WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 2, 599-617. Review Article ISSN 2277– 7105

A REVIEW ON POST-PARTUM DEPRESSION

Dr. Satish S.*[1] and Aiswarya T. V.[2]

[1]Professor, Department of Pharmacology.

[2]Student, PharmD, Department of Pharmacy Practice, Srinivas College of Pharmacy, Mangalore, Karnataka-574143.

Article Received on
28 November 2022,

Revised on 18 Dec. 2022,
Accepted on 08 Jan. 2023,

DOI: 10.20959/wjpr20232-26973

***Corresponding Author**
Dr. Satish S.
Professor, Department of Pharmacology.

ABSTRACT

Postpartum depression (PPD) is a devastating mental disorder affecting 10-20% of new mothers. Psychiatric disorders always go unnoticed, even with the high prevalence. This review summarizes the variousanticipated pathophysiological mechanisms contributory to PPD, by highlighting clinical and basic science research findings. Additionally, the review discussed the risk factors, management, treatment, and biomarkers of PPD. This study aimed to review the related study on PPD and provide a current update on the concept, treatment, and future perspective. The extensive literature search was carried out using major search engines like PubMed, Embase, and Scopus using the Boolean operators. ProQuest, in the period 2012-2022, published articles with keywords post-partum depression, risk factors, treatment, pathophysiology, biomarkers, and management. Data generated from this current review can be used for developing a screening tool and a preventative program for high-risk pregnant women. The PPD mechanism study provides insight into the development of early diagnosis and treatment of the condition. The update on the PPD offers researchersthe voids that need to be filled in the area of diagnosis and management of the condition The current review provides an update on PPD. It also recommends prioritizing mental health care and carrying out more studies on the early identification of risk for the development of PPD. It is anticipated that emerging knowledge on pathophysiology and risk factors will lead to the developmentof new treatments for PPD.

KEYWORDS: Post-partum depression, Risk factors, Psychiatric disorder, Treatment, Management.

INTRODUCTION

Post-partum depression (PPD) is a debilitating understudied (clinically and experimentally). and underdiagnosed psychiatric disorders. PPD occurs in 6.5% to 20% of women in the postpartum period. Pregnancyand childbirth are crucialperiods in women's life. It upsurgespsychological, physiological, and social changes, which require adaptation and emotional support. Sometimes the intensities of these changes can negatively impact the mother to the extent thatapproximately 20% of mothers with PPD commit suicide.[1-2] PPDmanifests asfluctuations in mood, change in appetite, lack of interest in daily activities, sleep disorders, fear of harm, excessive concerns about the baby, grief, crying, doubt, trouble concentrating, and thoughts of death and suicide. Symptoms usually appear in the later period, andmost women conceal them because they feel terrible about being doomed when they are meant to be cheerful; hence PPD usually goes unnoticed. Mothers consider the birth of their child to be the happiest time of their lives. However, PPD creates many issues for the mother, child, and family, and it may damage the relationship between mother and child and the mother's learning of baby care and parenting role.[3-5]

There are three types of postpartum psychiatric disorders: post-partum blues, post-partum psychosis, and PPD. Post-partum blues affects 300–750/1000 mothers globally, typically resolve in a couple of days to a week, has minimal harmful consequences, and requires reassurance and comfort to the mothers. Post-partum psychosis has a global prevalence encompassing 0.89-2.6/1000 births. It is a severe condition that develops within four weeks of childbirth and necessitates hospitalization. PPD can develop soon after childbirth or as a result of prenatal depression and must be managed.[6]

PPD pathogenesis is yet unknown. It has been proposed that various factors like genetics, psychology, hormones, and stresses in one's social life play a role in the progressionof PPD. Alteration in multiple biological and endocrine systems can cause PPD. There is substantial evidence suggesting that changes in reproductive hormones cause dysregulation of certain depressive conditions in sensitive women. A quick change in reproductive hormones such as oestradiol and progesterone after childbirth can be a potential source of stress in sensitive women, leading to depressive symptoms. The major risk factors for PPD area history of despairand anxiety, risky pregnancy with emergency cesarean section and hospitalization, lack of social support, domestic violence and verbal abuse from the spouse, lifestyle like eating habits, sleep cycle, smoking and drinking habits and physical activities.[7-9] PPD can be

