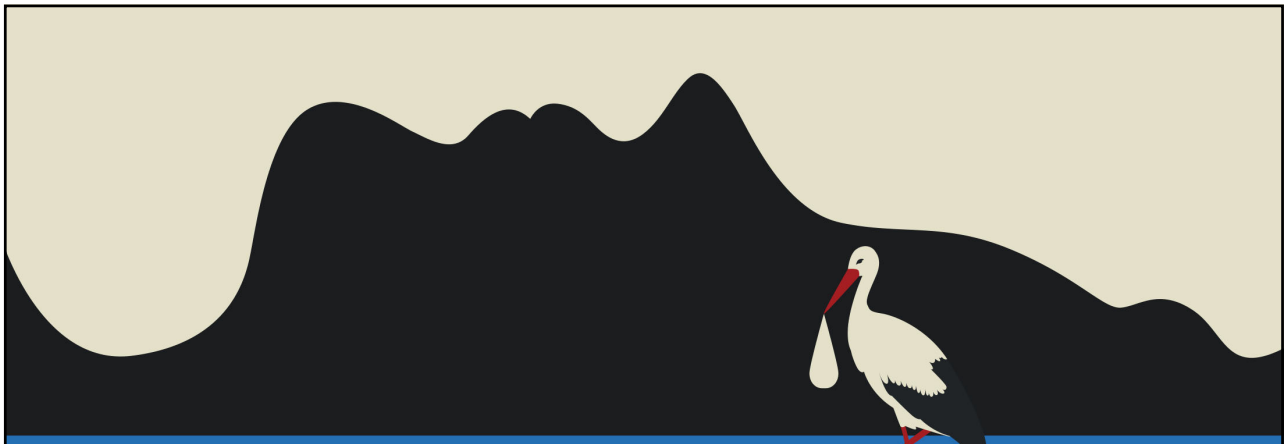


NEUROBIOLOGICAL MECHANISMS IN POSTPARTUM DEPRESSION

Implications for Current and Future Treatments

Jointly provided by Partners for Advancing Clinical Education (PACE) and Miller Medical Communications, LLC.

This activity is supported by an independent educational grant from Sage Therapeutics, Inc.

This educational activity is jointly provided by Partners for Advancing Clinical Education (PACE) and Miller Medical Communications, LLC.

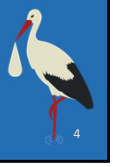
This activity is supported by an independent educational grant from Sage Therapeutics, Inc.

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Disclosures

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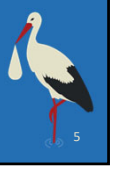
- Consultant, Advisor, Speaker: Seven Starling, SixSense Strategy Group

Tiffany A. Moore Simas, MD, MPH, MEd

- Consultant, Advisor, Speaker: ACOG, AIM, Beacon Health Options, MA Dept of Mental Health, MCPAP for Moms
- Employee: UMass Memorial Health, UMass Chan Medical School
- Executive Role: SASGOG
- Researcher: ACOG, CDC, NIH, PCORI, Perigee Fund

Lauren M. Osborne, MD

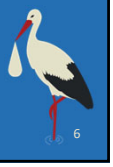
- Has nothing to disclose



Educational objectives

Upon completion of this activity, participants should be able to:

- Recognize the short- and long-term consequences of undiagnosed and untreated PPD
- Describe key pathophysiological mechanisms implicated in PPD
- Describe the safety and efficacy of existing and emerging therapies for PPD
- Initiate treatment of women with suspected PPD and follow up appropriately to ensure continuity of care



PPD, postpartum depression



Epidemiology and Impact of Delayed Diagnosis and Treatment

Perinatal mental health conditions are one of the most common complications of pregnancy and postpartum

1 in 5



Women around the world will suffer from a mental health complication

World Maternal Mental Health Day – 3 May 2023. Accessed July 13, 2023. https://wmmhday.postpartum.net/

Perinatal depression affects 1 in 7 individuals, with rates higher in various populations

1 in 7



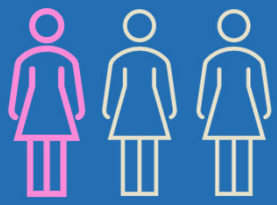
experience postpartum depression

Perinatal depression affects 1 in 7 individuals, with rates higher in various populations

1 in 7

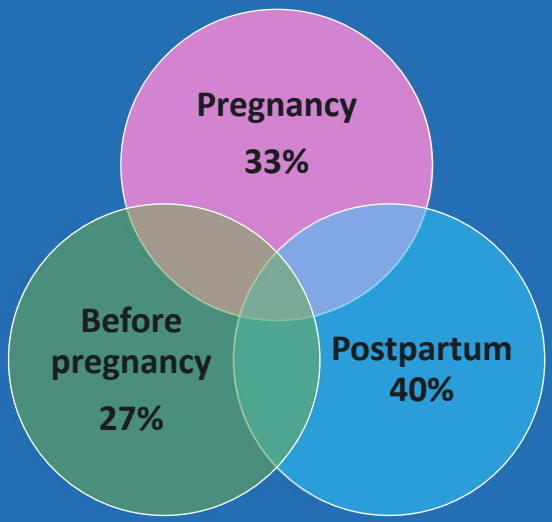


experience postpartum depression



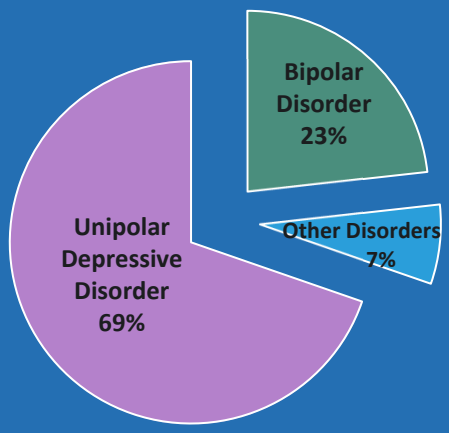
- Adolescents
- Veterans
- Persons marginalized by racism & socioeconomically disadvantaged

Two-thirds of perinatal depression begins before delivery



Wisner KL, et al. *JAMA Psychiatry*. 2013;70(5):490-498

Bipolar disorder needs to be considered with a positive depression screen especially prior to initiating pharmacotherapy



- Prescribing unopposed antidepressant can precipitate mania and increase risk of other negative outcomes

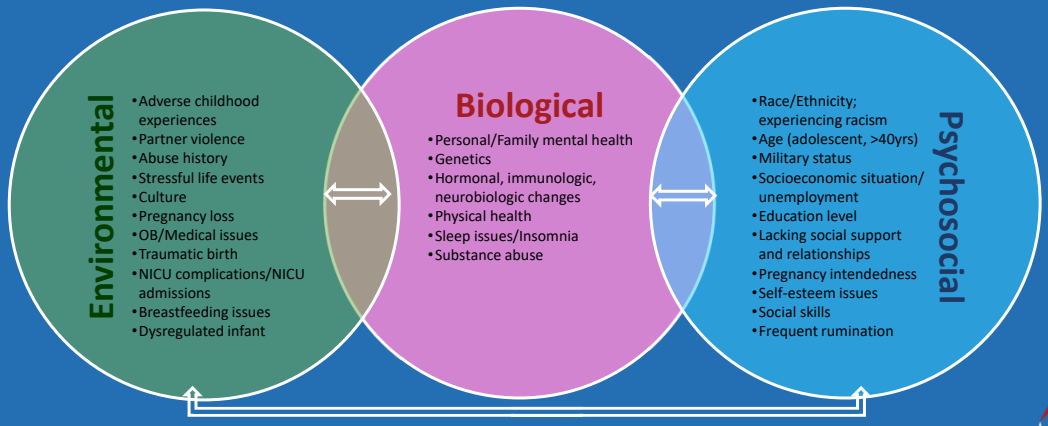
Wisner KL, et al. *JAMA Psychiatry*. 2013;70(5):490-498

Baby blues vs perinatal depression

	Baby Blues	Depression
What?	Common and temporary experience after childbirth; dysphoric mood, mood lability, anxiety, irritability	DSM5 criteria for depression; SIGECAPS ≥ 2 wks
When?	Peak @ 3-5d pp; resolves 10-12d pp; lasts hrs to wks	In pregnancy or 1st yr pp; most common 3 mos pp; onset may be gradual; lasts ≥ 2 wks to yrs
Who?	85%	15%+
Tx?	Self-resolving; support, sleep hygiene	Psychotherapy, pharmacotherapy, adjunctive interventions

DSM5, *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition; SIGECAPS, sleep, interest, guilt, energy, concentration, appetite, psychomotor, suicide; pp, postpartum; d, days; hrs, hours; wks, weeks, mos; months; yrs, years; Tx, treatment
Massachusetts Child Psychiatry Access Program For Moms. Obstetric provider toolkit. 2014. Accessed May 11, 2023. https://www.mcpapformoms.org/Toolkits/Toolkit.aspx

Risk factors

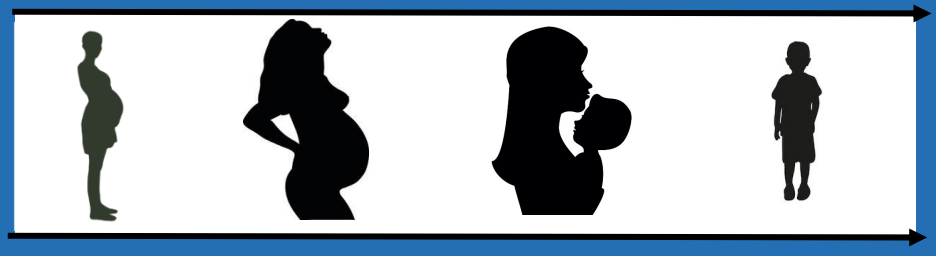


NICU, neonatal intensive care unit
Adapted from Moore Simas TA, Hoffman MC, Miller ES, Metz T. *Obstet Gynecol*. 2023;141(6):1232-1261

Perinatal depression affects mom, child, and family

Preterm delivery
Low birth weight
NICU admissions

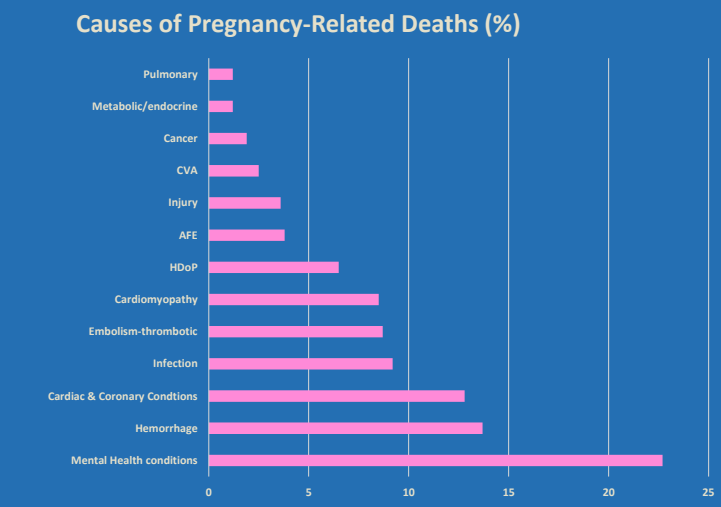
Cognitive delays
Motor & growth issues
Behavioral problems
Mental health disorders



Less engagement in medical care
Smoking and substance use

Lactation challenges
Bonding issues
Adverse partner relationships

Mental health conditions are the lead cause of pregnancy-related deaths (22.7%)



Centers for Disease Control and Prevention, US Department of Health and Human Services

Pregnancy-related deaths: data from Maternal Mortality Review Committees in 36 US States, 2017-2019

Trost S, Beauregard J, Chandra G, et al

2022

CVA, cerebrovascular accident; AFE, amniotic fluid embolism; HDoP, hypertensive disorders of pregnancy

Trost SL, Beauregard J, Njie F, et al. Pregnancy-Related Deaths: Data from Maternal Mortality Review Committees in 36 US States, 2017–2019. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2022. Accessed May 11, 2023. https://www.cdc.gov/reproductivehealth/maternal-mortality/docs/pdf/pregnancy-related-deaths-data-mmrcs-2017-2019-h.pdf

Pregnancy-related mental health deaths

Health Affairs (Millwood)

Preventing pregnancy-related mental health deaths: insights from 14 US Maternal Mortality Review Committees, 2008-17

