Mood Disorders in the Perinatal Period

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Learning Objectives

Discuss	Review	Identify	Describe
Discuss prevalence, clinical presentation, screening and differential diagnosis	Review biopsychosocial risk factors	Identify risks of untreated depression in the perinatal period	Describe considerations of antidepressant use in pregnancy and lactation

Terminology

Sex – biologically based ⟷ Gender – culturally based (with or without biological influence)

Limitations

- Many studies assume a gender binary
- Few studies differentiate between sex and gender
- Data is very limited on transgender pregnant patients
- Neuroactive properties of hormones on perinatal brain in XX genotypes

Perinatal Depression

DSM 5 peripartum onset specifier= pregnancy up to 4 weeks postpartum

–Used as a specifier for mood disorders

–Defined as 4 weeks given hormonal flux

In clinical and research usage, “perinatal” means during pregnancy and for up to a year postpartum

–Studies show heightened risk of depression for at least the first year after delivery

–Became the preferred term instead of “postpartum depression” when data showed most postpartum depression starts during pregnancy

- HPI: 27 year old G3P1 woman with a history of major depressive disorder, currently 33 weeks pregnant, received an Edinburgh Postnatal Depression score of 22. Current symptoms include 6 weeks of worsening mood, irritability, low motivation, poor appetite, poor concentration, restless sleep pattern and increased fatigue. She feels “incapacitated” by everyday life and feels “dark, like living is painful.” She endorses feelings of worthlessness and passive death wish. She denies active suicidal ideation, intent or plan.
- PPH: She has no past suicide attempts or hospitalizations. Her history is significant for mild depressive episodes since adolescence, often occurring in the days prior to menses and during major life transitions such as her first year of college and the transition to parenthood with her first child. Her most severe depressive episode occurred after the birth of her daughter 3 years ago.
- FH: Family history is notable for bipolar disorder in her mother. Her maternal grandmother also required psychiatric admissions following the birth of two of her four children.
- **WHAT CLINICAL FEATURES STAND OUT REGARDING PERINATAL DEPRESSION?**

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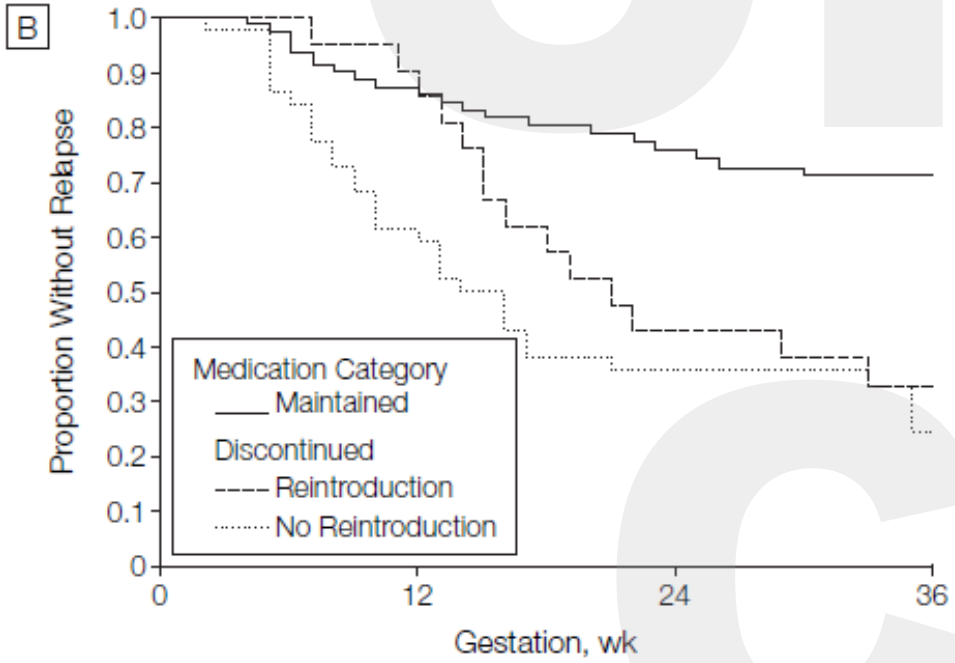
Pregnancy and the Postpartum are NOT Protective

