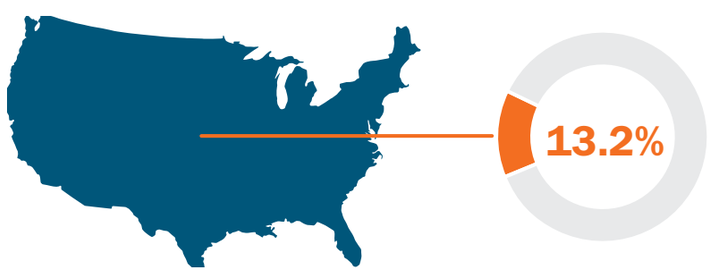
Postpartum Depression (PPD) is a Serious Medical Illness[1,2]

PPD is a serious illness, generally defined as a major depressive episode[a] with onset during or after pregnancy[1,2]

In 2018, 13.2% of patients with a live birth in the US self-reported experiencing symptoms of PPD[3,b]



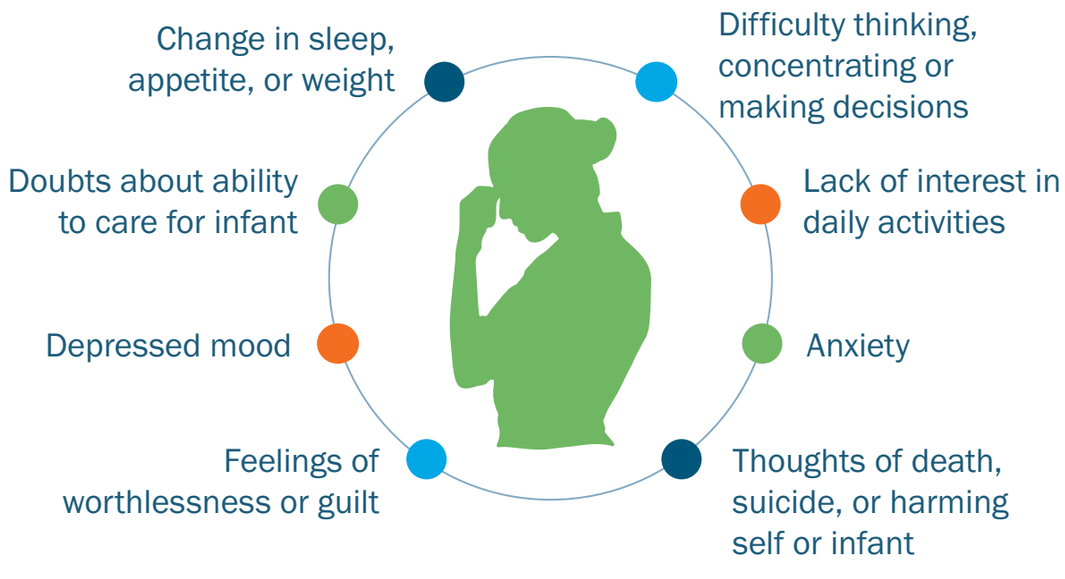
Risk factors for PPD include psychological, obstetric, biological, lifestyle, and social factors[4]

Patients with a history of depression or other mental health disorders may have an increased risk of developing PPD[4,5]

PPD symptoms can have a broad impact on the patient, child, and family[6-9]

PPD symptoms can be debilitating and impact function[10,11]

Clinically relevant symptoms can include[1,10]:



Suicide is a leading cause of pregnancy-related mortality[12]

Child development and family relationships can be negatively impacted by PPD[6-8]

PPD was associated with infant attachment difficulties[8,c]

Partners of patients with PPD faced increased levels of stress, anxiety, and depression[6,7]

PPD negatively impacted outcomes across multiple childhood developmental domains[8,c]

Unresolved PPD symptoms may impose a sizeable economic burden on society due to increased health care costs for the patient with PPD and others in their household[13,14]

PPD is distinct from the baby blues[10,11]

Baby blues[10,11]

- Mild symptoms, such as mild mood changes, feelings of worry, unhappiness, and exhaustion
- Peak within first week postpartum
- Resolve without treatment within 2 weeks postpartum
- Do not cause functional impairment