treated with antidepressants, psychotherapy, and hormone therapy. Light therapy and exercise are also commoninterventions adopted in the treatment. Physical activity has a significant influence on both the physical and mental well-being of pregnant mothers.[10] The American College of Obstetricians and Gynaecologists recommends weekly 2.5 hours of mild physical activity for pregnant women and after childbirth. Exercise during pregnancy enhances post-partum recovery and lowers depression symptoms. Physical activity during the post-partum period promotes blood circulation, strengthens the stomach and spine muscles, stimulates lactation, accelerates uterine contraction, reduces urogynaecological dysfunction, and enhances mothers' mental and physical health.[11]

PPD has evolved into a huge global health issue. Nonetheless, many women with this psychological disorder wentundiagnosed. According to World Health Organization (2021) over280 million individualswere affected by depression, but still, the condition is not taken seriously worldwide.[12]

Maternal mortality in India is steadily declining, which suggests that the present focus of care is to move towards minimizing maternal morbidity, even related to mental health illnesses. Worldwide much awareness of mental health and depression is rooted. Developing countries like India also prioritizea different kindsof mental health and related disorders. However, though India's national mental health program was established in 1982, maternal mental health remains a modest component. Maternal mental health treatments are severely underserved in healthcare facilities, and healthcare providers lack mental health training.[6] In outlying healthcare facilities, the availability of mental health experts is limited or non-existent. Furthermore, no screening tool is currently certified for clinical practice, and no information on the fraction of perinatal women with PPD is routinely gathered. The current review aims at extensive literature on PPD, its pathophysiology, risk factor management, and treatment.

PATHOPHYSIOLOGY

As previously mentioned, the pathophysiology of PPD is highly multifaceted and not entirelyunderstood. However, there is some indication that PPD is acompositeinterface of social, psychological, and biological elements, together with the effect of hereditary and environmental factors.

Hormones

Hormones usuallyregulate various biological systems linked to depression, like thyroid hormones, lactogenic hormones, the hypothalamic–pituitary–adrenal axis, the immunological system, and genetic expression.[14] Pregnancy is a roller coaster of hormones, gonadal hormones (estrogen and progesterone) are generated at extremely high levels through pregnancy and on the contrary, suddenly decline after childbirth. Multiple sources of evidence have stated that alteration in ovarian hormones during pregnancy can contribute to developing post-partum mood disorders in women. Moreover, several brain imaging investigations have indicated that gonadal hormones modify the neurocircuitry associated with normal and pathological emotional states[15] Reproductive hormones have essential functions in the brain and spinal cord; hormone receptors are situated throughout the brain tocontrol neurotransmission and neuroplasticity through both genomic-related and non-genomic-related mechanisms.[16] A review conductedby Stewart etal.says that changes in reproductive hormone levelscan provoke affective dysregulation, particularly in women with a hereditary predisposition.[15]

The neurosteroid allopregnanolone (progesterone metabolite) is a positive allosteric modulator of γ-aminobutyric acid (GABA) receptors and lowers anxiety and depression symptoms significantly in animal models. The rapid decrease in allopregnanolone concentrations following childbirth induces trouble in GABA adaptations, triggering PPD.[14,17-19] This hypothesis also led light towards brexanolonedevelopment, an exclusive formulation of allopregnanolone that can be used in treating PPD.[20-21] The childbirth and lactation hormone oxytocin also displays an inverse with PPD; however, there are not many studies to justify its role.[22]

Recent neuroimaging data displayed the significance of sex steroids in controllingbehavioralchanges related to psychiatric diseases, such as affective processing, cognition, stimulation, and motivation. Multiple brain regions (cortical and subcortical) have different activities, which can be seen by functional MRI/PET in moms with depression to infants'emotional signals. Furthermore, functional MRI has revealed different brain patterns that separate anxiety and depression during the perinatal period from other times in adult female life. These specificoutlines might significantly affect the mother–infant relationship.[23,13]