Depression



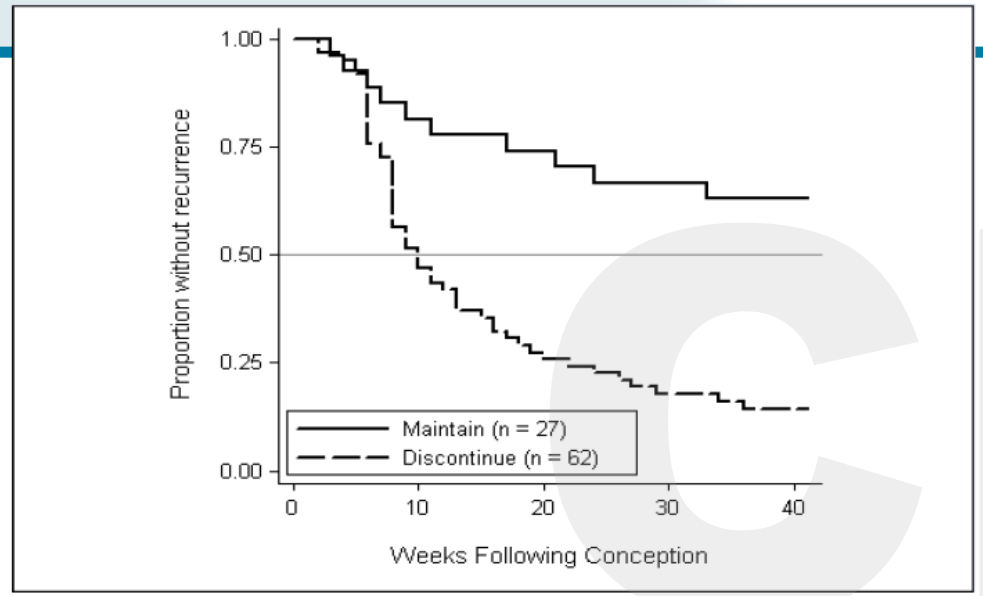
Cohen, et. al, *JAMA 2006*

Epidemiology and Course

- Common complication of childbirth, higher than gestational diabetes.
- 10-15% in developed countries
- Of those who develop, 30% still with symptoms after first year postpartum and 10% after second year.
- Risk for chronicity higher if depressive episode began before delivery, financial strain, history of prior depression.

Kroska and Stowe 2020; Torres et al 2019

Bipolar: Discontinuation of medication in pregnancy



Viguera et al. *Am J Psychiatry* 2007

www.mghcme.org

- 2 fold increased risk of relapse
- Greater after rapid discontinuation than gradual
- Shorter time to recurrence
- More symptomatic weeks
- Not greater than in periods outside of pregnancy BUT more depressive episodes in pregnancy v/ hypo/manic

Viguera 2007: Salm 2018

Bipolar Disorder Postpartum

- Consistent evidence of high rates of INITIAL and RECURRENCE
- Approx 15% with postpartum recurrence.
- Greater risk of psychiatric hospitalization than at any other point in their lives
- Increased SI
- Heightened risk for mania and psychosis

(Wesseloo 2016, Conejo Galindo 2022, Gilen 2021, Sharma 2017)

The diagnostic criteria for depressive disorders are unchanged during pregnancy and postpartum, but somatic symptoms may be confused with normal perinatal changes.

5 of 9 symptoms

2 weeks

Impairment

Not attributable to medical, substance or other psychiatric

Perinatal Focus:

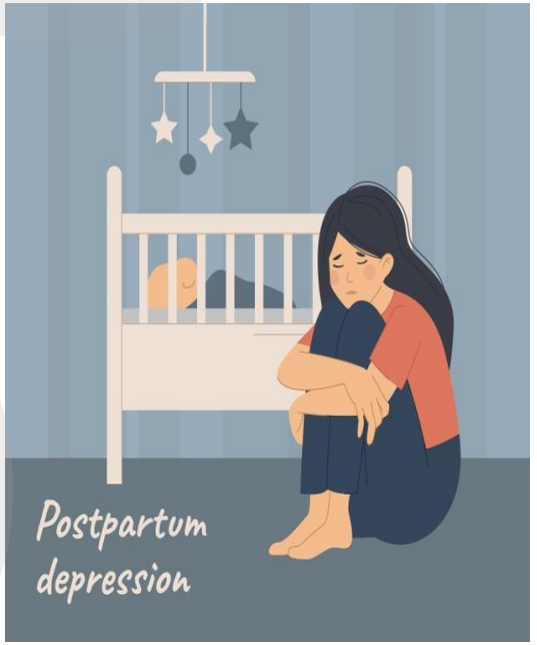
- Sleep changes:
  - Can’t sleep even when baby sleeps (or during pregnancy, when fetal movement, pain or need to urinate aren’t present)
- Anergia and concentration:
  - Fatigue and difficulty focusing even after good sleep
- Changes in appetite
  - More or less than expected weight change
- Guilt/Negative cognitions

Expecting negative judgment (e.g., “if baby is crying, people will think I can’t care for her”)

Intense maternal responsibility (e.g., “Good mothers ALWAYS put their baby’s needs first”)

Maternal role idealization (e.g., “It is wrong to have mixed feelings about my baby”)

- Interest
  - Level of attachment/interest/bonding with infant
- Hopelessness
  - Thoughts of harm to self or infant