Trost SL, Beauregard JL, Smoots AN, et al

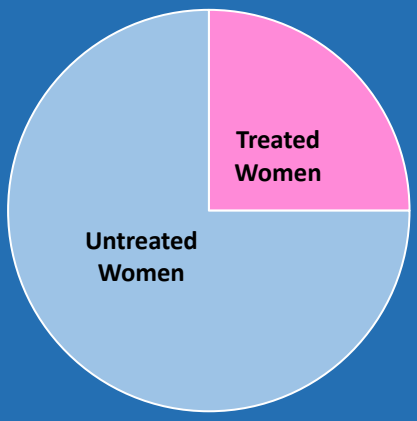
2021;40(10):1551-1559

100%

of pregnancy-related mental health deaths were determined to be preventable

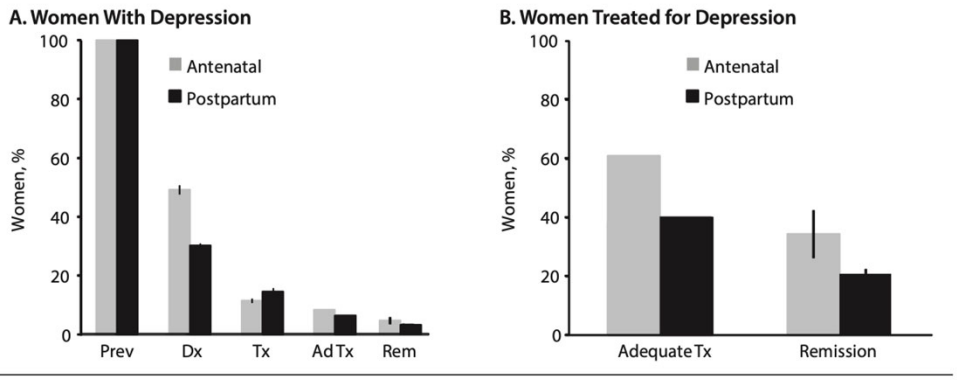
Trost SL, et al. *Health Aff (Millwood)*. 2021;40(10):1551-1559

Perinatal depression is under-detected and under-treated



Byatt N, et al. *Obstet Gynecol*. 2015;126(5):1048-1058

Percentage of US women at each step of the perinatal depression treatment cascade



Abbreviations: Ad Tx = adequate trial of treatment, Dx = diagnosis, Prev = prevalence, Rem = remission, Tx = treatment

Cox EQ, Sowa NA, Meltzer-Brody SE, Gaynes BN, The perinatal depression treatment cascade: baby steps toward improving outcomes, *The Journal of Clinical Psychiatry*. 77, 1189-1200, 2016. Copyright 2016, Physicians Postgraduate Press. Reprinted by permission.

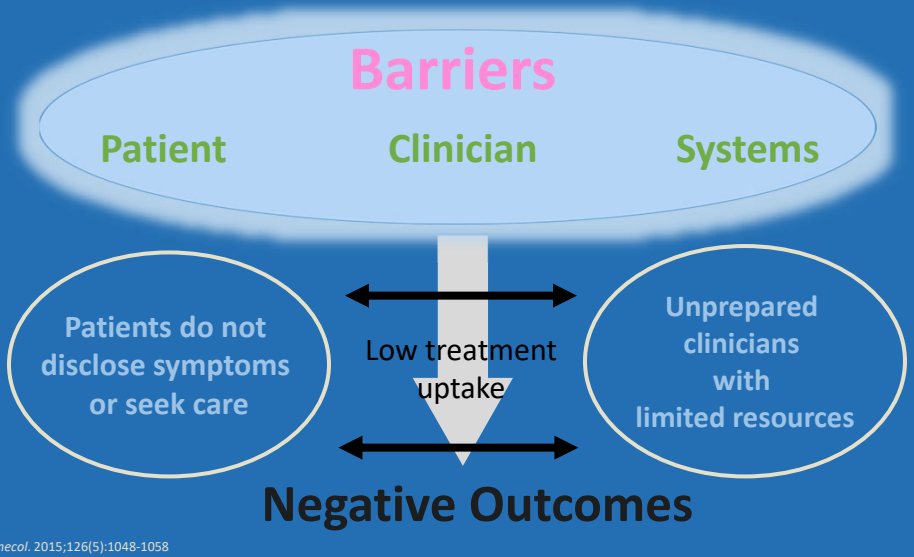
Many obstetric care clinicians historically have been inadequately prepared to address PND

- Not part of professional identity
  - Lack of guidance
  - Lack of training
- Lack of processes
- Lack of resources and referrals



PND, postnatal depression

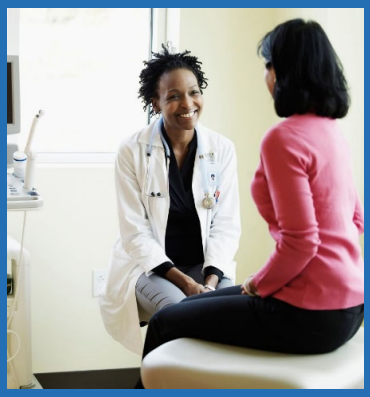
Multi-level barriers to perinatal depression exist



Byatt N, et al. *Obstet Gynecol.* 2015;126(5):1048-1058

Perinatal period is ideal for the detection and treatment of depression

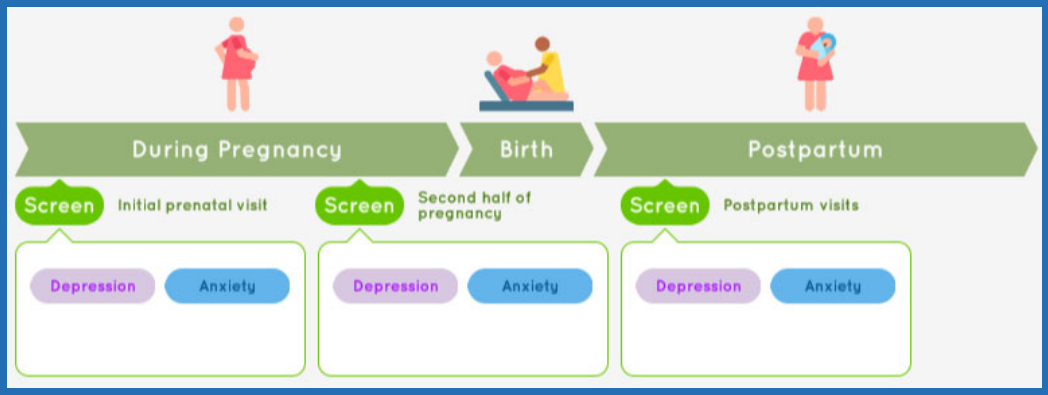
- Regular opportunities to screen and engage women in treatment
- Perinatal care professionals have a pivotal role
  - Increased patient acceptability
  - Decrease stigma
- Most mental health conditions are treated by primary care professionals
  - 80% PCP vs 20% Psych



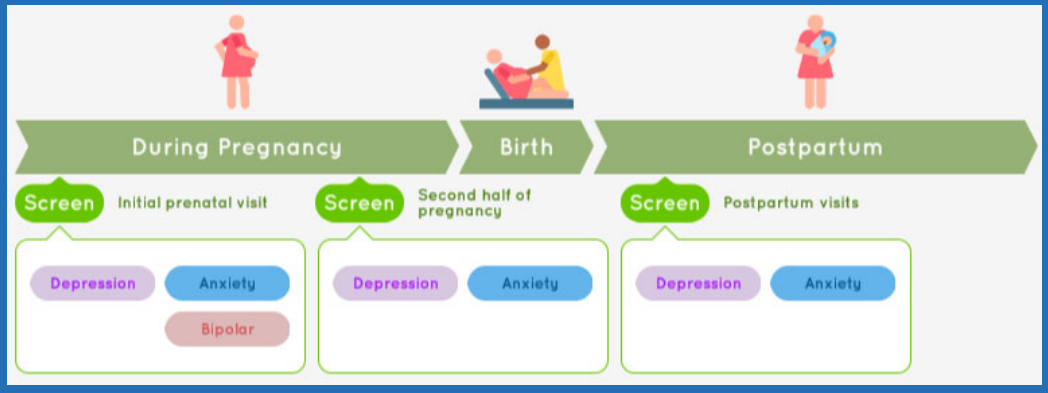
PCP, primary care physician; Psych, psychiatrist

Professional societies and policy makers recommend screening

When to screen



When to screen



Mental health care pathway

- Understanding the mental health care pathway is critical to integrating obstetric and mental health care and thus addressing PMH conditions



PMH, past medical history

Resources

- There now exists a suite of resources to help integrate obstetric and mental health care

AIM ALLIANCE FOR INNOVATION ON MATERNAL HEALTH

Institute for Healthcare Improvement

ACOG The American College of Obstetricians and Gynecologists

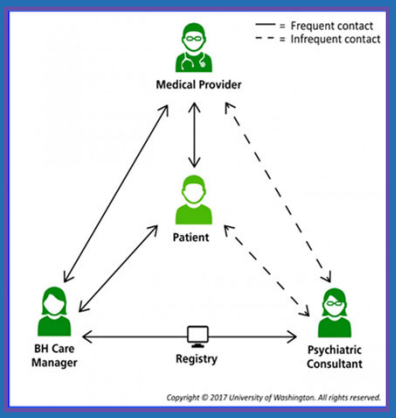
University of Massachusetts Medical School UMASS

Lifeline for moms

Toolkit eModule Guide Access Programs

Collaborative care

- A systems-level approach to addressing perinatal depression that has been associated with improved treatment access and outcomes



Principles of Collaborative Care*

- Patient-Centered Team Care
- Population-Based Care
- Measurement-Based Treatment to Target
- Evidence-Based Care
- Accountable Care

*Provision of psychiatric services in primary care/obstetric settings
BH, behavioral health
YouTube: The Collaborative Care Model. Accessed May 11, 2023. https://www.youtube.com/watch?v=zXZTgq3GyPw
© University of Washington. Used with Permission from the University of Washington AIMS Center, 6/26/2023

Benefits of collaborative care model

1. **Established Evidence Base**
   CoCM has a robust evidence base of over 80 randomized controlled trials and has been shown to be the best approach to treating depression in many populations and settings.

2. **Better Medical Outcomes**
   CoCM is linked to better medical outcomes for patients with diabetes, cardiovascular disease, cancer, and chronic arthritis.

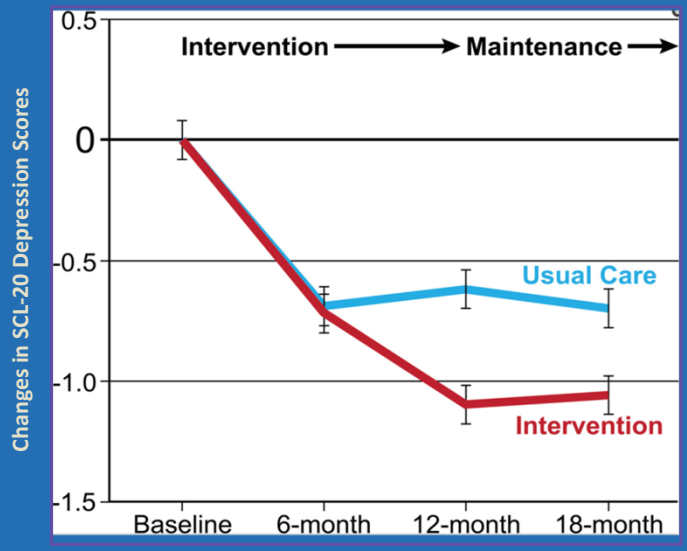
3. **Help with Challenging Patient Cases**
   Many challenging cases likely have patients with untreated or undertreated behavioral health conditions. Behavioral health providers do the follow-up and intervention tasks that a busy PCP doesn't have time to do, but make a big difference for patients.

4. **Faster Improvement**
   A 2016 retrospective study at Mayo Clinic found that the time to depression remission was 86 days in a CoCM program while in usual care it was 614 days.

5. **It Takes a Team**
   CoCM uses an enhanced care team to provide a population based, treat-to-target approach to care. Through shared care planning, the team makes proactive changes in treatment to make sure that no patients fall through the cracks.

CoCM, collaborative care model
© University of Washington. Used with Permission from the University of Washington AIMS Center, 6/26/2023

Improving care for depression in obstetrics and gynecology



SCL-20, Symptom Checklist (20 items)
Melville JL, Reed SD, Russo J, et al. Improving care for depression in obstetrics and gynecology: a randomized controlled trial. *Obstetrics & Gynecology*, 123, 6, 1237-1246, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4052378/. *Obstetrics & Gynecology* is the official publication of The American College of Obstetricians and Gynecologists.