VS

PPD

- Feelings of extreme sadness, anxiety, and fatigue[10,11]
- Symptom onset can occur during pregnancy or postpartum[1,2]
- May persist for months or, in some cases, years[11]
- Causes functional impairment[10]

[a]The first criterion of a major depressive episode is that five or more depressive symptoms are present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.[1] [b]Based on 2018 data from 31 Pregnancy Risk Assessment Monitoring System (PRAMS) sites in the US.[3] [c]According to a global meta-analysis of 191 studies.[8]

PPD = postpartum depression; US = United States.

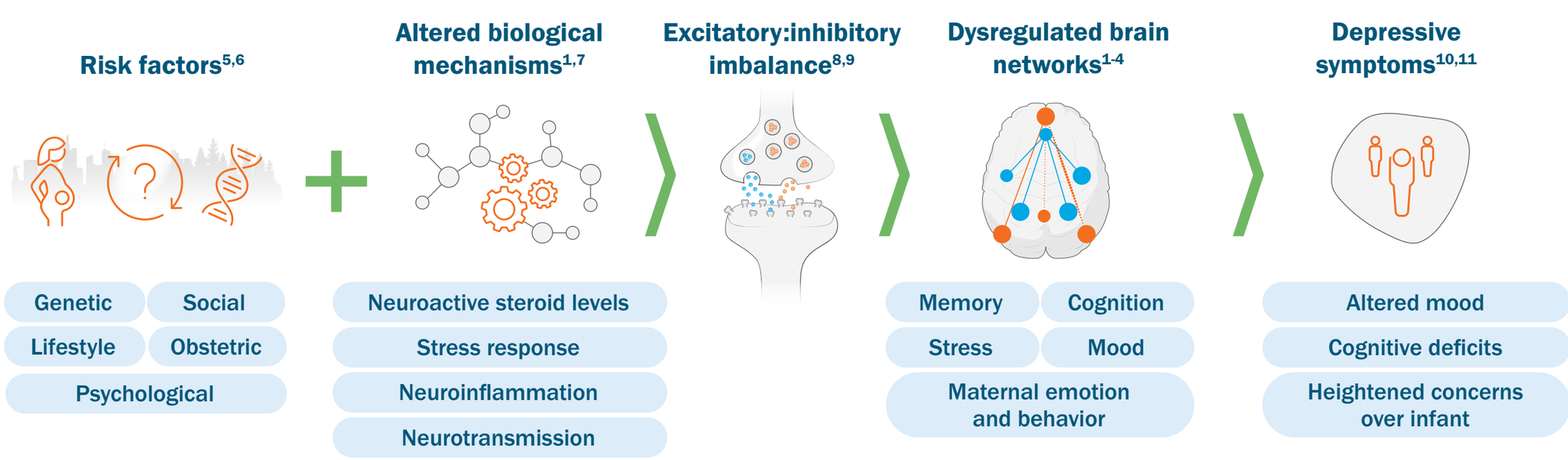
1. American Psychiatric Association. Depressive disorders. In: *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed., Text Revision. American Psychiatric Association Publishing; 2022. **2.** Thompson KS, Fox JE. *Ment Health Fam Med*. 2010;7:249-257. **3.** Bauman BL, et al. *MMWR Morb Mortal Wkly Rep*. 2020;69(19):575-581. **4.** Ghaedrahmati M, et al. *J Educ Health Promot*. 2017;6:60. **5.** Wisner KL, et al. *JAMA Psychiatry*. 2013;70(5):490-498. **6.** Goodman JH. *J Adv Nurs*. 2004;45(1):26-35. **7.** Moore Simas TA, et al. *Curr Med Res Opin*. 2019;35(3):383-393. **8.** Rogers A, et al. *JAMA Pediatr*. 2020;174(11):1082-1092; **9.** Lilja G, et al. *J Caring Sci*. 2012;26(2):245-253. **10.** National Institutes of Mental Health. https://www.nimh.nih.gov/health/publications/perinatal-depression. Accessed July 31, 2023. **11.** Thurgood S, et al. *Am J Clin Med*. 2009;6:17-22. **12.** Campbell J, et al. *J Womens Health*. 2021;30(2):236-244. **13.** Luca DL, et al. *Am J Public Health*. 2020;110(6):888-896. **14.** Epperson CN, et al. *Curr Med Res Opin*. 2020;36(10):1707-1716.