Van Niel et al *2020*

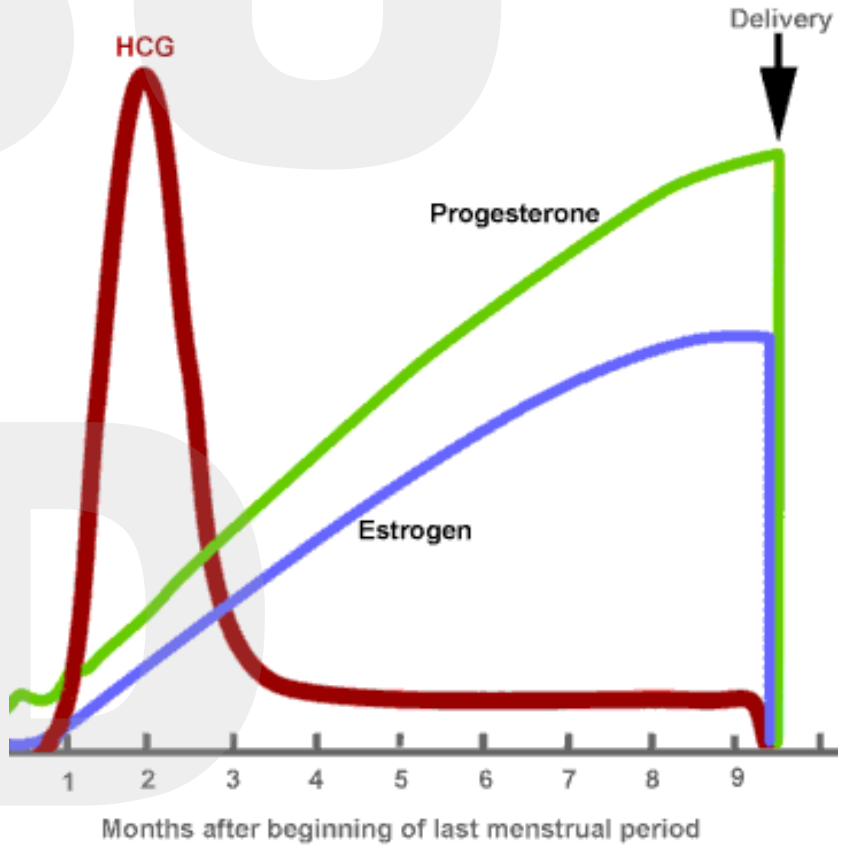
Risk Factors

- Depression during current pregnancy
- History of depression
- Postpartum blues
- Family history of mood disorder or perinatal mood changes
- Gestational diabetes
- Higher maternal age
- Hx PMS/PMDD
- Stressful life events
- Relationship strain/low social support
- Low SES
- Unplanned/unwanted pregnancy

Hutner, et al 2021; Kroska 2020

Etiology and Pathophysiology

- Multifactorial
  - Alterations in function of HPA axis (catecholamines, placental perfusion)
  - Changes in immune system and inflammation (changes with pro-inflammatory TH1, anti-inflammatory TH2)
  - Epigenetics
  - Sensitivity to hormonal shifts (ALLO and GABA receptor upregulation timing)
  - Physiologic stress of sleep deprivation, metabolic changes
  - Pain
  - 1/3 genetics unique compared to non perinatal mood



Hutner et al 2021

Estrogen

Enhances serotonergic function and potentiates norepinephrine

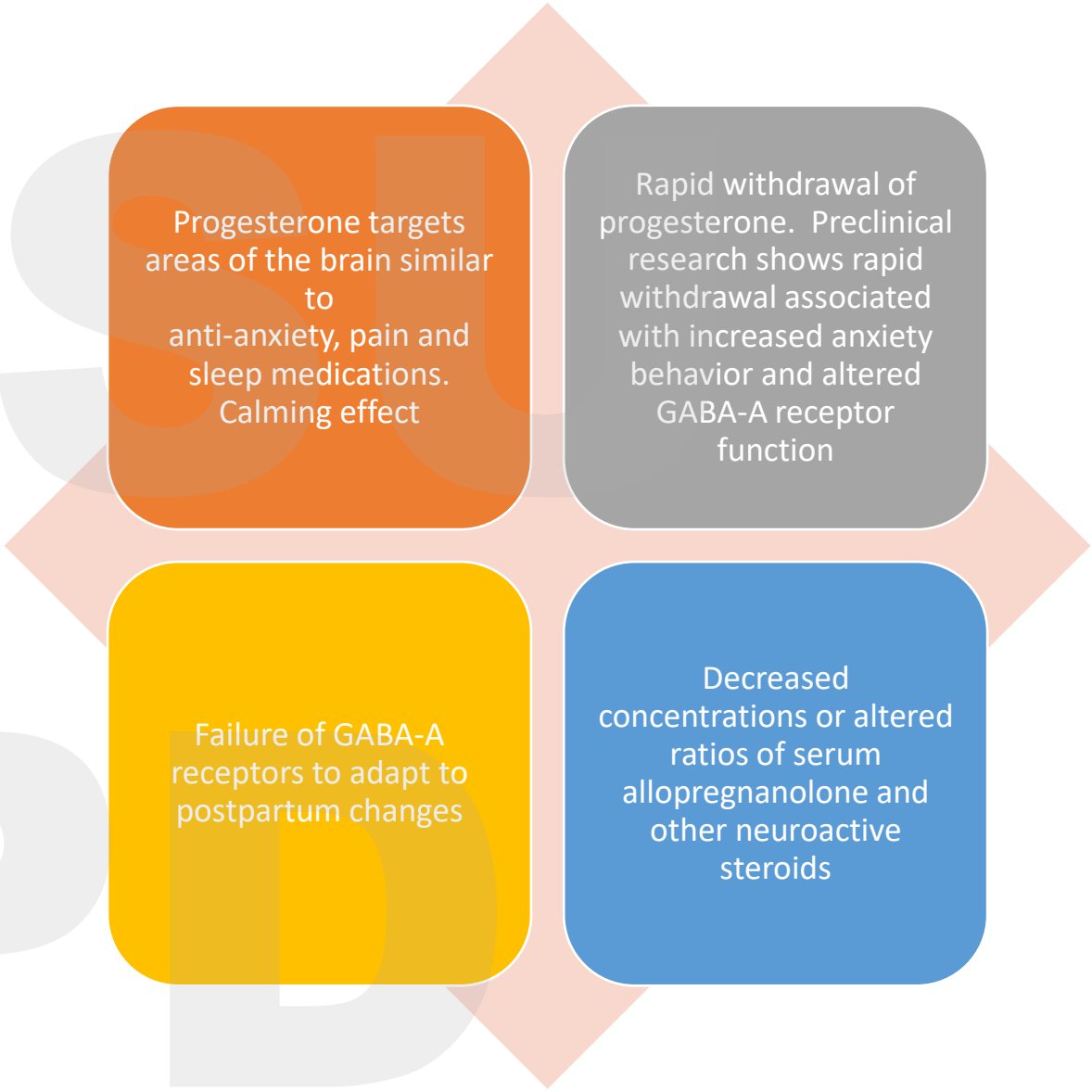
Alters expression of 5-HT2A receptor, serotonin transporter genes, vesicular monamine transporter

