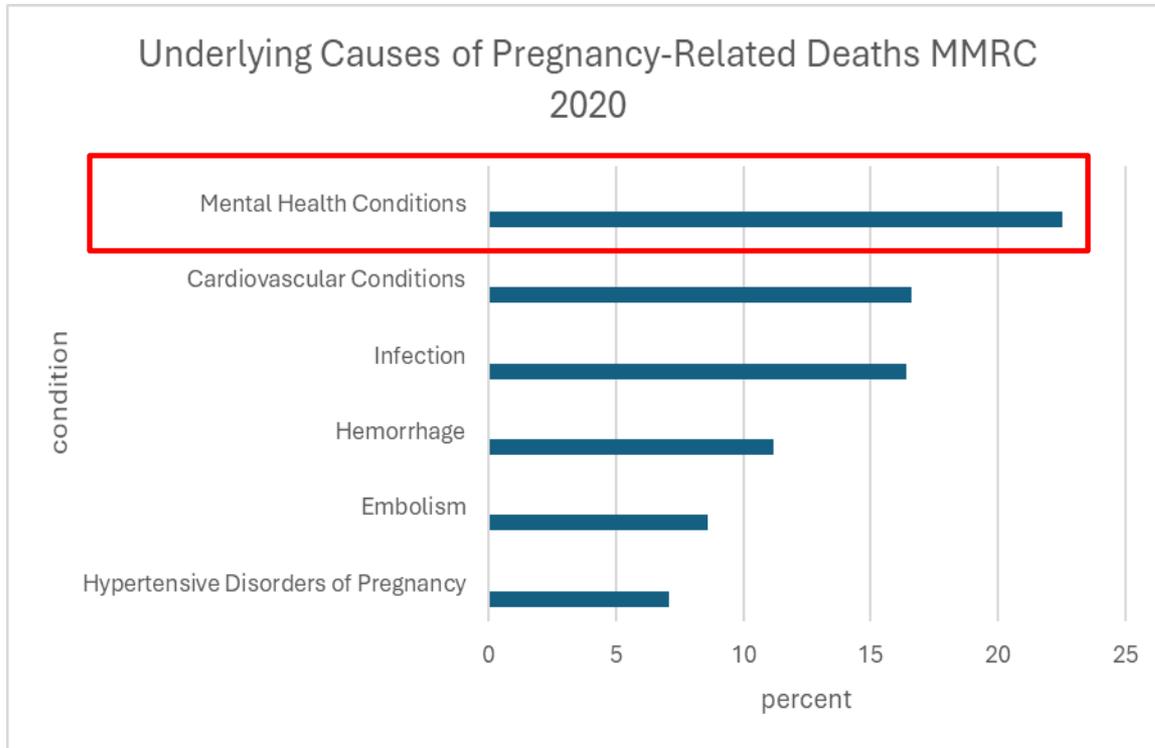
No financial Disclosures

All medication discussed when used in pregnancy are off label

Objectives

- Review bio-psycho-social consideration in pregnancy
- Review the principals of evaluation and management in perinatal psychiatry
- Risk assessment of psychopharm treatment in pregnancy
 - SSRI
 - Benzodiazepines
 - Mood stabilizers
 - Antipsychotics
 - neurosteroids

Mental health conditions are a leading cause of pregnancy-related deaths



Mental health conditions include deaths of suicide, overdose/poisoning related to substance use disorder, and other deaths determined by the MMRC to be related to a mental health condition, including substance use disorder.

Trost SL, Busacker A, Leonard M, et al. Pregnancy-Related Deaths: Data from Maternal Mortality Review Committees in 38 U.S. States, 2020. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; 2024 *U.S.*

Screening and treatment of perinatal mental health conditions is now recommended by



Major Depressive Disorder

- 17.3 million adults in the USA have had at least 1 episode of MDD, this represents 7.1% of the U.S. adults
- Prevalence of MDD is higher in adult females than males, 8.7% vs 5.3%

<https://www.nimh.nih.gov/health/statistics/major-depression>

Anxiety Disorders in Pregnancy

- Often comorbid with mood disorders
- OCD
 - 35% of women with peripartum depression have obsessive thoughts
 - 32% report OCD symptoms began perinatally
- Panic
 - High risk of relapse postpartum
 - May be related to lower levels of progesterone and allopregnone