Genetics

Data from various research implicated that genetics is also a potential factor in the pathophysiology of PPD. Compelling evidence from genetic epidemiological and linkage studies has demonstrated the involvement of genetic variables in PPD and its enhanced heritability compared to depression occurring other thanthe perinatal period.[24] The potential gene identified for PPDisVal66Met polymorphism, serotonin transporter gene, tryptophan hydroxylase- gene, monoamine Oxidase, COMT, and BDNF gene which is widely studied in major depressive disorder.[25-26] More than 1,200 women participated in genome-wide linkage studies, which revealed genetic varianceson chromosome 1q21.3–q32.1 and 9p24.3–p22.3 and in Hemicentin-1, which includes severalestrogen-binding sites and concurrently appear to upsurgewomen's vulnerability to PPD.[24] An epigenetic study demonstrated HP1BP3 and TTC9B genes, have diverse methylation patterns in PPD individuals based on the time of symptom development.[27-28] However, these preliminary findings necessitate replication, and overall, the mechanism of action in PPD remains to be established. PPD has also been linked to estrogen-induced epigenetic DNA methylation alterations. An outstanding systematic review of the genetics implicated with PPD has been published; nevertheless, these conclusions will need to be confirmed by bigger independent research.[29] Genomics is a blooming and still expanding area, genome-wide association research using contemporary genomics methods has not been conductedyet for PPD and may require several global collaborations and associations to absorbmany patients. Positively, these kinds of studies are presently in progress.

Immune Function

An accelerated immune response characterizes the transition from pregnancy into the post-partum period.[30] Consequently, alterations in immunity at the end of pregnancy may predict PPD. Women with PPD, appear to have diverse gene expression that is functionally associatedwith the body's immune system.[31] In some but not all studies, IL-6 levels are higher in PPD individuals compared to postpartum women without depression. Furthermore, leptin a protein hormone with inflammatory functions may also be linked to PPD, and lower levels of serum leptin before delivery are linked to aincreased risk of PPD.[32]

Considering studies on many prenatal immunological indicators of PPD have yielded inconsistent results, the role of immune function in PPD remains uncertain. In conclusion, it is believed that the disruption of the crosstalk amid the immunological components and the

HPA stress axis is connected with the beginning of PPD. Future research is required to better comprehend how exactly psychological and biological factors interact in PPD.[33]

Psychosocial factors

Social and psychological stressors ignite the development of PPD and are linked to lower newborn or child outcomes. A history of unfavorable early life events can significantly impact a mother's capability to form a strong connection with her newborn infant. Adverse life events and a history of trauma are more common in women who progress post-partum mood disorders than in women who develop mood disorders outside of the perinatal period. Social support can contribute to mitigating the effects of PPD on the mother and child. The degree of tangible care provided by the mother's social network and the partner tends to have the greatest effects on PPD when compared toother psychosocial risk factors. There is a medium-to-strong association of PPDs with marital complications, migration status, and antenatal depression. PPD is also connected with poverty, age(early pregnancy), substance abuse, higher parity, multiple births, an undesired pregnancy, pregnancy issues, obesity, neuroticism, andnewborn disorders.[34-36]

Sleep disruption

Sleep is significantly disturbedthroughout the perinatal as well post-partum period. Pregnancy is subject to poorer sleep quality, increased rousing, and moresleep–wake transitions. Similarly, new moms have recurrent night waking, reducednighttime sleep, nappingin daytime, and an inconsistent sleep pattern, all of which are thought to raise the risk of PPD.[37-38]

Sleep and circadian rhythm disturbance can also trigger the commencement of psychiatric disorders in the post-partum period, especially manic episodes. As a result, it is surprising that circadian rhythm disturbance has not gotten greater attention as a potential cause of PPD.[39] According to recent studies, sleep issues are linked to PPD. Given that poor sleep is a DSM-V (American Psychiatric Association) diagnostic criterion for depression, it is critical to study poor sleep and depression at various periods to uncover a potential causative link between variations in sleep and the emergence of PPD.[40]

A study found that sleep complications in pregnancy and the early post-partum period are related to advanced depressivesymptoms at 17–36 weeks after childbirth.[41] Another study by Okun and colleaguesexamined the effect of poor sleep on depressionamong post-partum

women and the efficacy of the antidepressant medication. Participants completed the Pittsburgh Sleep Quality Index(PSQI), and the Hamilton Rating Scale for Depression, through the first 17 weeks post-partum. The study results revealed that increases in the PSQI (indicating inadequate sleep) were linked to a high rate of depression.[42]

Further investigation into the underlying mechanisms that interrupted maternal sleep patterns during the perinatal period revealed reduced melatonin amplitude in post-partum women compared to non-pregnant women, as well as differences in circadian rhythms among perinatal women with and without depression.