Increases serotonin transporter mRNA in brain areas involved with emotion and behavior (Low estrogen states associated with decreased serotonin transporter gene expression)

Decreases MAO-A and COMT expression

Hantsoo et al *2015*

Progesterone, Allopregnanolone



Hantsoo et al 2015

Kanes et al *2017*

Screening

Edinburgh Postnatal Depression Scale (EPDS)

- Reduces confounds from normal perinatal somatic change
- Also screens for anxiety
- Translated in many languages
- 9-12 at risk
- >12 high risk

Patient Health Questionnaire (PHQ-9)

- Readily available
- Validated during pregnancy and postpartum

NEED WORKFLOW FOR WHAT TO DO AFTER POSITIVE SCREEN!

Kroska 2020, Hutner 2021

Case #1

- 31 yo 6 days postpartum:

Uncharacteristically snapped at her partner when they mentioned calmly that the house was getting cluttered. Later that day started sobbing when heard a love song that would usually think of as kind of trite. Mood is overall very happy but changes quickly and intensely when set off by something.

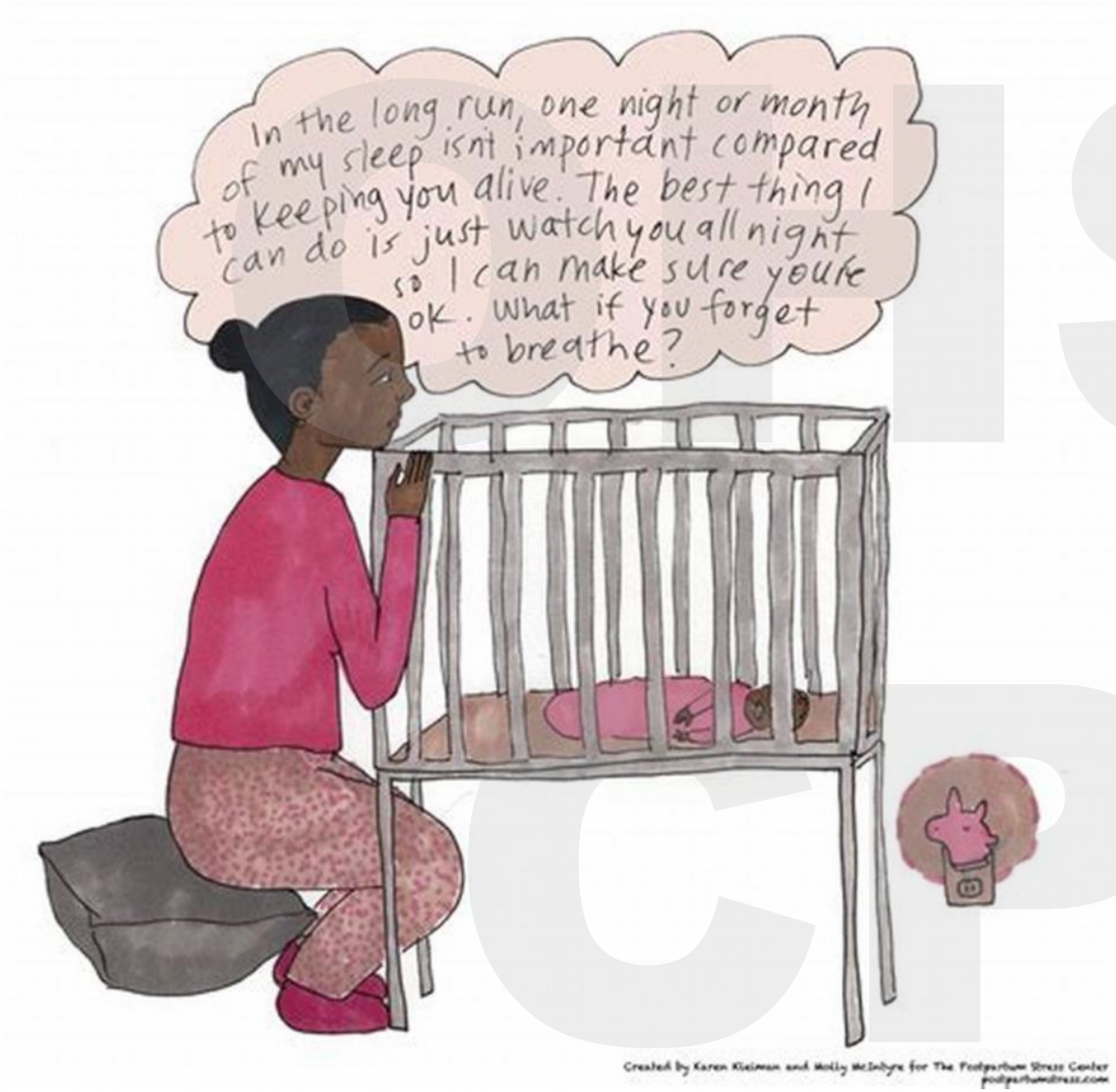
Postpartum Blues

- 40-80%
- Mood lability, irritability, crying, insomnia, difficulty concentrating, dysphoria, anxiety, also happiness!
- Begin postpartum day #3-5, resolve in 2 weeks
- Does not impair functioning