Bipolar Affective Disorder

Lifelong illness affecting 2.6% of US population over 18 years old

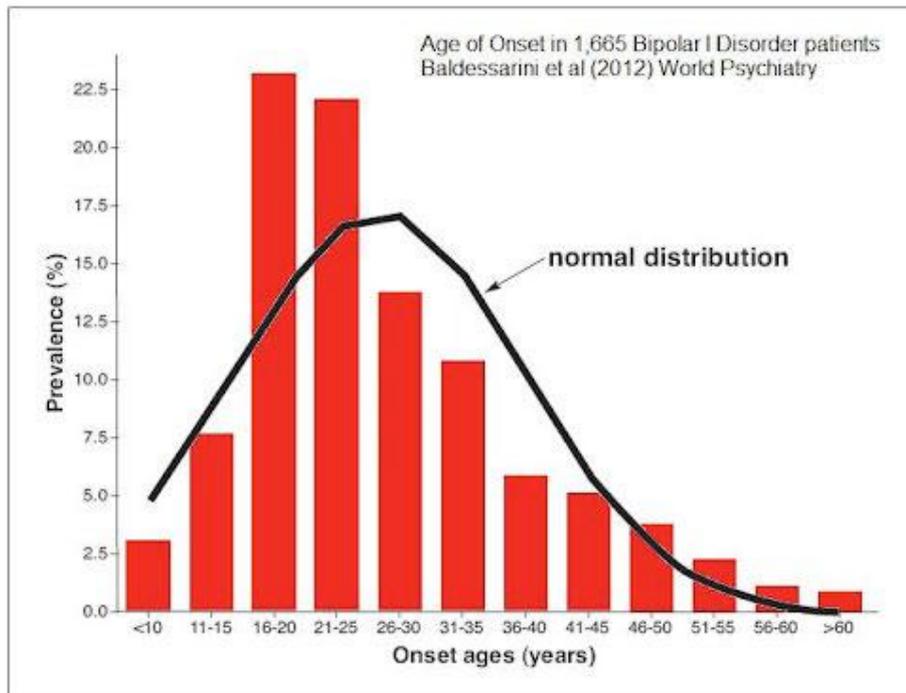
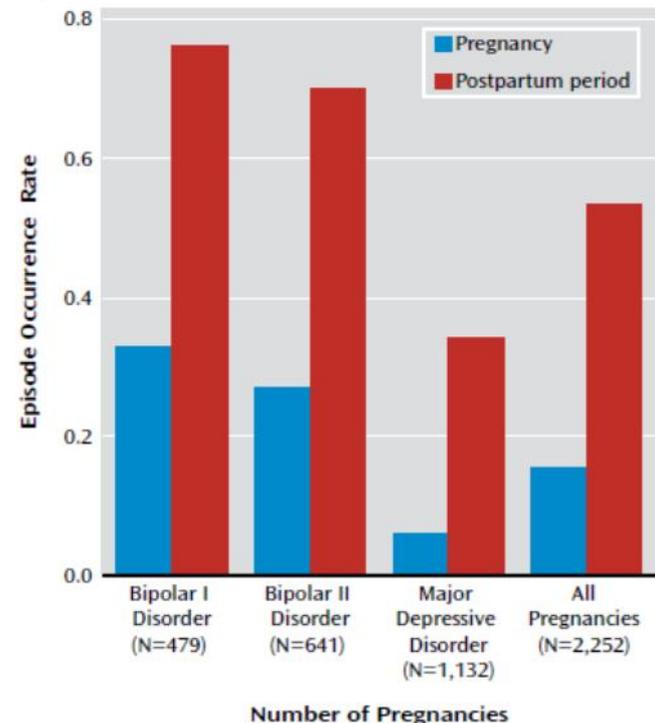


FIGURE 1. Episode Occurrence Rates of Major Affective Episodes During Pregnancy and During the Postpartum Period in 1,162 Women With Bipolar I, Bipolar II, or Major Depressive Disorder^a



WHO, NIMH

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

Bio--

- Pharmacokinetic/dynamic changes
 - Increased volume of distribution
 - Changes in protein binding, low albumin
 - Changes in renal clearance
 - Increased cardiac output
- Hormonal/Neuroendocrine changes
 - Estrogen is a mediator of serotonin
 - Elevated placental CRH leads to increased cortisol
 - Progesterone is a hepatic inducer

Fredericksen Seminars in Perinatology 2001; Freeman et al J Clin Psychopharm 2008
Kammerer et al. Arch Womens Ment Health 2006