Risk factors

The thorough assessment of the literature highlighted the five domains of risk factors involved in PPD, which are represented in the figure and the table below (Table 1)

Table 1: Putative risk factors of Postpartum depression.

Domain	Risk factors
Social factors	Number of children born[43]
	Sexual and domestic violence[44]
	Education and low income[45-46]
Psychological factors	Reluctance to reveal the gender of the baby and lack of self-esteem[47-48]
	Poor social support and neuroticism[48]
	History of moderate to severe premenstrual syndrome[49]
Obstetric factors	PPD is greater in multiparous women[50]
	Labour complications likeumbilical cord prolapse, meconium passage, & obstetric hemorrhages[51-52]
	Mothers who gave birth to a baby weighing less than 1500 g[53]
	Breastfeeding negatively affects PPD[54]
	Low hemoglobin level[55]
Biological factors	Pregnancy age of below 25 and above 35[56]
	Vitamin D status[57]
	Serotonin and tryptophan levels and nutritional deficiencies[58]
	Glucose metabolism disorders[59]
	Alteration in hormonal levels[60]
Lifestyle	Nutritional balance[61]
	Sleep[62]
	Rate of fatigue[63]
	Exercise and physical activity[64]
	Smoking[65]

MANAGEMENT

PPDmanagement necessitates a thorough, typically multidisciplinary strategy. Education on PPD can motivate people to seek help and promote early detection of symptoms.

Psychosocial measures to boost self-care, improve practical and emotional support, and limit the occurrence and/or impact of unpleasant life events or stressors are indicated for all women after the diagnosis is made and comorbid medical and psychiatric disorders are addressed.[66]

Non-pharmacologic therapies

In individuals with mild to moderate peripartum depression, psychotherapy is viewedas the first-line treatment, however, in patients with severe symptoms, psychotherapy is frequently coupled with medicines. Most data support the effectiveness of cognitive behavior therapy. Participation in partner psychotherapy may also seem to improve symptom scores.[67]

There is evidence that aerobic exercise and infant behavioral sleep therapies that result in more maternal sleep can reduce PPD symptoms and increase maternal happiness. Women with minor symptoms may benefit from psychosocial measures such as peer support or nondirective counseling from a professional on their own.[66]

Other approaches to treatment with hormone therapies have been investigated. In one short study, transdermal estrogen treatment improved PPD symptoms, although further research is needed. Postpartum depression symptoms were exacerbated by progestin therapy.[68] One experiment found that allopregnanolone outperformed placebo in alleviating depressed symptoms in 21 women with severe PPD, but further research is needed.[21]

Evidence for CAM treatments (such as massage and acupuncture) is lacking.[69] In severe or treatment-refractory condition of depression, electroconvulsive therapy (ECT) may be considered. ECT is not an attractive option for most women because it needs a general anesthetic and might have negative effects like memory impairment.[15]

Pharmacological therapies

Antidepressants including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) are the mainstay of drug therapy for post-partum anxiety and depression disorders. These treatment lines can be used on their own or in conjunction with psychosocial or psychological components[13].SSRIs are the foundation of moderate to severe peripartum depression therapy.In a systematic study, patients receiving SSRIs had a considerably greater pooled remission rate (46.0%) than those getting a placebo (25.7%).[70] In anRCT comparing common antidepressants with community-based

psychosocial intervention based treatment for PPD, SSRIs were found to be superior.[71] Although there is no sufficient evidence to support the use of one SSRI over another, there are a few factors to consider before choosing an agent. If the patient has a history of responding to a certain SSRI, it is fair to commence with that medicine.[72]