- Management: Support, education, guidance to seek care if sx's do not resolve

Tosto 2023

Case #2

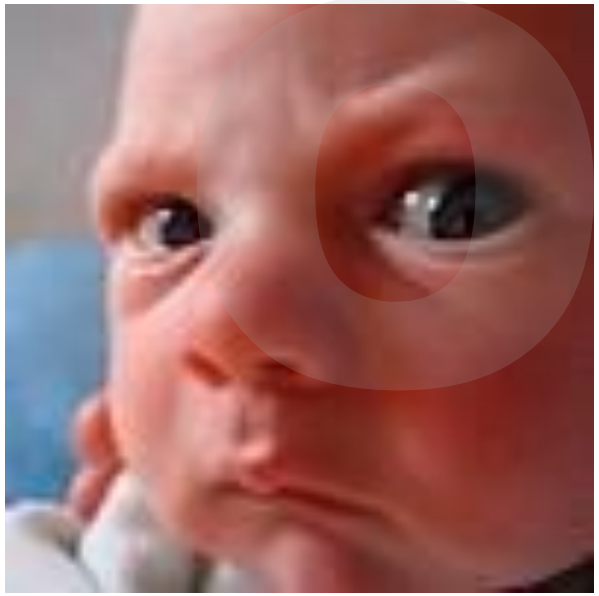
28 yo 6 days postpartum with intrusive ego-dystonic thoughts to harm baby and a strong need to clean for hours/day to keep the baby safe



Anxiety Spectrum Disorders

- Intrusive images are common in healthy controls as well as depression, OCD
- OCD and Panic have slightly higher rates, esp of new onset
- PTSD may develop from childbirth, NICU, infant loss
- Often content changes postpartum—more of a focus on the baby's health
- Important to differentiate intrusive thoughts of harming infant from HI

Hutner et al 2021



31 yo 6 days postpartum

Patient has not been sleeping and appears confused. Partner found them whispering while cleaning the house stating that they have to clean because the baby is possessed.

Case #3

Postpartum psychosis

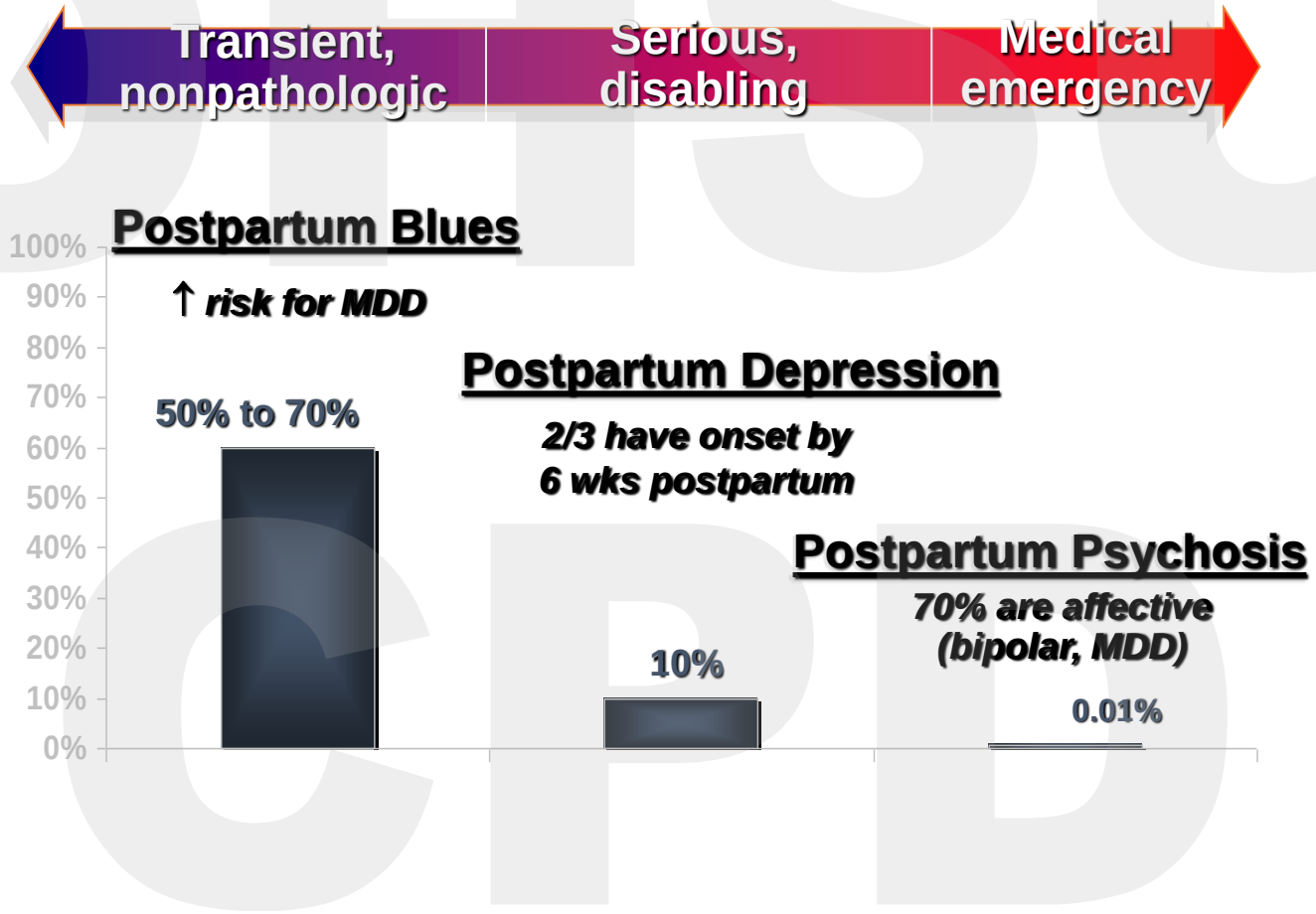
- 1-2/1000
- Severe, rapid onset within first two weeks
- Mood changes, delusions and hallucinations
- Delirium like presentation
- May be first presentation of bipolar
- Subset isolated postpartum episodes only with no mood disorder outside perinatal period
- HIGH RISK for infanticide or suicide
- EMERGENCY—hospitalize, mood stabilizers, ECT