Psycho--

- Major life/role transition. Focus shifts on parent-baby dyad
- New balancing act
- Risks affect both the patient and fetus and other children
- Adaptation to new body image
- Efficacy of parenting
- Attachment
- Physical limitations (bed rest)

Social--

- Changing relationship with partner
- Work changes
- Custody
- Finances

MDD and PPD

Diagnosis

- Same principals hold true as when not pregnant
- DSM diagnostic criteria
 - Peripartum—onset during pregnancy and up to 4 weeks post partum
- HISTORY HISTORY HISTORY
 - Assess what is impairing functioning versus normative
- Screening
 - EPDS, PHQ-9
 - Ask about sleep initiation, enjoyment of activities, anxiety

Diagnostic Impression

- Prior depression is the largest risk factor for peripartum depression
- Reproductive risk factors
 - Personal hx of PPD
 - Family hx of PPD
 - Hx of mood changes related to hormonal changes
- General risk factors
 - Younger age
 - Hx of trauma
 - Hx of sexual abuse
 - Psychosocial stressors
 - IPV
 - Chronic medical conditions
 - Race

Major Depressive Disorder

- Up to 13% of women have an episode during pregnancy, up to 22% in the first year post partum
 - Neurovegetative symptoms overlap with symptoms of pregnancy (poor sleep, appetite, energy, body aches)
 - May look more like anxiety/agitation versus sadness
 - Thoughts about harming baby are not uncommon, usually very low risk if ego-dystonic
- Post partum blues is more of an adjustment disorder, usually self limited.
 - Increased emotionality
 - Underlying mood is happy
 - Continue to be able to care for self and infant
 - About 50% of women
 - Peaks in first week

Risks of untreated MDD

- Reduced prenatal care, premature birth, reduced weight, small head circumference,
- Newborn: excessive crying, increased NICU admission, inconsolable
- Babies: poor growth, increased risk of infection, sleep difficulties
- Children: difficult temperament, autism, higher rates of depression, behavioral disturbance, lower IQ

Marcus et al. *Can J Clin Pharmacol* 2009; Li et al. *Hum Reprod* 2009; Henrichs et al. *Psychol Med* 2010; Zuckerman et al. *J Dev Behav Pediatr* 1990; Huot et al *Ann N Y Acad Sci* 2004; Muzik 2009; Bodnar et al. *Journal of Clin Psych* 2009; Cripe et al. *Pedi and Perinatal Epidemiology* 2011; Forman et al *Dev and Psych* 2007; Brennan et al *Dev Psychol* 2000; Hay et al *J Child Psychol Psychiatry* 2008

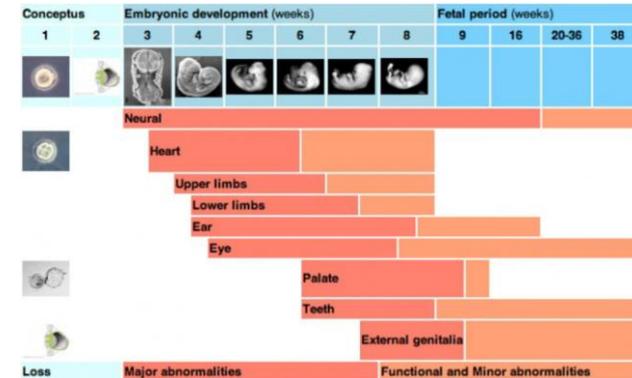
Risks of untreated MDD

- Epigenetics
 - Maternal cortisol can affect fetal HPA axis
 - Maternal depression is associated with increased methylation affecting glucocorticoid receptor gene expression
 - Studies on grandchildren of Holocaust survivors, pregnant women on 9/11
 - Elevated placental CRH leads to thinning of selective cortical regions & commensurate cognitive and emotional deficits in childhood

Glover et al. Psychoneuroendocrinology 2009; Oberlander et al Epigenetics 2008; Gunnar AJP 2018; Cowan et al Genes Brain & Behavior 2015; Yahuda et al Jour Clinical Endocrinology & Metabolism 2005

General Treatment Principles

- Clarify the diagnosis
- **There are no risk-free/exposure-free choices**
- Optimize non-pharm 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
- Med management
 - What has worked in the past?
 - Monotherapy when possible
 - Lowest **EFFECTIVE** dose
 - FDA categories are misleading



Difficulties in interpreting the literature

- Health habits confound associations
- Use of other meds is more common in pregnant women who use antidepressants
- No RCT, almost all studies are registry based
- Poor control for parental & genetic factors, especially in fathers