There has been no research into the duration of antidepressant therapy required for new-onset PPD, anxiety, or a similar disorder. Nonetheless, practitioners are advised to follow general population standards for these illnesses. The treatment course for depression should be carried out for 6 months to 1 year following remission; extended periods are essential for severe and/or recurring illness.[73]

Concerning the use of antidepressants during breastfeeding, theroute of SSRIs and SNRIs into breast milk varies between drugs. However, most transfer into breast milk at 10% of the maternal dose, which is safe for breastfeeding. Sertraline is frequently advised as a first-line pharmacological treatment for new-onset PPD due to its low transit into breast milk. However, in individuals with a history of psychiatric illnesses, medications that have previously demonstrated benefit, including those with less data on safety while nursing, should be evaluated. Other SSRIs, SNRIs, and mirtazapine (an unusual antidepressant) have negligible transit into breast milk and are hence unlikely to be a reason for concern. Older antidepressants and/or additional therapies, such as benzodiazepines or antipsychotics, may be indicated in cases of severe depression.[74,13]

Biomarkers for PPD

A range of biomarkers, including neuroendocrine, epigenetic, and neuroinflammatory biomarkers, have been proposed as potential identifiers for patients at risk for PPD. However, many of these biomarkers have not been repeated across studies, which may be attributable to patient population variability.[75]

The separate steady conducted by Wójcik et al.[76] and Roomruangwong et al.[77] revealed aassociation between the severity of common depressive symptoms and reduced serum zinc concentration. Due to the regulatory function of vitamin D in the immune system can act as a neurosteroid, making it a potential candidate as a PPD biomarker.[78] Christesen et al.[79] in their study showed low serum level of vitamin D during pregnancy mightbe responsible for PPD. Brandenburg et al.[80] reported that poor early-pregnancy vitamin D status was linked to increased depressive symptoms during pregnancy. Gur et al.[81] discovered that lower

maternal 25(OH) D3 levels were connected with greater levels of PPD at all time points, suggesting that PPD development may be influenced by this factor.

A corresponding study conducted by Robinson et al.[82] also observedmoderately low vitamin D in pregnancy as a risk factor for developing PPD-related symptoms. A cross-sectional study.[83] showed large amount of dietary intake ofvitamin D directly correlated with the lower occurrence of depressive symptoms throughout pregnancy. Another prospective study discovered a link between lower prenatal log 25(OH)D levels and considerably worse PPD symptoms in women with greater levels of inflammatory markers.[84] Fu et al. [85] discovered a link amid lower serum 25(OH)D levels and PPD in a controlled trial. High kynurenine levels have also been linked to depression induction. Increased catabolism of tryptophan (T) into kynurenine (K) is associated with depressive and anxiety symptoms in the early puerperium, and increases in plasma kynurenine and the K/T ratio were positively correlated with both depression and anxiety ratings in the puerperium.[86]

Since there is the existence of coordination between the gut and brain, the gut microbiome could be the potential biomarker of PPD. There are few studies, and therefore not much has been known concerning what role the gut-brain axis might play in developing PPD. A result of a study comprising 400 pregnant women,[87] revealed that probiotic intervention with *Lactobacillus rhamnosus* in pregnancy and post-partum period reduces the incidence of PPD in women.

Metabolomics was recently used to determine the body fluid metabolomic profile of PPD.A case-control study conducted in Greece on ten women with PPD and a healthy control (HC) group (n = 10) found five increased levels of five metabolites in the case group.[88] A metabolomic profiling of urine samples of females with PPD, post-partum women without depression (PPWD), and HCs should that 22 differential metabolites. Among them 14 were up-regulated and 8 were down-regulated and has the ability to discrete PPD individuals from both HCs and PPWD group.[89] Recently, Zhang et al.[90] discovered that the urine metabolomic profiles of PPD patients differed from those of healthy controls. Ten distinguishing metabolites were discovered to be the primary contributors to this variance.

It is also vital to recognize the limitations of biomarker identification, such as patient population variability, restricted availability of samples (mostly circulating components in the

blood), and a reduced amount of control over experimental circumstances in the clinical sector.