Psychiatry access programs support obstetric practices providing perinatal mental health care

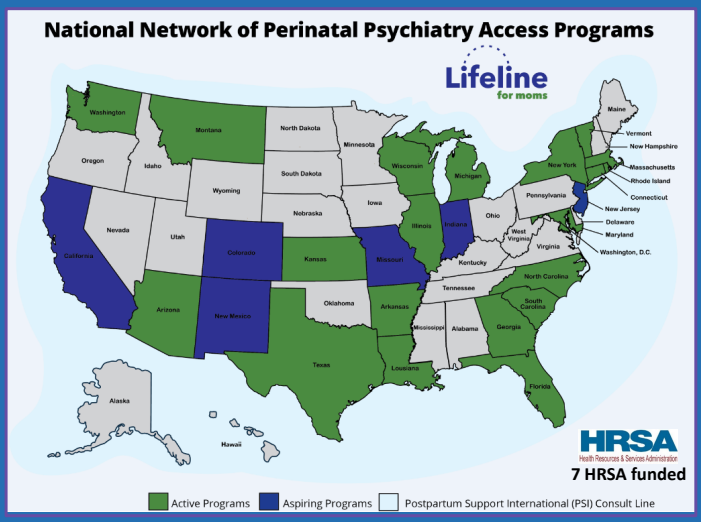


Clinician-facing Warm Line (M-F, business hours)

M-F, Monday through Friday

Perinatal psychiatry access programs

- Programs exist throughout the country as state or health care-based entities, including 2 national consult lines (PSI, VA)



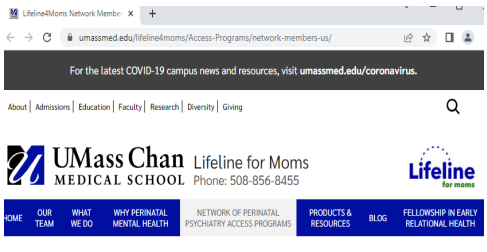
PSI, Postpartum Support International; VA, Veterans Affairs

Resources

UMASS MEDICAL SCHOOL

Lifeline for moms

www.Lifeline4Moms.org Phone: 508-856-8455



https://www.umassmed.edu/lifeline4moms/Access-Programs/network-members-us/

National Maternal Mental Health Hotline

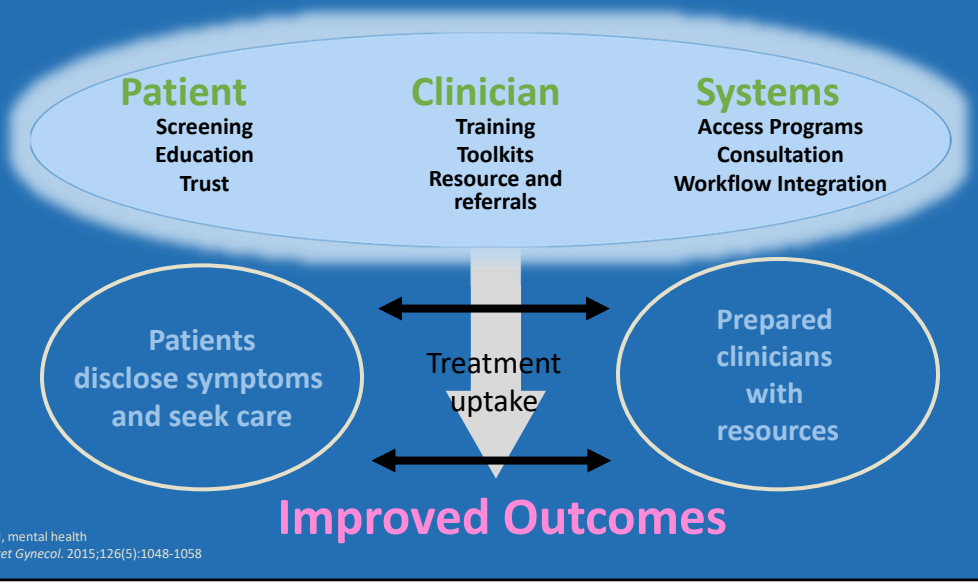
1-833-9-HELP4MOMS
(1-833-943-5746)

National Maternal Mental Health Hotline
HRSA Health Resources & Services Administration

PSI

Patient-facing Hot-Line (24/7)

With new resources and education that integrate OB and MH, we can better address the needs of our patients



OB, obstetrics; MH, mental health
Byatt N, et al. *Obstet Gynecol.* 2015;126(5):1048-1058

Integrating mental health care into our practices

- Integrating mental health care into our practices, and addressing perinatal depression, can be transformative for the perinatal individuals, children, and families we serve



Neurobiological Mechanisms of PPD

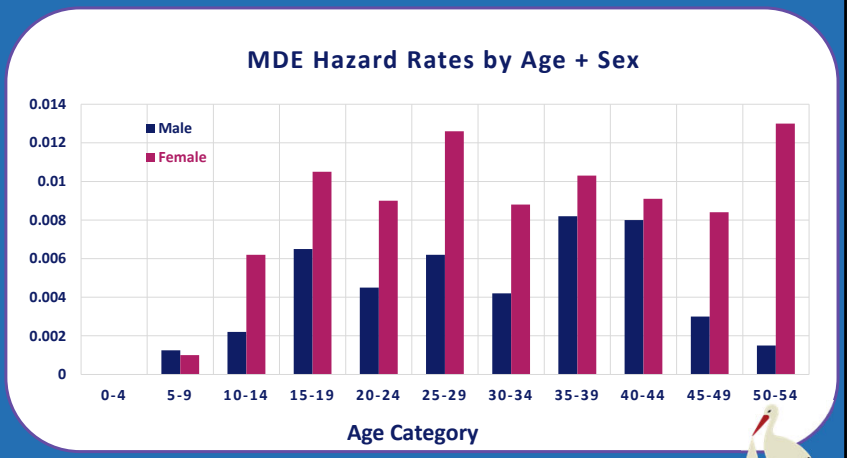
Presentation objectives

- Review hormone sensitivity in PPD and other reproductive psychiatric disorders
- Review genetic and epigenetic evidence indicating that PPD is different from MDD at other time points
- Review evidence for the contribution of other biological systems to the pathophysiology of PPD, a disease, not a weakness

MDD, major depressive disorder

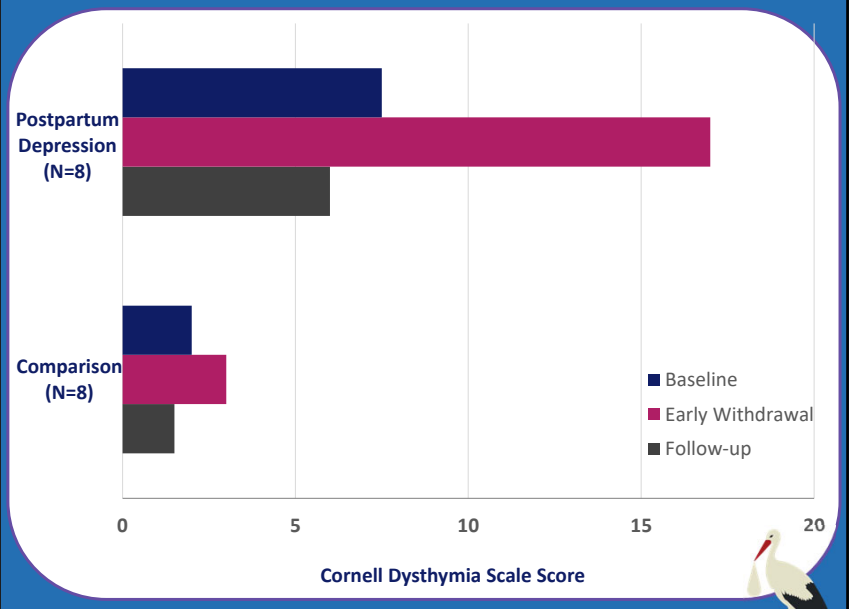
Depression in women and men across the reproductive years

Sex and depression in the National Comorbidity Survey I: Lifetime prevalence, chronicity and recurrence



Adapted from Kessler RC, et al. *J Affect Disord*. 1993;29(2-3):85-96

PPD as an abnormal response to normal hormonal fluctuation

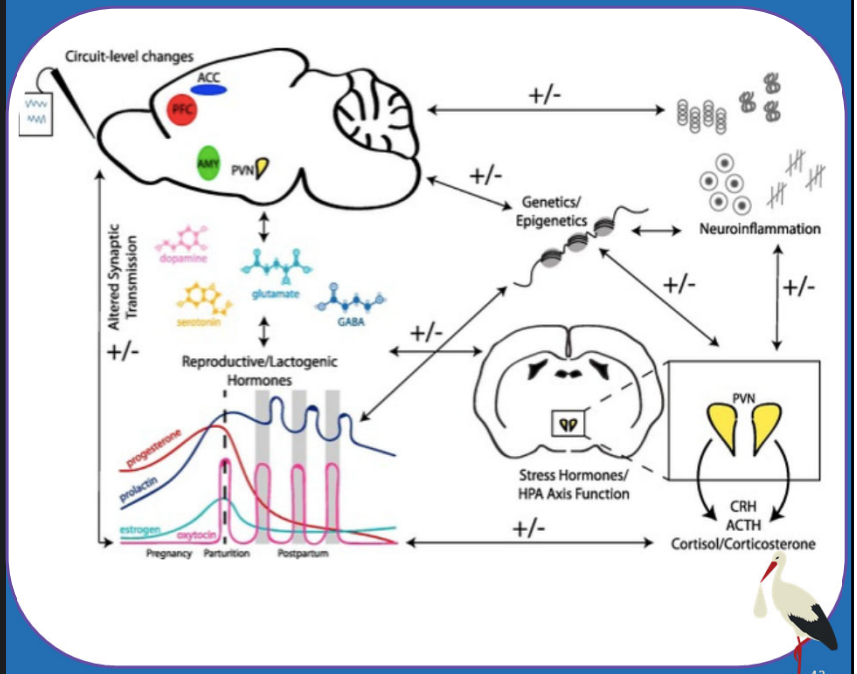


Adapted from Bloch M, et al. *Am J Psychiatry*. 2000;157(6):924-930

Biological factors involved in PPD

- Genetics and epigenetics
- Hormones
- Stress response system
- The immune system
- Neurotransmitters
- Circuits

Interaction among multiple systems



Reprinted from *Frontiers in Neuroendocrinology*, 52, Payne JL, Maguire J, Pathophysiological mechanisms implicated in postpartum depression, 165-180, Copyright 2019, with permission from Elsevier.

Genetics: Importance of timing

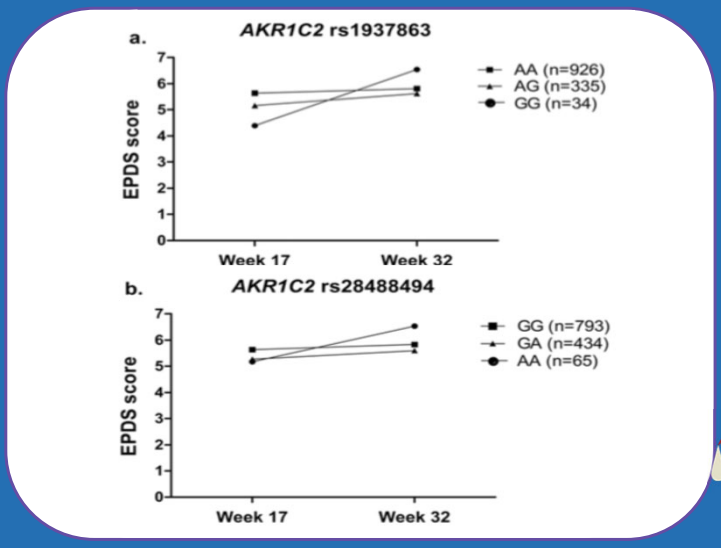
- Twin studies show a heritability of 38% for PPD
- Familiality with MDD for ***episodes that begin within 4 wks of delivery***
- Familiality also demonstrated with BPAD, but ***only for episodes that begin shortly after delivery***
- GWAS implicates numerous genes associated with estradiol changes and altered immune transcriptomic landscape
- Candidate gene studies have covered *SERT, COMT, BDNT, ESR1, OXTR HMNC1, MAOA, SIRT1* – mixed results, ***positive only for episodes that begin shortly after delivery***

BPAD, bipolar affective disorder; GWAS, genome-wide association studies

Treloar SA, et al. *Psychol Med*. 1999;29(3):645-654; Murphy-Eberenz K, et al. *J Affect Disord*. 2006;90(1):49-55; Forty L, et al. *Am J Psychiatry*. 2006;163(9):1549-1553; Payne JL, et al. *Bipolar Disord*. 2008;10(1):38-44; Mehta D, et al. *Transl Psychiatry*. 2021;11(1):155; McEvoy K, et al. *Curr Psychiatry Rep*. 2017;19(12):94

Genetic contribution?