Hatters Friedman 2023

Postpartum Obsessions vs Psychosis

Obsessions (OCD or Depression)	Psychosis (Psychotic Disorder)
Intrusive thoughts that cause distress (Ego dystonic)	Aggressive thoughts without guilt or distress (Ego syntonic)
Anxiety, hypervigilance	Confusion, agitation
Fear of acting on or thinking the thoughts	Hearing voices or seeing things that other people don't see
Avoidance or rituals	Bizarre or violent behavior
Personal or family history of Anxiety	Personal or Family history of Bipolar
No history of violence	History of violence, impulsivity
Rapid Onset of Symptoms	Rapid Onset of Symptoms
Peak incidence 2-4 weeks PP	Peak incidence first 3 weeks PP
May screen negative for depression	May screen negative for depression

Spectrum of Postpartum Mood Changes



Cohen LS. *Depress Anxiety.* 1998:1:18-26.

Differential

- Baby Blues
- MDD
- Bipolar
- Anxiety
- Postpartum Psychosis
- OCD
- SUD
- Medical—THYROID, ANEMIA

Review

Mood disorders have lower rates during pregnancy:

True

False

Review

<u>Mood disorders have lower rates during pregnancy:</u>

True

False

Mood disorders have similar rates during pregnancy. Bipolar mood episodes are much higher postpartum than outside the perinatal period.

Review

Which statement below is inaccurate?

A) Allopregnanolone impacts GABA receptors
B) Postpartum OCD is associated with higher rates of infanticide
C) History of premenstrual mood changes is a risk factor for postpartum depression
D) The PHQ-9 and EPDS have both been validated for use in the perinatal period

Review

Which statement below is inaccurate?

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B) Postpartum OCD is associated with higher rates of infanticide

C) History of premenstrual mood changes is a risk factor for postpartum depression

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Postpartum psychosis is associated with higher rates of infanticide

ACOG
The American College of Obstetricians and Gynecologists

CLINICAL PRACTICE GUIDELINE

NUMBER 5

JUNE 2023

REPLACES PRACTICE BULLETIN NUMBER 92, APRIL 2008

Treatment and Management of Mental Health Conditions During Pregnancy and Postpartum