CONCLUSIONS

PPD is a severe health concern for new mothers, with negative repercussions for mothers and children. Because of its wide frequency, it creates serious public health issues. A wide range of risk factors, counting biological, psychological, and even environmental factors, are likely to influence PPD. PPD has several etiological theories. So far, no agreement has been achieved. Psychotherapy and pharmacotherapy, in the form of counseling and antidepressant drugs, are common therapies for PPD. It also recommends prioritizing mental health care and carrying out more studies on the early identification of risk for the development of PPD. It is anticipated that increased knowledge on pathophysiology and risk factors will lead to the formation of new PPD treatments.

REFERENCES

1. Lindahl V, Pearson JL, Colpe L. Prevalence of suicidality during pregnancy and the post-partum. Archives of Women's Mental Health, 2005; 8(2): 77-87.
2. Öztora S, Arslan A, Caylan A, Dağdeviren HN. Post-partum depression and affecting factors in primary care. Nigerian journal of clinical practice, 2019; 22(1).
3. Ghaedrahmati M, Kazemi A, Kheirabadi G, Ebrahimi A, Bahrami M. Postpartum depression risk factors: A narrative review. Journal of education and health promotion, 2017; 6.
4. Norhayati MN, Hazlina NN, Asrenee AR, Emilin WW. Magnitude and risk factors for post-partum symptoms: a literature review. Journal of affective Disorders, 2015; 175: 34-52.
5. Qobadi M, Collier C, Zhang L. The effect of stressful life events on post-partum depression: Findings from the 2009–2011 Mississippi pregnancy risk assessment monitoring system. Maternal and child health journal, 2016 Nov; 20(1): 164-72.
6. Upadhyay RP, Chowdhury R, Salehi A, Sarkar K, Singh SK, Sinha B, Pawar A, Rajalakshmi AK, Kumar A. Postpartum depression in India: a systematic review and meta-analysis. Bulletin of the World Health Organization, 2017 Oct 10; 95(10): 706.
7. Mughal S, Azhar Y, Siddiqui W. Postpartum depression. InStatPearls [Internet], 2022 Jul 20. StatPearls Publishing.

8. Robertson E, Celasun N, Stewart DE. Risk factors for post-partum depression. Post-partum depression: Literature review of risk factors and interventions, 2003; 9-70.
9. Stewart DE, Robertson E, Dennis CL, Grace SL, Wallington T. Postpartum depression: Literature review of risk factors and interventions. Toronto: University Health Network Women's Health Program for Toronto Public Health, 2003; 1-289.
10. Fitelson E, Kim S, Baker AS, Leight K. Treatment of post-partum depression: clinical, psychological and pharmacological options. International journal of women's health, 2010 Dec 30: 1-4.
11. Kołomańska-Bogucka D, Mazur-Bialy AI. Physical activity and the occurrence of postnatal depression—a systematic review. Medicina, 2019; 55(9): 560.
12. https://www.who.int/news-room/fact-sheets/detail/depression
13. Meltzer-Brody S, Howard LM, Bergink V, Vigod S, Jones I, Munk-Olsen T, Honikman S, Milgrom J. Postpartum psychiatric disorders. Nature Reviews Disease Primers, 2018; 4(1): 1-8.
14. Schiller CE, Meltzer-Brody S, Rubinow DR. The role of reproductive hormones in post-partum depression. CNS spectrums, 2015; 20(1): 48-59.
15. Stewart DE, Vigod SN. Post-partum depression: pathophysiology, treatment, and emerging therapeutics. Annual review of medicine, 2019; 70: 183-96.
16. Sohrabji F, Miranda RC, Toran-Allerand CD. Estrogen differentially regulates estrogen and nerve growth factor receptor mRNAs in adult sensory neurons. Journal of Neuroscience, 1994; 14(2): 459-71.
17. Majewska MD, Harrison NL, Schwartz RD, Barker JL, Paul SM. Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor. Science, 1986; 232(4753): 1004-7.
18. Luisi S, Petraglia F, Benedetto C, Nappi RE, Bernardi F, Fadalti M, Reis FM, Luisi M, Genazzani AR. Serum allopregnanolone levels in pregnant women: changes during pregnancy, at delivery, and in hypertensive patients. The Journal of Clinical Endocrinology & Metabolism, 2000; 85(7): 2429-33.
19. Nappi RE, Petraglia F, Luisi S, Polatti F, Farina C, Genazzani AR. Serum allopregnanolone in women with post-partum "blues". Obstetrics &Gynecology, 2001; 97(1): 77-80.
20. Kanes SJ, Colquhoun H, Doherty J, Raines S, Hoffmann E, Rubinow DR, Meltzer-Brody S. Open-label, proof-of-concept study of brexanolone in the treatment of severe post-