- ALLO levels and depressive symptoms during pregnancy in relation to single nucleotide polymorphisms in the allopregnanolone synthesis pathway



ALLO, allopregnanolone; EPDS, Edinburgh Postnatal Depression Scale
Hellgren C, Comasco E, Skalkidou A, Sundström-Poromaa I. Allopregnanolone levels and depressive symptoms during pregnancy in relation to single nucleotide polymorphisms in the allopregnanolone synthesis pathway. *Hormones and Behavior*. 2017;94:106-113. https://www.sciencedirect.com/science/article/pii/S0018506X17300260?via%3Dihub. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY) and is available under Public License, https://creativecommons.org/licenses/by/4.0/legalcode.

Epigenetics

- Epigenetics – way of turning genes on/off; modifications to DNA are heritable
  - Can include **DNA methylation** (most studied), histone modification, and non-coding RNA-associated gene silencing
- 2 epigenetic biomarkers have been discovered and replicated, predicting PPD with accuracy of 87% – *HP1BP3* and *TTC9B*
  - Both genes have ties to estrogen signaling and may be involved in mediating synaptic plasticity
  - Replicated 6 times and heading for market
- Epigenetic regulation of OXTR has also been investigated; directionality of methylation changes depends on whether women have preexisting mood disorders

OXTR, oxytocin receptor polymorphism
Guintivano J, et al. *Mol Psychiatry*. 2014;19(5):560-567; Osborne L, et al. *Neuropsychopharmacology*. 2016;41(6):1648-1658; Bell AF, et al. *Front Genet*. 2015;6:243; Kimmel M, et al. *Psychoneuroendocrinology*. 2016;69:150-160; King L, et al. *Horm Behav*. 2017;96:84-94

Hormones

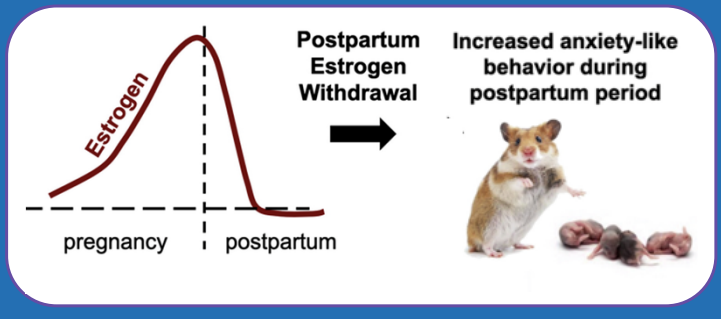
- Many hormones change across pregnancy and postpartum, especially estrogen and progesterone
- Estrogen and progesterone have direct effects on the brain
  - Modulate amygdala, prefrontal limbic connectivity
  - Affect critical molecules such as BDNF and affect other physiologic systems (thyroid, oxytocin, HPA, immune)

BDNF, brain-derived neurotrophic factor; HPA, hypothalamo-pituitary-adrenocortical axis

Schiller CE, et al. *CNS Spectr*. 2015;20(1):48-59; Schiller CE, et al. *Physiol Behav*. 2013;119:137-144; Stoffel EC, Craft RM. *Physiol Behav*. 2004;83(3):505-513; Li HJ, et al. *Arch Womens Ment Health*. 2020;23(3):401-412; Wisner KL, et al. *J Clin Psychopharmacol*. 2015;35(4):389-395; Gregoire AJ, et al. *Lancet*. 1996;347(9006):930-933; Ahokas A, et al. *J Clin Psychiatry*. 2001;62(5):332-336

Estrogen

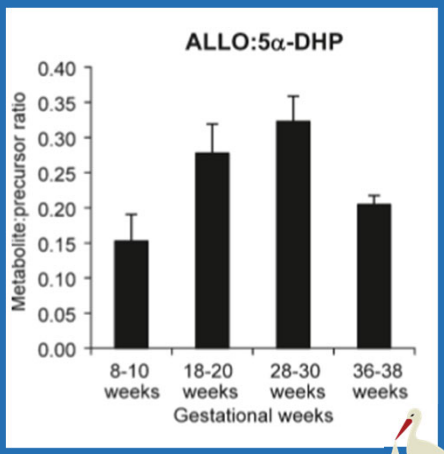
- Estrogen rises 100- to 1000-fold by the end of the 3rd trimester
- Estradiol withdrawal posited as an etiologic factor
- Transdermal estradiol has been studied as a treatment, with mixed results; needs further study



Adapted from Hedges VL, et al. *Biol Psychiatry*. 2021;89(9):929-938; Galea LA, et al. *Behav Brain Res*. 2001;122(1):1-9; Green AD, et al. *Physiol Behav*. 2009;97(2):259-265; Schiller CE, et al. *Physiol Behav*. 2013;119:137-144; Stoffel EC, Craft RM. *Physiol Behav*. 2004;83(3):505-513; Suda S, et al. *Biol Psychiatry*. 2008;64(4):311-319; Navarre BM, et al. *Physiol Behav*. 2010;99(1):59-66; Baka J, et al. *Neuroscience*. 2017;343:384-397; Zhang Z, et al. *Psychoneuroendocrinology*. 2016;66:138-149; Yang R, et al. *Eur Neuropsychopharmacol*. 2017;27(8):759-772

Progesterone metabolites: Neuroactive steroids (ALLO)

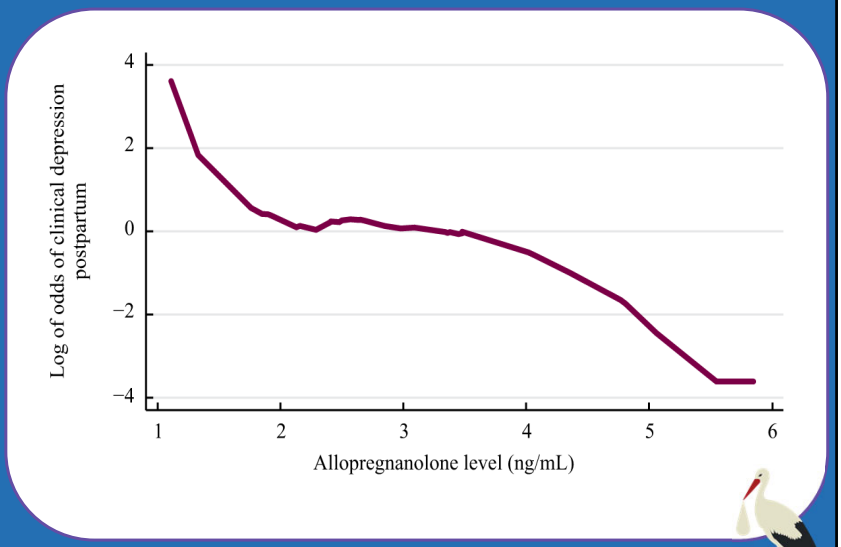
- ↑ Levels 7x-9x across pregnancy
- ↓ Expression GABA-A receptor subunit & binding capacity
- ↑ Within 48 hrs after delivery
- Ratio to precursor may ↓ before delivery
- Return to normal by 6 wks postpartum



GABA-A; gamma-aminobutyric acid-A; 5α-DHP, 5α-dihydroprogesterone
Adapted from Gilbert Evans SE, et al. *Gynecol Endocrinol*. 2005;21(5):268-279

48

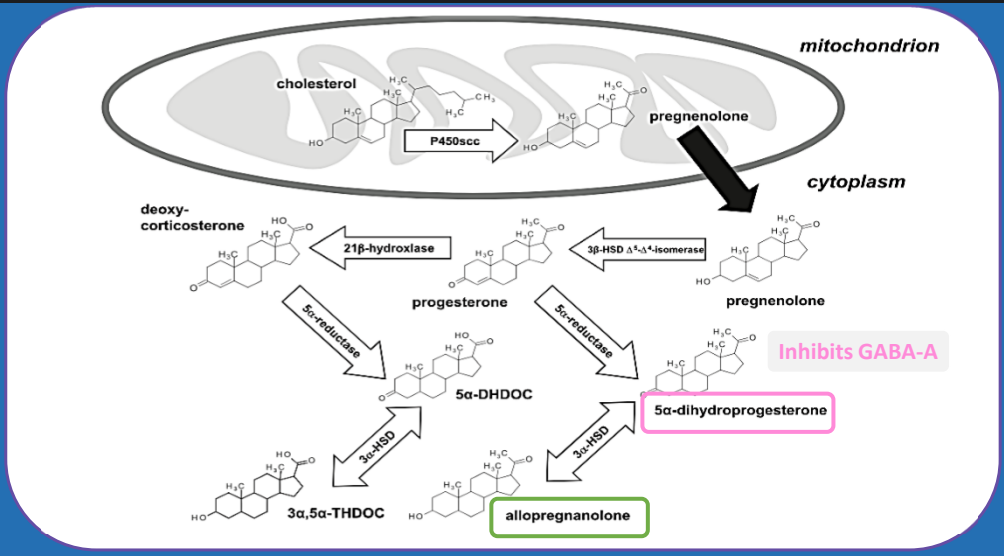
T2 ALLO and PPD



T2, second trimester of pregnancy
Reprinted from *Psychoneuroendocrinology*, 79, Osborne LM, Gispen F, Sanyal A, Yenokyan G, Meilman S, Payne JL, Lower allopregnanolone during pregnancy predicts postpartum depression: an exploratory study, 116-121, Copyright 2017, with permission from Elsevier.

49

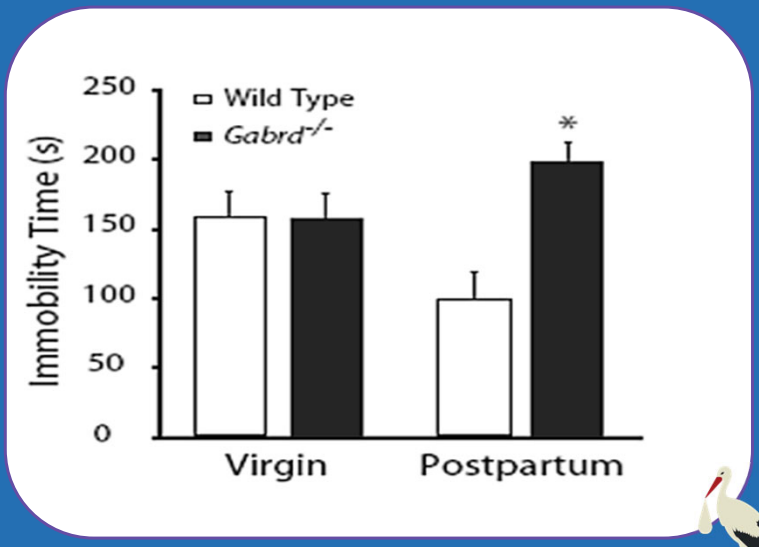
Action of receptors: Allosteric modulator GABA-A



Reprinted from *Progress in Neurobiology*, 113, Schüle C, Nothdurfter C, Rupprecht R, The role of allopregnanolone in depression and anxiety, 79-87, Copyright 2014, with permission from Elsevier.