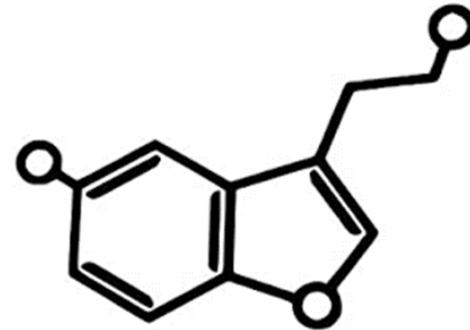
Non-Pharmacologic Intervention

- Early morning sun light exposure
- Light exercise
- Nutritious diet (Ω -3 fatty acids, FA, B-12, Fe, D)
- Adequate sleep
- Psychotherapy

Jeste et al Psychiatric Clinics of North America 2011

Risks of SSRI in Pregnancy

- NO major malformations consistently found
- No consensus on developmental issues, latest data says no concern
- May increase SAB
- Smaller size (in gm)
- Early labor (3-4 days)
- Preeclampsia
- Neonatal adaptation syndrome
 - Lasts 1-2 days
 - Respiratory distress, irritability, tremor, jitteriness, restlessness, changes in muscle tone, poor sleep, eating difficulties, Sz, prolonged QT
 - Affects about 30% of newborns
 - Taper does not appear to reduce risk



Moses-Kolko et al. *Jama* 2005; Huybrecht et al. *PLoS ONE* 2014; Byatt et al. *Acta Psych Scand* 2013

Pharmacologic Intervention

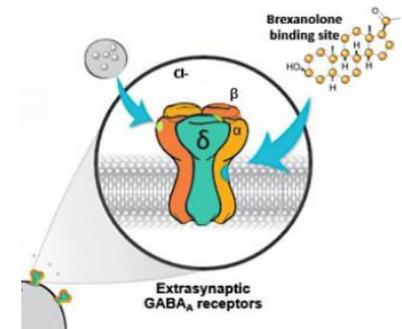
- Due to kinetic changes, many patients require dose increases at end of pregnancy (increased volume of distribution, increased filtration, increased estrogen/progesterone inducing enzymes)
- Postpartum considerations
 - Sedation to both infant and patient
 - Weight gain
 - Breastfeeding plans
 - Need for fetal monitoring

Wisner et al. AJP 1993; Hostetter et al. *Depress Anxiety* 2000; Feeman et al *J Clin Psychopharmacol* 2008; Yonkers et al. AJP 1992; Ross et al *JAMA Psychiatry* 2013

Novel treatment

– Brexanolone

- Allopregnanolone, a neurosteroid that acts at GABA_A receptors which are reduced in PPD
- In trials shows rapid reduction in depressive symptoms compared to placebo
- Indicated for moderate to severe PPD
- Requires 3 day IV infusion in monitored setting



– Zuranolone

- Oral pill to be taken for 2 weeks
- In RCT shows superiority to placebo at day 3
- Requires enrollment in Risk Evaluation and Mitigation Strategy (REMS)
- Requires rx to specialty pharmacy

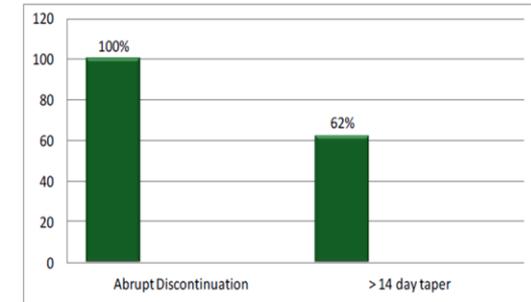
Anxiety Disorders in Pregnancy

- Benzodiazepines best avoided and SSRI used as 1st line treatment for management
- Slow taper if possible
- If can't discontinue benzo, recommend using lorazepam
 - Shorter half-life
 - Metabolized via glucuronidation
 - No active metabolites
- Risks
 - Dependence/withdrawal
 - Increased risk of SAB and premature delivery
 - Sedation at birth and respiratory difficulties
 - Floppy infant
 - Unknown implications for neurocognitive development
 - Possible cleft lip and palate

Shyken et al. Clinical OB & GYN 2019

Bipolar Affective Disorder

- In pregnancy most often due to discontinuation of medication
- Post partum period is highest risk of mood episode in woman's life