MRC-PPD-00693, Biogen-208280 08/2023

The Pathophysiology of Postpartum Depression (PPD) is Multifactorial[1]

The pathogenesis of PPD involves an interplay of genetic, biological, hormonal, environmental, and psychological factors[1]

Brain networks responsible for emotional regulation, mother-infant bonding, and maternal functioning may be dysregulated in PPD[2-4]



Depressive symptoms in PPD may result from dysregulated brain network activity in regions involved in key functions including mood, cognition, and motivation[1]

Multiple signaling pathways are hypothesized to contribute to PPD, including monoaminergic, glutamatergic, and GABAergic signaling pathways[1]

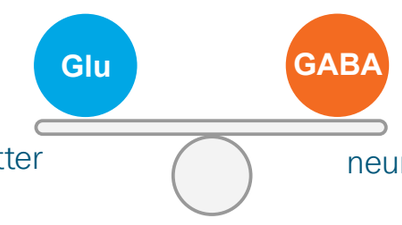
The monoamine hypothesis states that core pathophysiological features of depression include[12-14]:

- Imbalance of key monoaminergic functions
- Depletion of monoamine neurotransmitters
- Network signal dysregulation

Dysregulated monoaminergic signaling has been linked to PPD[1]

The **excitatory:inhibitory balance** in the brain is predominantly maintained by a balance between glutamatergic and GABAergic signaling[15]

Glutamate is the major **excitatory** neurotransmitter in the CNS[16]



GABA is the major **inhibitory** neurotransmitter in the CNS[16]

Dysregulation to the glutamatergic/GABAergic signaling balance is hypothesized to be a key feature associated with brain network dysregulation[1,8,17] and depression-related behaviors[18]

Impaired GABA system adaptability in response to changing neuroactive steroids during the peripartum period may contribute to PPD development[8,19,20]