partum depression. Human Psychopharmacology: Clinical and Experimental, 2017; 32(2): e2576.

21. Kanes S, Colquhoun H, Gunduz-Bruce H, Raines S, Arnold R, Schacterle A, Doherty J, Epperson CN, Deligiannidis KM, Riesenberg R, Hoffmann E. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. The Lancet, 2017; 390(10093): 480-9.
22. Cox EQ, Stuebe A, Pearson B, Grewen K, Rubinow D, Meltzer-Brody S. Oxytocin and HPA stress axis reactivity in post-partum women. Psychoneuroendocrinology, 2015; 55: 164-72.
23. Wei, S.M., Baller, E.B., Kohn, P.D., Kippenhan, J.S., Kolachana, B., Soldin, S.J., Rubinow, D.R., Schmidt, P.J. and Berman, K.F., 2018. Brain-derived neurotrophic factor Val66Met genotype and ovarian steroids interactively modulate working memory-related hippocampal function in women: a multimodal neuroimaging study. *Molecular Psychiatry*, *23*(4): 1066-1075.
24. Mahon PB, Payne JL, MacKinnon DF, Mondimore FM, Goes FS, Schweizer B, Jancic D, NIMH Genetics Initiative Bipolar Disorder Consortium, BiGS Consortium, Coryell WH, Holmans PA. Genome-wide linkage and follow-up association study of post-partum mood symptoms. American Journal of Psychiatry, 2009; 166(11): 1229-37.
25. Wei, S.M., Baller, E.B., Kohn, P.D., Kippenhan, J.S., Kolachana, B., Soldin, S.J., Rubinow, D.R., Schmidt, P.J. and Berman, K.F., Brain-derived neurotrophic factor Val66Met genotype and ovarian steroids interactively modulate working memory-related hippocampal function in women: a multimodal neuroimaging study. *Molecular Psychiatry*, 2018; *23*(4): 1066-1075.
26. Payne JL, Maguire J. Pathophysiological mechanisms implicated in post-partum depression. Frontiers in neuroendocrinology, 2019; 52: 165-80.
27. Osborne L, Clive M, Kimmel M, Gispen F, Guintivano J, Brown T, Cox O, Judy J, Meilman S, Braier A, Beckmann MW. Replication of epigenetic post-partum depression biomarkers and variation with hormone levels. Neuropsychopharmacology, 2016; 41(6): 1648-58.
28. Guintivano J, Arad M, Gould TD, Payne JL, Kaminsky ZA. Antenatal prediction of post-partum depression with blood DNA methylation biomarkers. Molecular psychiatry, 2014 May; 19(5): 560-7.