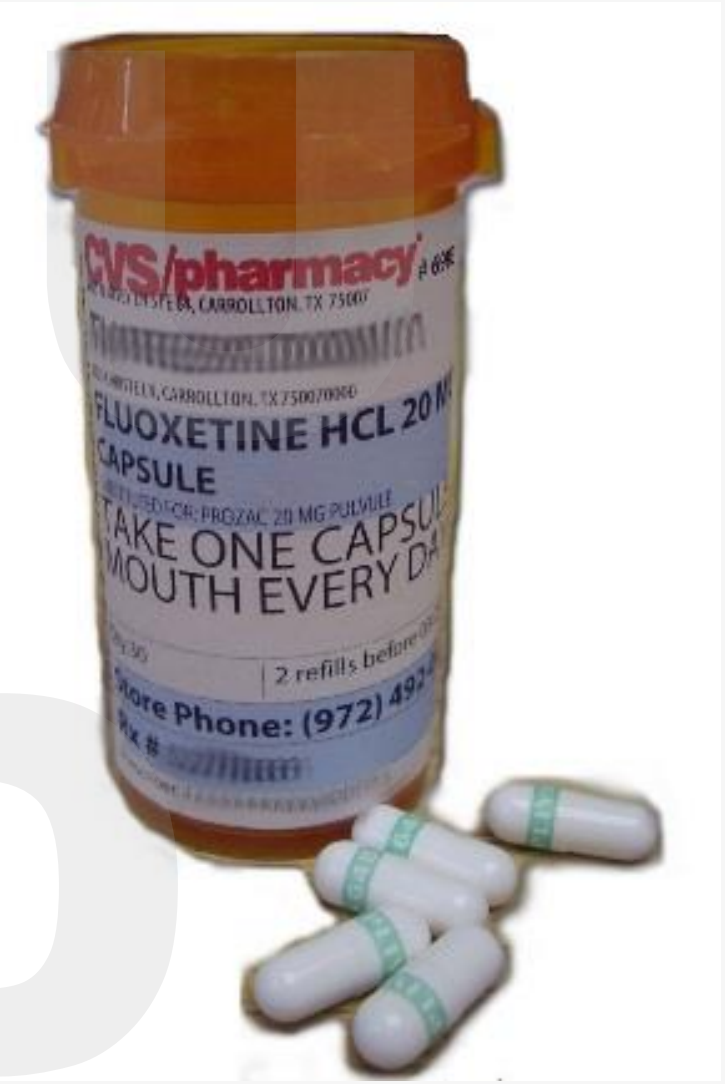
Committee on Clinical Practice Guidelines—Obstetrics. This Clinical Practice Guideline was developed by the ACOG Committee on Clinical Practice Guidelines–Obstetrics in collaboration with Emily S. Miller, MD, MPH; Torri Metz, MD, MS; Tiffany A. Moore Simas, MD, MPH, MEd; and M. Camille Hoffman, MD, MSc; with consultation from Nancy Byatt, DO, MS, MBA; and Kay Roussos-Ross, MD.

The Society for Maternal-Fetal Medicine endorses this document.

The Committee on Women's Mental Health of the American Psychiatric Association reviewed and provided feedback on this document.

Limitations of Studies

- Most studies are retrospective
- Many count prescriptions as medication exposures
- Many count diagnoses as symptom exposures rather than measuring symptom burden
- Studies vary in how well they rule out confounds
- What is control group?



Omission Bias

Clinicians and patients feel more responsible for causing harm if it results from something they do (e.g., prescribe/take a medication) than if it results from not doing anything (e.g., leave symptoms untreated)

Optimal care consists of understanding and explaining risks of symptoms and risks of medications with equal clarity

Valproate

- NTDs: 1-2% of fetuses= 10 to 20 fold increase over general population
- Other major congenital malformations: up to 10%
- Neurocognitive teratogen: IQ scores 6 to 9 points lower than children expose to lamotrigine, phenytoin, or carbamazepine. IQ scores related to maternal IQ scores in all exposure groups except valproate.

Obstetric Outcomes Bipolar Disorder

- Preterm birth
- C section
- Small for gestational age
- Gestational hypertension
- Hemorrhage
- One study showed pregnant individuals with BD who did not receive medication during pregnancy had infants with smaller head circumferences compared with both treated pregnant and healthy individuals even when controlling for confounders

Wisner 2019, Nagle-Yang 2021

ACOG Bipolar Disorder

- ACOG recommends against discontinuing mood stabilizers, except for valproate, during pregnancy due to the risk of recurrence or exacerbation of mood symptoms.
- Consider switch of carbamazepine or oxcarbazepine unless stable
- Otherwise if stable, continue current treatment
- Aim is remission of symptoms so use lowest EFFECTIVE dose
- If lacks decision making capacity seek ethics consultation, identify SDM if can't be restored to capacity

Implications of Undertreated Depression

Pregnancy

- Fewer prenatal visits
- Reduced diet quality impacting maternal nutritional requirements
- Substance use (e.g. tobacco 4x)
- <5% of depressed pregnant women meet physical activity guidelines

Obstetric/Neonatal

- Preeclampsia
- Preterm Labor and Birth
- Low Birth Weight

Postpartum

- Postpartum depression
- Relationship strain
- Impaired infant attachment (with long term developmental impacts)
- Suicide (leading preventable contributor to maternal mortality in US)

Hutner 2021; ACOG 2023

ACOG Depression

- Psychotherapy for mild to moderate
- SSRI first line
- SNRI reasonable alternative
- Choice individualized based on prior response to therapy
- If no prior history, sertraline or escitalopram first line.
- The dosage should be up-titrated with goal of remission of depression and anxiety symptoms

Psychosocial Treatment

Interpersonal therapy (IPT)	Cognitive Behavior therapy (CBT)	Exposure Therapies
Group (support groups) and Couples therapy	Mother-Infant therapies to facilitate bonding	Financial, community and family support
Family psychoeducation	Encourage self care and sleep preservation	Exercise, Nutrition, Hydration, Early Morning Sunlight

SSRI Risks

Reproductive Domain	Risk with SSRI treatment
Congenital Malformations	Early studies-cardiac; Recent—no or very low
Spontaneous Abortion	Equivocal, low OR and same for women who stop SSRI
Length of Pregnancy	Preterm Delivery (similar to untreated)
Size Effects	Small for Gestational Age (similar to untreated)
Short Term Risks	Neonatal Adaptation
Long Term Risks	Developmental Studies reassuring to date (autism showed no association when sibling analyses and paternal included)