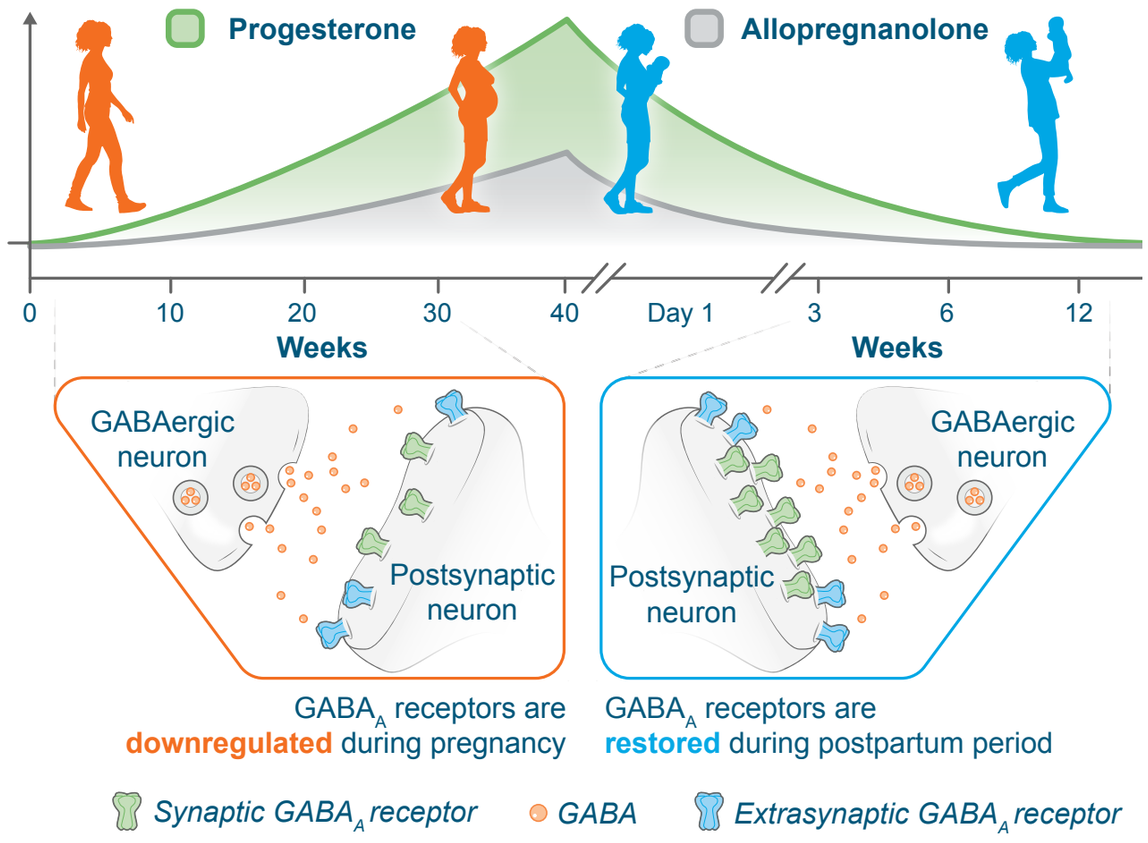
During pregnancy

- Endogenous neuroactive steroid (e.g. allopregnanolone) levels **increase**[8,17]
- In response, $GABA_A$ receptors are **downregulated** in some brain regions to avoid excessive neuronal inhibition[8,9]

At parturition

- Allopregnanolone levels **rapidly decline**[8,9]
- Subsequently, surface expression of $GABA_A$ receptors gradually **returns** to prepregnancy levels, thereby **restoring** the excitatory:inhibitory balance[8,9]

Disruption in the ability of the GABA system to adapt to changes in allopregnanolone levels during the peripartum period may mediate the onset of PPD symptoms[8,19,20]



CNS = central nervous system; GABA = γ-aminobutyric acid; Glu = glutamate; PPD = postpartum depression.

1. Payne JL, Maguire J. *Front Neuroendocrinol*. 2019;52:165-180. **2.** Moses-Kolko EL, et al. *Am J Psychiatry*. 2010;167(11):1373-1380. **3.** Morgan JK, et al. *Front Glob Womens Health*. 2021;2:744649. **4.** Silverman ME, et al. *CNS Spectr*. 2007;12(11):853-862. **5.** Ghaedrahmati M, et al. *J Educ Health Promot*. 2017;6:60. **6.** Couto TC, et al. *World J Psychiatry*. 2015;5(1):103-111. **7.** Meltzer-Brody S. *Dialogues Clin Neurosci*. 2011;13(1):89-100. **8.** Zorumski CF, et al. *Neurobiol Stress*. 2019;11:100196. **9.** Maguire J, et al. *J Neurosci*. 2009;29(30):9592-9601. **10.** American Psychiatric Association. Depressive disorders. In: *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed., Text Revision. American Psychiatric Publishing; 2022. **11.** National Institutes of Mental Health. https://www.nimh.nih.gov/health/publications/perinatal-depression. Accessed July 31, 2023. **12.** Li YF. *Pharmacol Ther*. 2020;208:107494. **13.** McEwen BS, et al. *Mol Psychiatry*. 2010;15(3):237-249. **14.** Otte C, et al. *Nat Rev Dis Primers*. 2016;2:16065. **15.** Fogaca MV, Duman RS. *Front Cell Neurosci*. 2019;13:87. **16.** Brosnan JT, Brosnan ME. *Amino Acids*. 2013;45(3):413-418. **17.** Maguire J. *Front Cell Neurosci*. 2019;13:83. **18.** Sarawagi A, et al. *Front Psychiatry*. 2021;12:637863. **19.** Mody I. *Cell*. 2019;176(1-2):1. **20.** Maguire J, Mody I. *Neuron*. 2008;59(2):207-213.

MRC-PPD-00693, Biogen-208280 08/2023