GABA-A receptor knockout mice

=**Increased** mood and anxiety-like behaviors postpartum



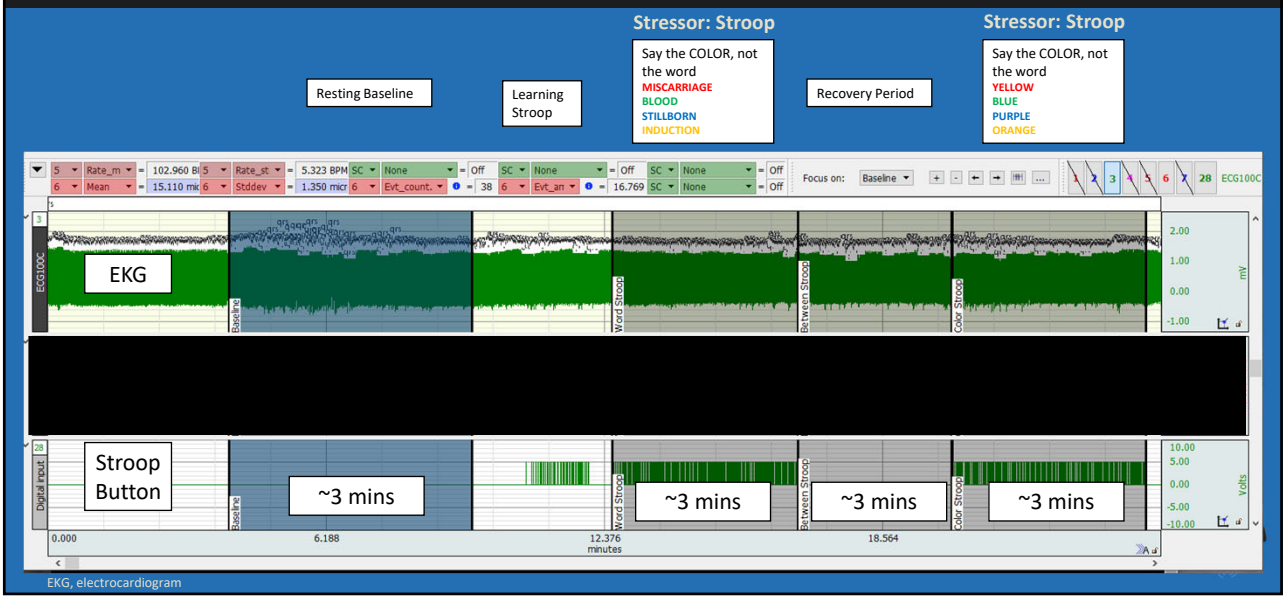
Adapted from Maguire J, Mody I. *Neuron*. 2008;59(2):207-213

Stress response system

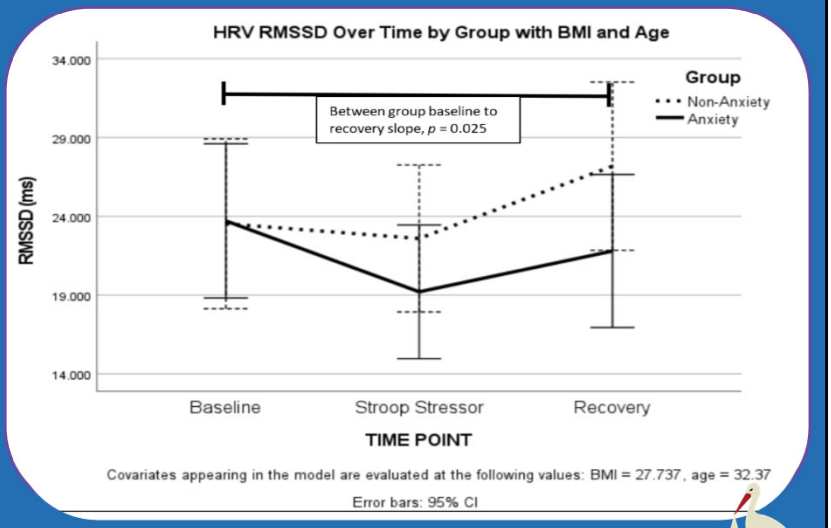
- Stress induces postpartum depressive-like behaviors in animal models
- Chronic stress alters maternal postpartum behaviors and induces anxiety and depression-like behavior in animal models
- Early life stress enhances PPD-like behaviors

Payne JL, et al. *Front Neuroendocrinol*. 2019;52:165-180; Pawluski JL, et al. *Trends Neurosci*. 2017;40(2):106-120; Murgatroyd CA, et al. *Neuropeptides*. 2015;52:103-111; Maguire J, Mody I. *Neural Plast*. 2016;2016:2762518

Heart rate variability: One measure of stress responsivity



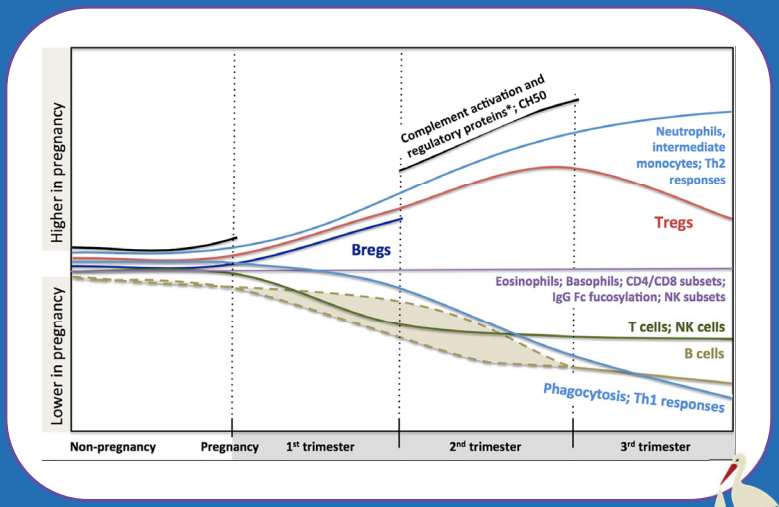
HRV RMSSD over time



HRV, heart-rate variability; RMSSD, root mean square of successive differences; BMI, body mass index

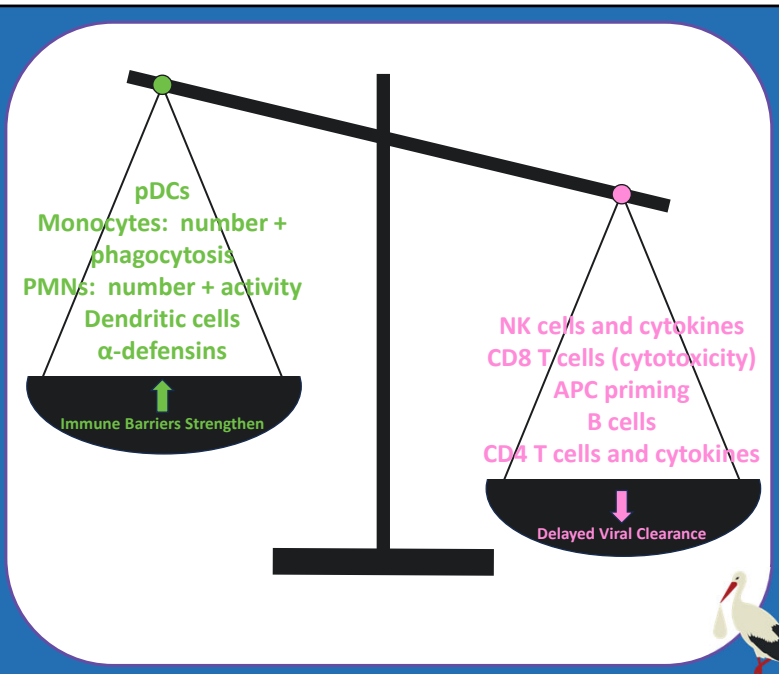
Riddle JN, Jager LR, Sherer M, Pangtey M, Osborne LM, Anxiety in pregnancy and stress responsiveness: an exploratory study of heart rate variability, cortisol, and alpha-amylase in the third trimester, *Journal of Neuroendocrinology*, 2023;e13238, John Wiley and Sons, © 2023 British Society for Neuroendocrinology. Reprinted with permission.

Immune system: Pregnancy dynamics



Abu-Raya B, Michalski C, Sadarangani M, Lavoie PM. Maternal immunological adaptation during normal pregnancy. *Frontiers in Immunology*. 2020;11:A575197. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7579415/pdf/fimmu-11-575197.pdf. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY) and is available under Public License, https://creativecommons.org/licenses/by/4.0/legalcode

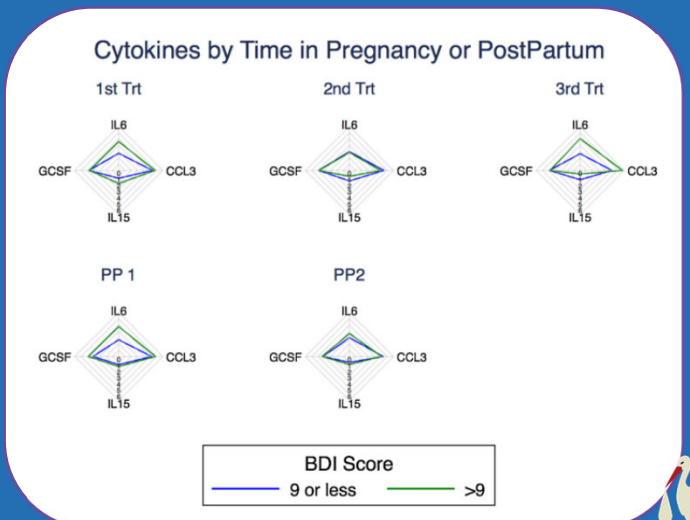
Toward a pregnancy immune phenotype



pDCs, plasmacytoid dendritic cells; PMNs, polymorphonuclear leukocytes; NK, natural killer; CD8, cytotoxic T-lymphocyte; APC, antigen-presenting cell; CD4, T-helper cell
Adapted from Pazos M, et al. *Immunol Res.* 2012;54(1-3):254-261

Innate immune activation?

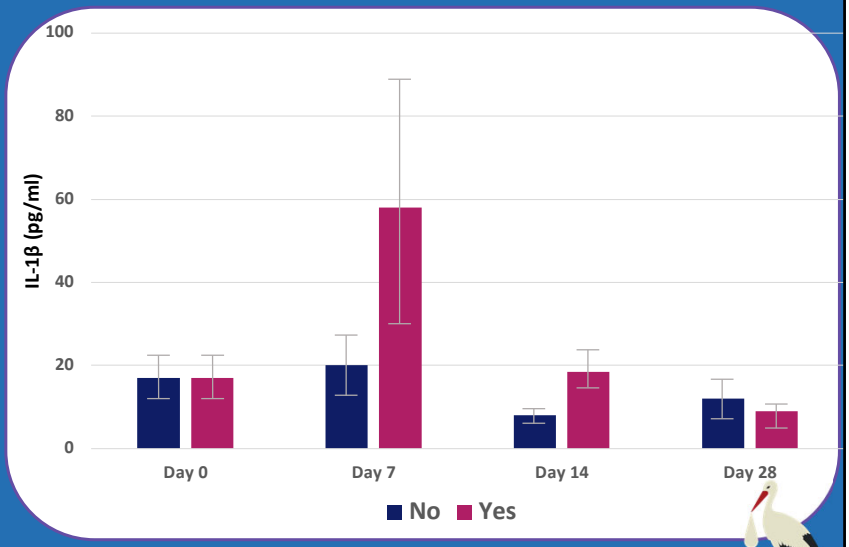
- **Plot is showing the differences in mean log-transformed cytokine levels**



Reprinted from *Psychoneuroendocrinology*, 99, Osborne LM, Yenokyan G, Fei K, et al, Innate immune activation and depressive and anxious symptoms across the peripartum: an exploratory study, 80-86, Copyright 2019, with permission from Elsevier .