Hutner 2021

Neonatal Adaptation Syndrome

- Respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying
- Up to 30% exposed
- Transient, self limited in most cases
- 0 – 48 hours after delivery
- No direct negative sequelae
- Not dose dependent, but polypharmacy can affect presentation
- ***No benefit*** from discontinuation in third trimester
- Baby is usually discharged with mom

Hutner 2021

Persistent Pulmonary Hypertension of the Newborn

Increased risk after exposure to serotonergic antidepressants near the end of pregnancy, when the lungs are maturing

Absolute risk is small– Unexposed 1-2 in 1,000 babies

Exposed 3-4 in 1,000 babies

Odds Ratio around 1.5

1,615 babies would need to be exposed to cause harm in one baby

No evidence that stopping in third trimester improves fetal outcomes

Ng et al 2018

ACOG 2023

Table 1. General Approach to Risk Counseling for Depression Psychopharmacotherapy

Risks of under-treatment or no treatment for depression during pregnancy include…	Risks of antidepressant use during pregnancy include…*
Limited engagement in medical care and self-care	PPHN
Substance use	Transient neonatal adaptation syndrome
Preterm birth	Preeclampsia (SNRIs)
Low birth weight	Spontaneous abortion (SNRIs)
Preeclampsia	
Postpartum depression	
Impaired infant attachment (which carries long-term developmental effects)	
Disrupted relationship with partner	
Suicide†	

PPHN, persistent pulmonary hypertension of the newborn; SNRI, serotonin-norepinephrine reuptake inhibitor.

*Data derived from literature that accounts for the underlying indication for antidepressant use.

†Suicide is a leading preventable contributor to maternal mortality in the United States, exceeding hemorrhage and hypertensive disorders.

Data from Trost SL, Beauregard J, Nijie F. Pregnancy-related deaths: data from maternal mortality review committees in 36 US states, 2017–2019. Centers for Disease Control and Prevention; 2022. Accessed December 7, 2022. https://www.cdc.gov/reproductivehealth/maternal-mortality/erase-mm/data-mmrc.html *and* Viswanathan M, Middleton JC, Stuebe A, Berkman N, Goulding AN, McLaurin-Jiang S, et al. Maternal, fetal, and child outcomes of mental health treatments in women: a systematic review of perinatal pharmacologic interventions. Comparative Effectiveness Review, No. 236. Agency for Healthcare Research and Quality; 2021. Accessed February 8, 2023. https://www.ncbi.nlm.nih.gov/books/NBK570101/

Novel PPD treatments

- **Allosteric modulators of GABA A receptors (ALLO hypothesis)**
- **Brexnanolone**—IV infusion over 60 hours, expensive
- **Zuranalone**--FDA-The first oral medication to be approved specifically for PPD in August 2023
- Works quickly; improvement seen as early as 3 days after starting it
- Only taken for 2 weeks
- Only studied on a relatively small number of people so far
- No long-term follow-up studies yet; not clear how long improvement lasts
- May cause drowsiness and decreased awareness or alertness

Deligianidis 2023

Management

- CONSIDER UNTREATED OR INADEQUATELY TREATED MH DISORDERS AN EXPOSURE
- Lowest effective dose
- Avoid polypharmacy
- Minimize switching
- Uptitration may be needed based on physiologic changes in pregnancy
- Downtitration in 3rd trimester is NOT associated with improved neonatal outcomes
- Continue for 6-12 months after remission and after postpartum

ACOG Lactation

- If stable on a medication during pregnancy, continue postpartum in most circumstances because fetal exposure supersedes exposure through lactation
- If initiate during lactation, consider Relative Infant Dose and personal history.
- RID influenced by: lipid solubility, half life, oral bioavailability, molecular weight, drug ionization, protein binding
- RID less than 10 considered compatible with breastfeeding
- Consider age of infant, preterm birth, active metabolites
- Sertraline best studied antidepressant

Review

Which statement is most accurate?

A) Most pregnant patients should change their antidepressant to sertraline given its stronger evidence base in pregnancy

B) Untreated depression has little impact on obstetric outcomes

C) Antidepressant choice should be individualized based on prior treatment response

D) Reducing antidepressant dose in the third trimester will lower risk for Persistent Pulmonary Hypertension of the Newborn and Neonatal Adaptation Syndrome

Review

Which statement is most accurate?

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C) Antidepressant choice should be individualized based on prior treatment response

D) Reducing antidepressant dose in the third trimester will lower risk for Persistent Pulmonary Hypertension of the Newborn and Neonatal Adaptation Syndrome

- Sertraline or escitalopram are considered first line if no prior treatment history
- Consider untreated MH conditions an exposure
- Downtitration in 3rd trimester is NOT associated with improved neonatal outcomes

Resources

Clinician Focused:

- National Library of Medicine Drugs and Lactation Database (LactMed)
- Reprotox—summarizes literature on medications in pregnancy
- Hale's Medications and Mother's Milk
- Postpartum Support International: Free consult line is available to medical professionals with mental health care questions for pregnant or postpartum patients and preconception planning

Patient Focused:

- National Maternal Mental Health Hotline 1-833-943-5746
- Postpartum Support International Help Line 1-800-944-4773
- Mother to Baby Program, Organization of Teratology Information Specialists (OTIS)—Patient focused fact sheets on specific medications
- MGH Center for Women's Mental Health: Blog and topic reviews

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