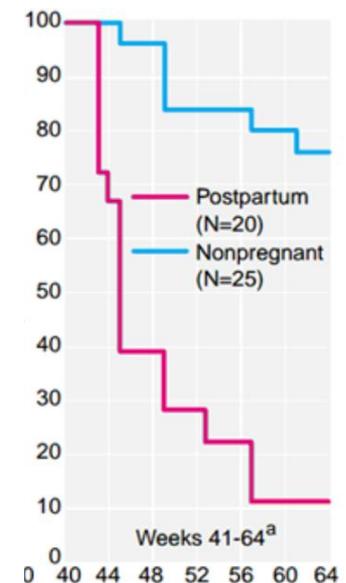


Yonkers et al. AJP 2004

- Post Partum Psychosis

- 1-2/1000 post partum women (about 75% have previous dx of BPAD or Schizoaffective DO)
- Rapid onset, within days usually before 4 weeks
- Irritable
- Paranoid, grandiose, bizarre delusions
- Disorganized
- Hallucinations
- Can appear like delirium
- EMERGENCY

Yonkers et al. AJP 2004; Harlow et al Arch Gen Psychiatry 2007



Viguera et al. AJP 2000

Treatment of BPAD

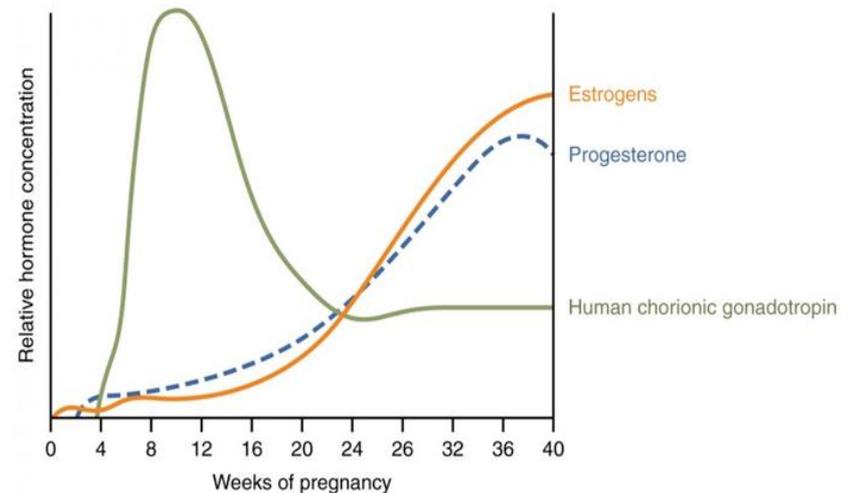
- PRECONCEPTION PLANING!!!
- Best if only expose to 1 agent
- Lowest **EFFECTIVE** dose
- Avoid switching
- **Folic Acid 4 mg daily pre-conception and throughout**
- **AVOID** valproate & carbamazepine in women of childbearing age
- Level 2 US 11-13 weeks for neural tube defects, cardiac and facial malformations
- **30-50% of pregnancies are unplanned**

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**

Treatment of BPAD—mood stabilizers

- Lamotrigine
 - GSK has registry
 - Lower malformation rates, still need FA
 - 1st trimester, possible increased risk of cleft lip & palate
 - May need dose increase due to metabolism induction by progesterone (just like with OCP)
 - Consider obtaining pre-pregnancy level, progestin potent inducer
 - High transmission in breast milk



Deligiannidis et al. J Clin Psychopharm 2013

Treatment of BPAD—mood stabilizers



- 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

Treatment of BPAD—antipsychotics

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

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

Treatment of BPAD—antipsychotics

- 2nd generation
 - 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
 - Aripiprazole may lower serum prolactin levels thus impeding initiation of lactation
 - Risk of premature birth and low birth weight
 - Increased risk of gestational diabetes

Huybrechts et al *Jama Psychiatry* 2016; Boden et al *Arch Gen Psychiatry* 2012; Tosato et al *J Clin Psychiatry* 2017; Galbally et al *ANZJOG* 2019

AVOID

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

Selection of mood stabilizer in gestation



Suggested monitoring of 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, offspring, 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

Helpful Resources

- MCPAP for Moms
 - <https://www.mcpapformoms.org/>
- LactMed—NIH
 - <https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>
- MGH—Center for Women’s Mental Health
 - <https://womensmentalhealth.org>
- Mother Risk--The Hospital for Sick Children, Toronto
 - <http://www.motherisk.org/>