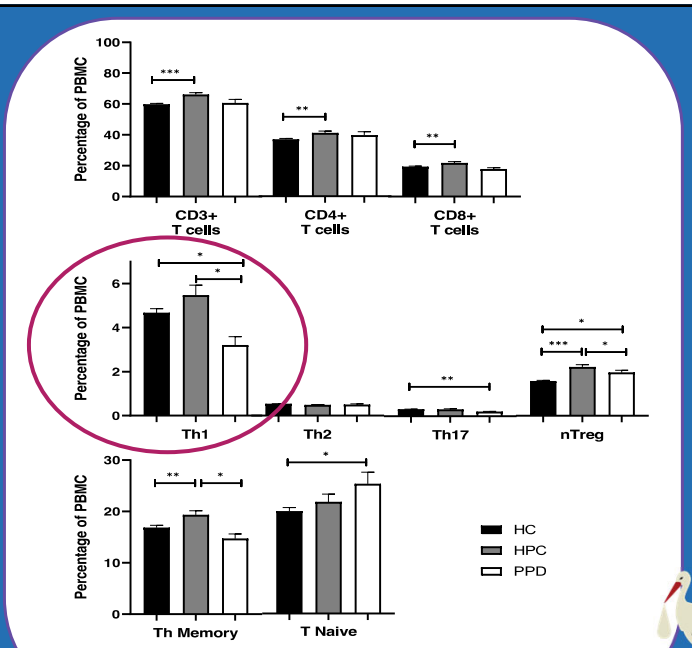
Inflammation and PPD

- **Symptoms of postpartum depression associated with elevated levels of IL-1β during the 1st month postpartum**



IL-1β, interleukin-1 beta
Adapted from Corwin EJ, et al. *Biol Res Nurs*. 2008;10(2):128-133

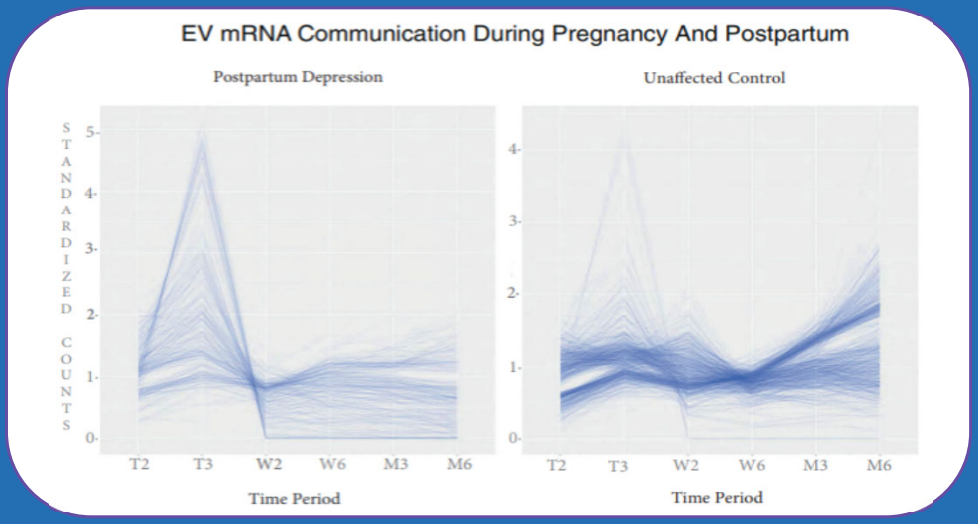
Failure of postpartum T-cell rebound



Percentage of T-cells and T-cell subset populations (% lymphocytes) in 3 populations: postpartum depression (PPD, N = 21 [white]); healthy postpartum controls (HPC, N = 39 [gray]); and healthy non-postpartum controls (HC, N = 114 [black])

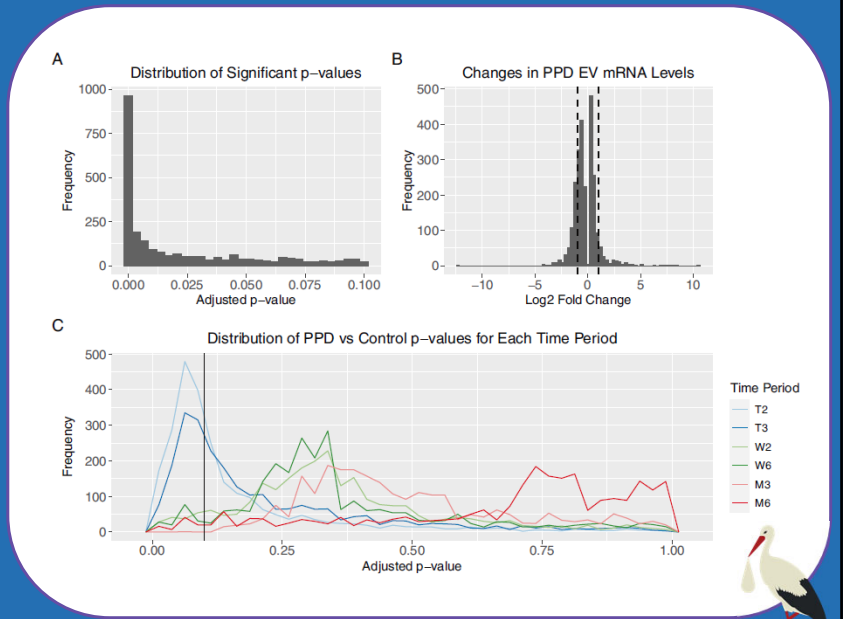
PBMC, peripheral blood mononuclear cell
Reprinted from *Brain, Behavior, and Immunity*, 87, Osborne LM, Gilden J, Kamperman AM, et al, T-cell defects and postpartum depression, 397-403, Copyright 2020, with permission from Elsevier.

Immune cell extracellular vesicles: mRNA communication is altered in postpartum depression



mRNA, messenger RNA; EV, extracellular vesicles
Osborne LM, et al. *Mol Psychiatry*. 2022;27(11):4526-4535

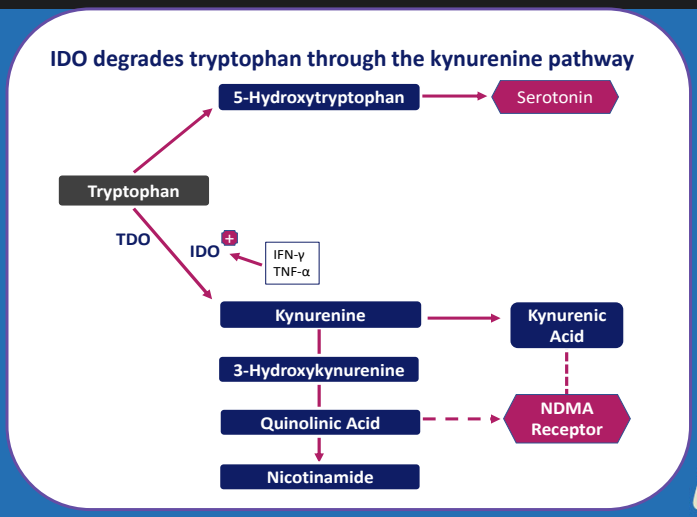
Altered EV mRNA levels during pregnancy that are associated with PPD



Osborne LM, et al. *Mol Psychiatry*. 2022;27(11):4526-4535

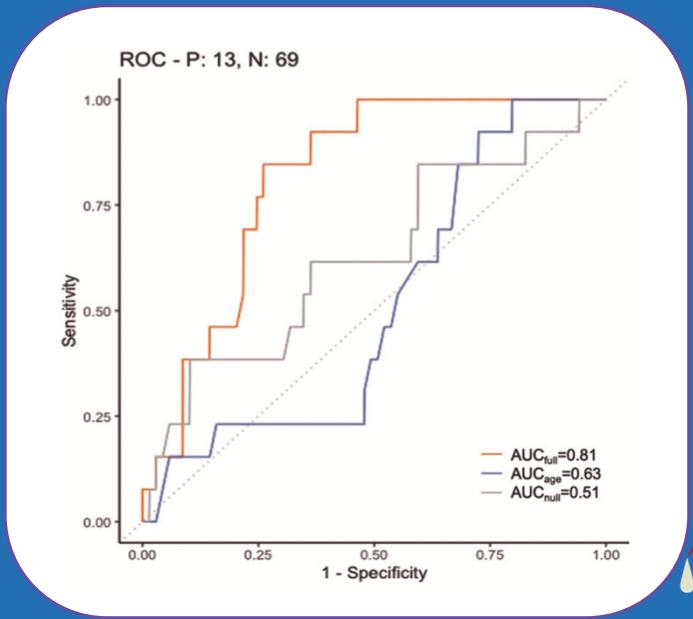
Neurotransmitters

- Reduction in platelet serotonin levels
- Higher MAOA density
- 5-HT at 20 weeks' pregnancy correlated with later PPD
- Serotonergic pathway implicated in treatment
- Kynurenine pathway



MAOA, monoamine oxidase A; 5-HT, 5-hydroxytryptamine; TDO, tryptophan dioxygenase; IDO, indoleamine dioxygenase; IFN, interferon; TNF, tumor necrosis factor; NMDA, *N*-methyl-D-aspartate
Adapted from Dantzer R, et al. *Nat Rev Neurosci*. 2008;9(1):46-56; Maurer-Spurej E, et al. *J Psychiatry Neurosci*. 2007;32(1):23-29; Sacher J, et al. *Neuropsychopharmacology*. 2015;40(2):429-435; Cao S, et al. *Int J Gynaecol Obstet*. 2020;151(3):438-442; Choi JE, et al. *J Nutr Biochem*. 2020;84:108417; Abdul Aziz NU, et al. *Brain Sci*. 2020;10(10):733

Prediction model

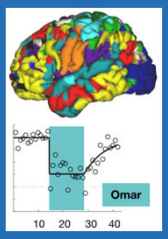


ROC, receiver operating characteristics; AUC, area under the curve

Sha Q, Madaj Z, Keaton S, et al. Cytokines and tryptophan metabolites can predict depressive symptoms in pregnancy. *Translational Psychiatry*. 2022;12(1):35. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8789799/. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY) and is available under Public License, https://creativecommons.org/licenses/by/4.0/legalcode.

Circuits

- Striking plasticity of the maternal brain; neural circuits that govern maternal behavior are triggered by endocrine changes; medial preoptic area significant for caregiving; plasticity in hippocampus
- Reductions in gray matter volume in postpartum
- Enhanced plasticity, altered neurogenesis in hippocampus
- Little to distinguish function in PPD, but some evidence suggests lowered connectivity between amydgala, insula, and orbitofrontal cortex and PP stress associated with reduced activity in RmPFC in response to infant cry; also altered connectivity between amygdala and other areas such as insular cortex, posterior cingulate cortex
- Disruption of frontal subcortical circuits and possibly disrupted interhemispheric structural connectivity in PPD compared with healthy controls



RmPFC, rostromedial prefrontal cortex
Rupprecht R, et al. *World J Biol Psychiatry*. 2021;1-20; Maguire J, et al. *Handb Clin Neurol*. 2020;171:97-116; Chase HW, et al. *Soc Cogn Affect Neurosci*. 2014;9(8):1069-1075; Wonch KE, et al. *Soc Neurosci*. 2016;11(6):600-617; Lynch CJ, et al. *Cell Rep*. 2020;33(12):108540; Newbold DJ, et al. *Neuron*. 2020;107(3):580-589.e6

Summary/Conclusions

- PPD is distinct from depression at other points in life
- Many people with PPD have “reproductive depression” phenotype, which includes a vulnerability to fluctuations in reproductive hormones
- The stress response system and the immune system interact with hormone fluctuation and contribute to PPD pathology
- All of these systems converge at the level of neural circuits, and our knowledge of how these function in PPD is slim

Current and Future Treatments for PPD

Presentation agenda



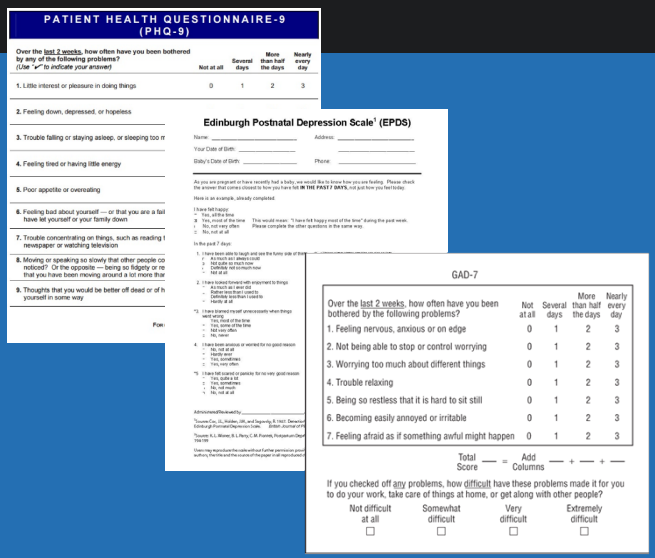
- Safety and efficacy of currently available treatments for PPD: clinical and real-world experience
- Correlations between available PPD treatments and the neurobiology of PPD
- An overview of investigational treatments for PPD

Possible costs of untreated mental illness

- 2017: Study found that untreated mood and anxiety disorders among pregnant and postpartum parents cost 14.2 billion/year when following the mother and child-pair for 5 yrs post-birth

Luca DL, et al. *Am J Public Health*. 2020;110(6):888-896

When to treat?



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				
3. Trouble falling or staying asleep, or sleeping too m				
4. Feeling tired or having little energy				
5. Poor appetite or overeating				
6. Feeling bad about yourself — or that you are a fail have let yourself or your family down				
7. Trouble concentrating on things, such as reading t newspaper or watching television				
8. Moving or speaking so slowly that other people co noticed? Or the opposite — being so fidgety or re that you have been moving around a lot more than				
9. Thoughts that you would be better off dead or of h yourself in some way				

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
   - 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

Administered/Reviewed by: _____

[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 Depr 354-199

Users may reproduce the scale without further permission provid author, the title and the source of the paper it will reproduced in

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

Total Score ___ = Add Columns ___ + ___ + ___

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?

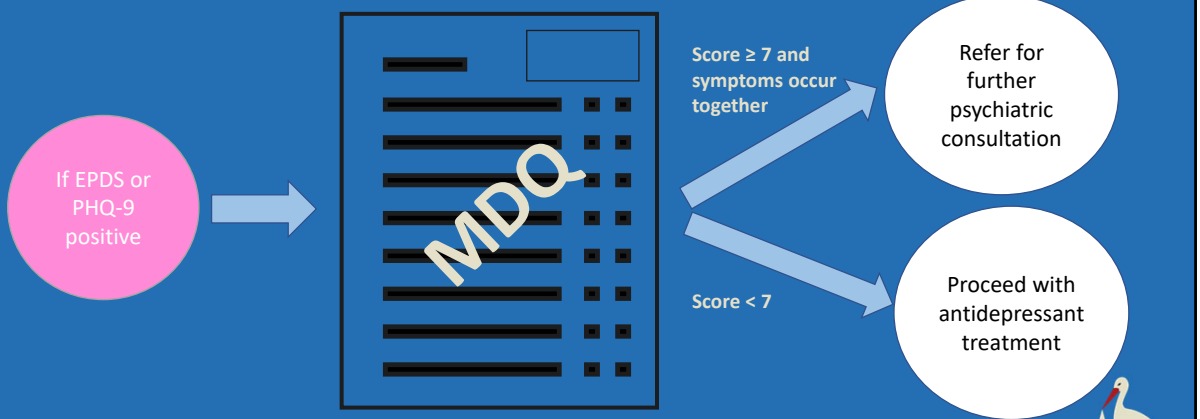
Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

- Mild to moderate symptoms can be effectively treated with psychotherapy and other nonmedication treatments
- Moderately severe to severe symptoms are best treated with pharmacotherapy and psychotherapy
- Most often pharmacotherapy will more quickly reduce the symptoms of depression and anxiety

GAD-7, General Anxiety Disorder-7

Spitzer RL, et al. Patient Health Questionnaire-9. Accessed June 21, 2023. https://www.apa.org/depression-guideline/patient-health-questionnaire.pdf; Spitzer RL, et al. Arch Intern Med. 2006;166(10):1092-1097; Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: development of the 10-item Edinburgh Postnatal Depression Scale. *The British Journal of Psychiatry*. 1987;150:782-786. Edinburgh Postnatal Depression Scale (EPDS); Spitzer RL, et al. GAD-7 anxiety. Accessed June 21, 2023. https://adaa.org/sites/default/files/GAD-7_Anxiety-updated_0.pdf

When to treat?



MDQ, Mood Disorder Questionnaire
Clark CT, et al. *Depress Anxiety*. 2015;32(7):518-526

Treating with antidepressants

- Begin treatment at the first sign of symptoms lasting beyond 2 weeks and outside of the baby blues (first 10-14 days)

Acute: Treat for 6 to 12 weeks. Aim for full remission and return to patient's baseline

Continuation: Continue treatment for an additional 4 to 9 months, ideally aim for a total of 1 year
Don't stop treatment abruptly or taper during significant life stressors

Maintenance: Continue treatment in patient with >3 past depressive episodes
Counsel about high risk of recurrence if patient has history of severe episodes, strong family history, prior suicide attempt, significant life stressors as perceived by patient

Gelenberg AJ, et al. *J Clin Psychiatry*. 2010;71(7):e15

Mental illness impacts infant outcomes



- Disrupts cognitive, emotional, and social development
  - *Harvard University 2009*: Children raised by clinically depressed mothers perform lower on cognitive, emotional, and behavioral assessments than children of non-depressed caregivers, and are at risk for later mental health problems, social adjustment difficulties, and difficulties in school

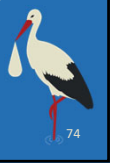
Center on the Developing Child at Harvard University (2009). *Maternal Depression Can Undermine the Development of Young Children: Working Paper No. 8.* Accessed May 11, 2023. http://www.developingchild.harvard.edu



Nonpharmacologic Treatment

Support, sleep, and exercise

- Emphasize support, sleep, and exercise
- When possible, encourage patients to utilize circle of support for help
  - Taking a nap or shower, and/or walk
- Sleep deprivation is a risk factor for depression and anxiety
  - Aiming for 4-hr uninterrupted blocks overnight and naps are recommended
  - Reduce disruption by breastfeeding, pumping extra during the day to be used by partner or other support overnight or supplementation with formula overnight is recommended to reduce the number of interruptions
- Once cleared for exercise, 30 min of cardio 3-4/wk or 1 hr of yoga 2 times a week helps to improve symptoms

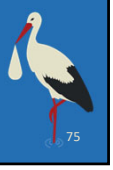


min, minutes

Buttner MM, et al. *Complement Ther Clin Pract*. 2015;21(2):94-100; Dørheim SK, et al. *Sleep*. 2009;32(7):847-855

Rule out other contributors or causes of symptoms

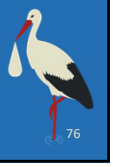
- Thyroid dysfunction and vitamin deficiencies have been implicated in postpartum depression
- To rule out the contribution of a thyroid disorder to the patient's presentation, patients should be screened
- Vitamin D deficiency can further compound feelings of fatigue or depression and should be replaced if deficient
- Vitamin B12 should also be screened for and replaced if deficient



Buttner MM, et al. *Complement Ther Clin Pract*. 2015;21(2):94-100; Dørheim SK, et al. *Sleep*. 2009;32(7):847-855

Psychotherapy

- Individual and/or group cognitive behavioral therapy or interpersonal therapy
- Depression-focused psychotherapy or other nonmedication therapies may be considered first for some women, especially those with mild to moderate depression
- Psychotherapy should be considered as part of the treatment plan whenever possible

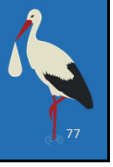


Becker M, et al. *Curr Psychiatry Rep*. 2016;18(3):32; Gelenberg AJ, et al. *Am J Psychiatry*. 2010;167(10):1-118; Scope A, et al. *BMC Psychiatry*. 2013;13:321; Stuart S. *Clin Psychol Psychother*. 2012;19(2):134-140

ECT, TMS, and light therapy are other nonpharmacologic treatment options

- ECT
  - Procedure, performed under anesthesia to deliver electrical currents to the brain and trigger a brief seizure
  - For severe depression
- TMS
  - Procedure that uses magnetic fields to stimulate parts of the brain to improve symptoms
  - Remission rates were 66% – 90% in open-label trials with women with PPD
  - Daily over 4 to 8 weeks
- Light therapy
  - Inconclusive, mixed results in 5 studies
  - 30 min within 10 min of waking up. 10,000 lux light box
  - Offsets low light exposure, helps reset sleep, addresses serotonergic dysregulation





ECT, electroconvulsive therapy; TMS, transcranial magnetic stimulation
Cox EQ, et al.*J Affect Disord*. 2020;264:193-200; Crowley SK, et al. *J Physiol Anthropol*. 2012;31(1):15; EmPower Psychiatry & Sleep LLC. Accessed July 13, 2023. atlantatms.clinic/tms

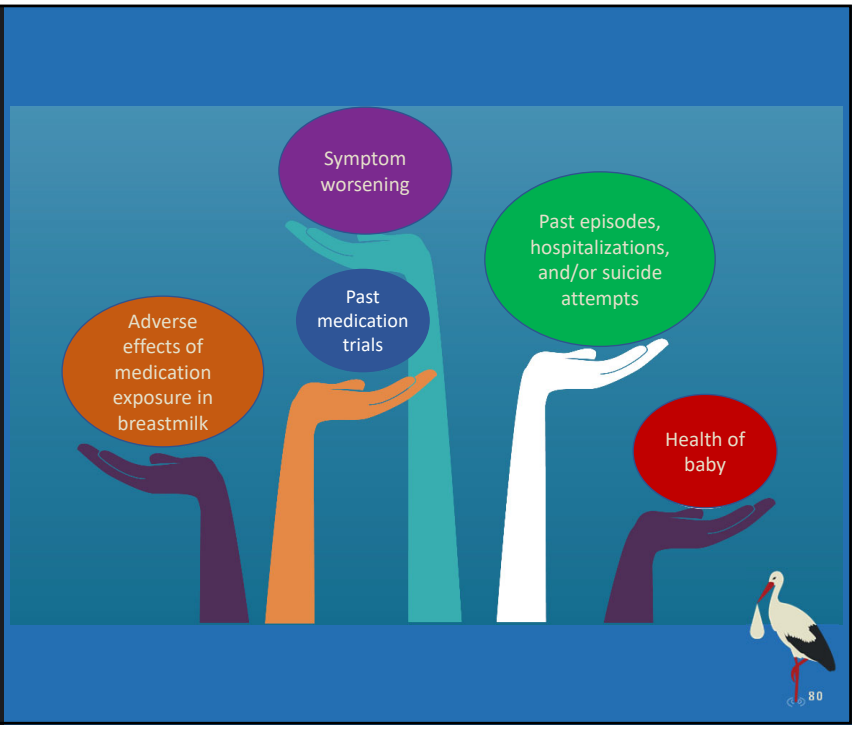


Pharmacologic Treatment

Considerations for choosing an antidepressant

- Severity of symptoms
- Concern for bipolar disorder (screen before treating)
- Medications that were effective prior to pregnancy
- Family history (effective treatments for immediate family members)
- Transfer into breastmilk
- Tolerability and adverse side effects
- Potential drug interactions
- Patient preference

Risk-risk assessment



Lactation and drug transfer in breastmilk



- All medications transfer through the breastmilk, but vary in the degree of transfer to the infant
- Exposure to antidepressants is much less than during gestation
- Infant serum levels often undetectable/very low
- Most data: case reports and small study samples
- Adverse effects (eg, irritability, poor feeding, or sleep disorders) observed in babies who are exposed to antidepressants through breastmilk are often nonspecific and may be due to other causes, such as viral infections

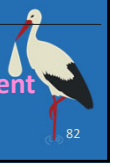
National Library of Medicine. Drugs and lactation database (LactMed®). National Institute of Child Health and Human Development; 2006. Bethesda, MD. Accessed May 11, 2023. https://www.ncbi.nlm.nih.gov/books/NBK501922/

Antidepressants can be taken while breastfeeding

- Most evidence-based data: SSRI & TCA
- Sertraline and paroxetine have low to undetectable levels in the infant; no reports of adverse events
- Higher transfer for citalopram, fluoxetine, venlafaxine, and desvenlafaxine
- Levels peak 6 to 8 hrs post dose
- Studies up to 1 year of age show normal development
- Newer agents, less studied – levomilnacipran, milnacipran

	Antidepressant	Breastmilk Transfer Relative Infant Dose, % (lower risk: <10)
SSRIs	Citalopram	Low transfer; RID 3–10
	Escitalopram	Low transfer; RID 3–6
	Fluoxetine	High transfer; RID <12
	Fluvoxamine	Low transfer; RID < 2
	Paroxetine	Low transfer; RID 0.5–3
	Sertraline	Low transfer; RID 0.5–3
SNRIs	Venlafaxine	High transfer; RID 6–9
	Desvenlafaxine	High transfer; RID 5.5–8.1
	Duloxetine	Low transfer: RID <1

Use the medication that works best for the patient



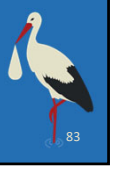
SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; SNRI, serotonin and norepinephrine reuptake inhibitor; RID, relative infant dose
Chad L, et al. *Can Fam Physician*. 2013;59(6):633-634

Other antidepressant treatments

- MAOIs: generally avoided in breastfeeding because little data are available

Antidepressant	Breastmilk Transfer Relative Infant Dose, % (lower risk: <10)	Other Considerations
Bupropion	Low transfer, RID <2	2 reports of seizures in 6-mos-old breastfed infants
Mirtazapine	Low transfer, RID 0.5 – 3	
Nortriptyline	Low Transfer	
Trazodone	Low transfer	

Medication for newer medications have much less data

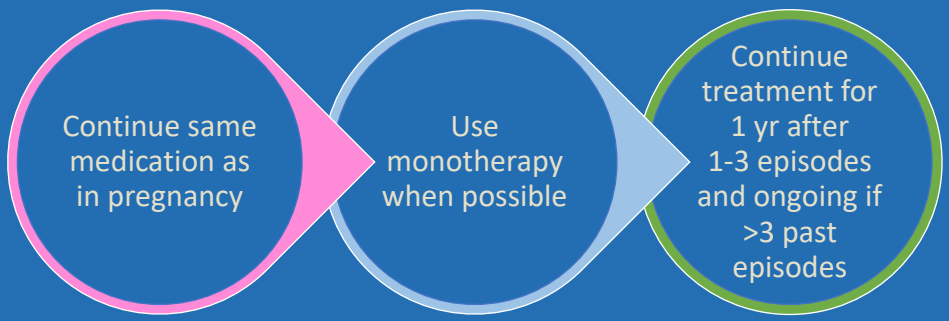


MAOI, monoamine oxidase inhibitor
Neuman G, et al. *Ann Pharmacother*. 2014;48:928-931; Chaudron LH, et al. *J Clin Psychiatry*. 2004;65:881-882; Chad L, et al. *Can Fam Physician*. 2013;59(6):633-634; National Library of Medicine. Drugs and lactation database (LactMed®). National Institute of Child Health and Human Development; 2006. Bethesda, MD. Accessed May 11, 2023. https://www.ncbi.nlm.nih.gov/books/NBK501922/

Additional considerations and review of pharmacology treatment

- To treat or not to treat – it's a risk-risk discussion
- Risk of untreated illness must be weighed against risk of breastmilk exposure
- Use lowest dose that achieves full symptom remission
- Coordinate care with members of treatment team – pediatrician, therapist
- Infants should be assessed by pediatrician for any concerns in behavioral changes – sleep disturbances, irritability, agitation, excessive crying, or poor weight gain

Additional considerations and review of pharmacology treatment (continued)





Other Treatments, Novel Therapies and Future Directions

Hormonal treatment

- Dysregulation of gonadal steroid fluctuations can increase the risk of mood disorder symptom and disorder onset
- Two randomized controlled trials found that transdermal estradiol compared with placebo rapidly reduces symptoms
  - Gregoire et al (1996): 61 postpartum women randomized to either transdermal E2 (200 mcg/d) or placebo
    - Significant effect was noticed in 1 month and 80% of those receiving E2 had a response compared with 31% of those receiving placebo by 3 months
  - Ahokas et al (2001): treated 23 severely depressed inpatient women with sublingual estradiol (average dose 4.8 mg/d)
    - 19 of 23 had full remission of symptoms by 2 weeks

E2, estradiol

Ahokas A, et al. *J Clin Psychiatry*. 2001;62(5):332-336; Gregoire AJ, et al. *Lancet*. 1996;347(9006):930-933

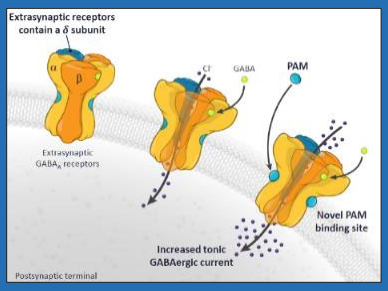
Hormonal treatment

- There is minimal transfer of estradiol in breastmilk, but it is unclear if it impacts milk supply
- Not to be used as first line; antidepressants should be used first
- Requires more randomized controlled trials before routine clinical use
- Concerns about thrombosis must be addressed

Ahokas A, et al. *J Clin Psychiatry*. 2001;62(5):332-336; Gregoire AJ, et al. *Lancet*. 1996;347(9006):930-933

Brexanolone injection

- Brexanolone injection is hypothesized to work in PPD by increasing GABA function
  - Proprietary IV formulation of allopregnanolone
  - First drug approved for PPD
  - 60-hour infusion
  - Positive allosteric modulator of $GABA_A$ receptors



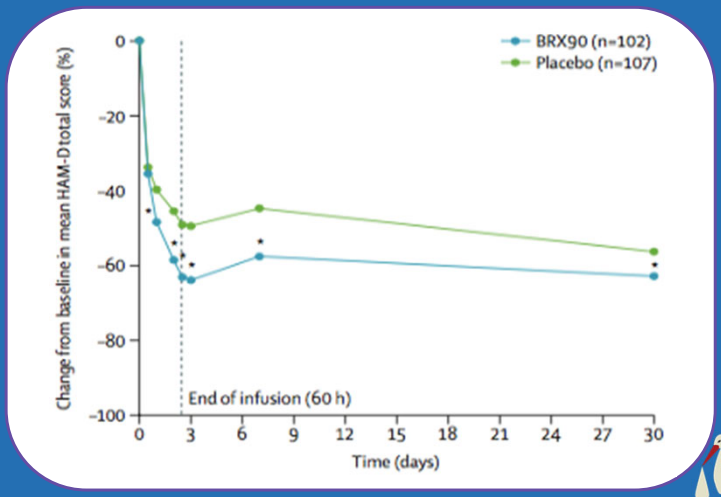
- Therapeutic rationale for use
  - GABAergic hypofunction has been associated with PPD
  - Brexanolone injection is a positive allosteric modulator of $GABA_A$ receptors
  - **Therefore, brexanolone injection may have therapeutic potential in PPD by increasing GABAergic function**

IV, intravenous; PAM, positive allosteric modulator

Luscher B, et al. *Molecular Psychiatry* 2011; 16(4):383-406; Deligiannidis KM, et al. *Psychoneuroendocrinology*. 2016;70:98-107; Epperson CN et al *Psychopharmacology* 2006; 186(3):425-433; Maguire J, Mody I. *Psychoneuroendocrinology*. 2009;34 suppl 1:S84-S90; Bialer M, et al. *Epilepsy Res* 2015; 11:85-141

Brexanolone

- Integrated analysis



HAM-D, Hamilton Rating Scale for Depression; BRX, brexanolone
Reprinted from *The Lancet*, 392, Meltzer-Brody S, Colquhoun H, Riesenberg R, et al, Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials, 1058-1070, Copyright 2018, with permission from Elsevier.

Brexanolone

- Risks include loss of consciousness, excessive sedation, hypoxia – requires monitoring by REMS specialist
- Breastfeeding: RID 1.3%, 12 women studied, no data on infant levels, 3 days post-infusion maternal levels were not detectable

REMS, Risk Evaluation and Mitigation Strategy
Epperson CN, et al. *J Affect Disord*. 2023;320:353-359

Future innovative treatment: Zuranolone

- Neuroactive steroid that is a $GABA_A$ receptor positive allosteric modulator
- 14-day oral therapy instead of infusion
- Includes supportive data from 7 studies including 2 trials (SKYLARK and ROBIN) in adult postpartum patients with depression
- Rapid response with sustained remission of symptoms
- Generally well tolerated (i.e., no associated weight gain or sexual dysfunction)

Biogen. News Release. December 6, 2022. Accessed May 12, 2023. https://investors.biogen.com/news-releases/news-release-details/biogen-and-sage-therapeutics-complete-rolling-submission-new

Zuranolone clinical data

RCT: Effect of Zuranolone vs Placebo in Postpartum Depression: A Randomized Clinical Trial

POPULATION

150 Women

Women ages 18-45 y with postpartum depression and Hamilton Rating Scale for Depression (HAMD-17) score ≥26

Mean (SD) age, 28.3 (5.4) y

INTERVENTION

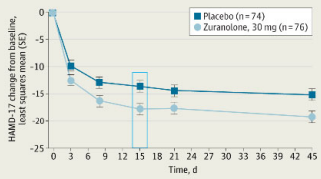
153 Individuals randomized

76 Zuranolone
Oral zuranolone, 30 mg, every evening with food for 14 d

74 Placebo
Oral placebo capsule every evening with food for 14 d

FINDINGS

Individuals with postpartum depression who received zuranolone for 2 wk displayed significantly greater reductions in depressive symptoms compared with placebo at day 15



Difference in change in depressive symptoms at 15 wk, zuranolone vs placebo:
−4.2 (95% CI, −6.9 to −1.5); *P* = .003

SETTINGS / LOCATIONS

27 Clinical sites in the US

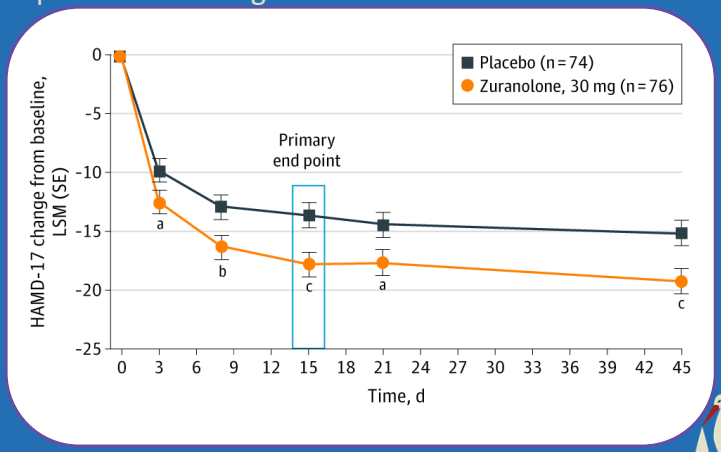
PRIMARY OUTCOME

Change from baseline in depressive symptoms at day 15, as measured by HAMD-17 score (range, 0-52, with higher scores indicating more severe depression)

Deligiannidis KM, Meltzer-Brody S, Gunduz-Bruce H, et al. Effect of zuranolone vs placebo in postpartum depression: a randomized clinical trial. *JAMA Psychiatry*. 2021;78(9):951-959. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8246337/?report=printable. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY) and is available under Public License, https://creativecommons.org/licenses/by/4.0/legalcode.

Zuranolone trials in PPD

- FDA granted Fast Track designation to zuranolone for PPD in 2022
- A phase III trial shows therapeutic effect for Major Depression at 50 mg

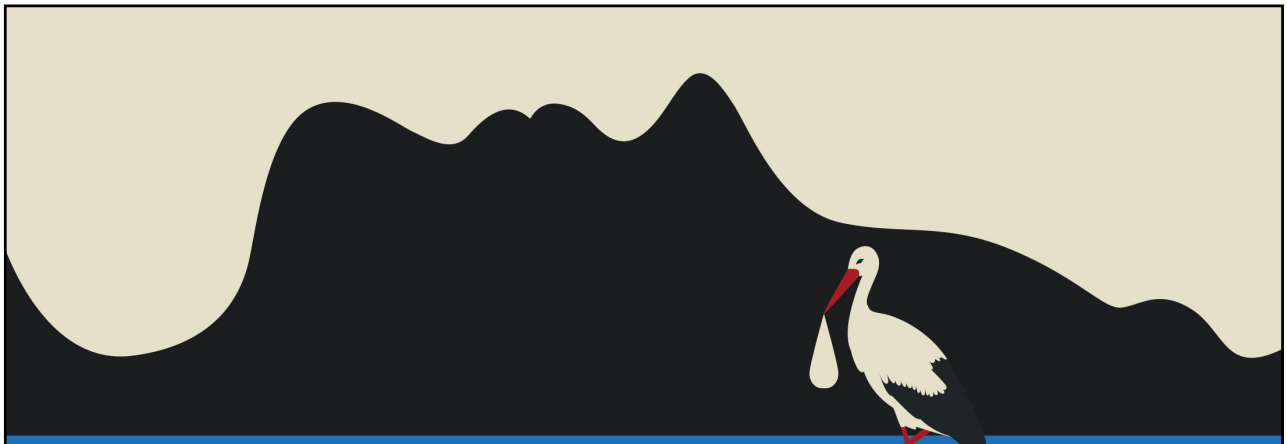


FDA, US Food and Drug Administration; LSM, least-squares mean; SE, standard error

Deligiannidis KM, Meltzer-Brody S, Gunduz-Bruce H, et al. Effect of zuranolone vs placebo in postpartum depression: a randomized clinical trial. *JAMA Psychiatry*. 2021;78(9):951-959. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8246337/?report=printable. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY) and is available under Public License, https://creativecommons.org/licenses/by/4.0/legalcode.

Summary

- Determine the treatment best for your patient on the basis of past history of mental illness, past effective treatments, and patient preference
- Make sure to have and document the risk-risk discussion
- Encourage psychotherapy, optimization of sleep, exercise, and nutrition as adjuncts to any treatment
- If using pharmacotherapy, continue for 6-12 months (at least a year for patients with recurrent episodes) and educate the patient to not stop the medication abruptly



NEUROBIOLOGICAL MECHANISMS IN POSTPARTUM DEPRESSION

Implications for Current and Future Treatments

Jointly provided by Partners for Advancing Clinical Education (PACE) and Miller Medical Communications, LLC.

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