29. e Couto TC, Brancaglion MY, Alvim-Soares A, Moreira L, Garcia FD, Nicolato R, Aguiar RA, Leite HV, Corrêa H. Postpartum depression: A systematic review of the genetics involved. World journal of psychiatry, 2015; 5(1): 103.
30. NILSEN-HAMILTON MA, Liu Q, Ryon J, Bendickson LE, Lepont P, Chang Q. Tissue involution and the acute phase response. Annals of the New York Academy of Sciences, 2003; 995(1): 94-108.
31. Segman RH, Goltser-Dubner T, Weiner I, Canetti L, Galili-Weisstub E, Milwidsky A, Pablov V, Friedman N, Hochner-Celnikier D. Blood mononuclear cell gene expression signature of post-partum depression. Molecular psychiatry, 2010; 15(1): 93-100.
32. Skalkidou, A., Sylvén, S.M., Papadopoulos, F.C., Olovsson, M., Larsson, A. and Sundström-Poromaa, I., Risk of post-partum depression in association with serum leptin and interleukin-6 levels at delivery: A nested case–control study within the UPPSAT cohort. *Psychoneuroendocrinology*, 2009; *34*(9): 1329-1337.
33. Corwin EJ, Pajer K, Paul S, Lowe N, Weber M, McCarthy DO. Bidirectional psychoneuroimmune interactions in the early post-partum period influence risk of post-partum depression. Brain, behavior, and immunity, 2015; 49: 86-93.
34. Gonzalez A, Jenkins JM, Steiner M, Fleming AS. Maternal early life experiences and parenting: The mediating role of cortisol and executive function. Journal of the American Academy of Child & Adolescent Psychiatry, 2012; 51(7): 673-82.
35. XIE RH, Yang J, Liao S, Xie H, Walker M, Wen SW. Prenatal family support, postnatal family support and post-partum depression. Australian and new zealand journal of obstetrics and gynaecology, 2010 Aug; 50(4): 340-5.
36. Howard LM, Molyneaux E, Dennis CL, Rochat T, Stein A, Milgrom J. Non-psychotic mental disorders in the perinatal period. The Lancet, 2014; 384(9956): 1775-88.
37. Marques M, Bos S, Soares MJ, Maia B, Pereira AT, Valente J, Gomes AA, Macedo A, Azevedo MH. Is insomnia in late pregnancy a risk factor for post-partum depression/depressive symptomatology?. Psychiatry research, 2011; 186(2-3): 272-80.
38. Parry, B.L., Meliska, C.J., Sorenson, D.L., Lopez, A.M., Martinez, L.F., Nowakowski, S., Elliott, J.A., Hauger, R.L. and Kripke, D.F., 2008. Plasma melatonin circadian rhythm disturbances during pregnancy and post-partum in depressed women and women with personal or family histories of depression. *American Journal of Psychiatry*, *165*(12): 1551-1558.
39. Lewis KJ, Foster RG, Jones IR. Is sleep disruption a trigger for post-partum psychosis?. The British Journal of Psychiatry, 2016; 208(5): 409-11.

40. American Psychiatric Association. Diagnostic and statistical manual for mental disorders. DSM-IIIR, 1987; 3-24.
41. Thomas KA, Spieker S. Sleep, depression, and fatigue in late post-partum. MCN. The American journal of maternal child nursing, 2016; 41(2): 104.
42. Miguel-Hidalgo JJ, Waltzer R, Whittom AA, Austin MC, Rajkowska G, Stockmeier CA. Glial and glutamatergic markers in depression, alcoholism, and their comorbidity. Journal of affective disorders, 2010; 127(1-3): 230-40.
43. Lee DT, Yip AS, Leung TY, Chung TK. Identifying women at risk of postnatal depression: prospective longitudinal study. Hong Kong Med J., 2000 Dec 1; 6(4): 349-54.
44. Ludermir AB, Lewis G, Valongueiro SA, de Araújo TV, Araya R. Violence against women by their intimate partner during pregnancy and postnatal depression: a prospective cohort study. The Lancet, 2010; 376(9744): 903-10.
45. Huang T, Rifas-Shiman SL, Ertel KA, Rich-Edwards J, Kleinman K, Gillman MW, Oken E, James-Todd T. Pregnancy hyperglycaemia and risk of prenatal and post-partum depressive symptoms. Paediatric and perinatal epidemiology, 2015 Jul; 29(4): 281-9.
46. Chien LY, Tai CJ, Yeh MC. Domestic decision-making power, social support, and post-partum depression symptoms among immigrant and native women in Taiwan. Nursing research, 2012 Mar 1; 61(2): 103-10.
47. Lee DT, Yip AS, Leung TY, Chung TK. Identifying women at risk of postnatal depression: prospective longitudinal study. Hong Kong Med J., 2000 Dec 1; 6(4): 349-54.
48. Leigh B, Milgrom J. Risk factors for antenatal depression, postnatal depression and parenting stress. BMC psychiatry, 2008 Dec; 8(1): 1-1.
49. Buttner MM, Mott SL, Pearlstein T, Stuart S, Zlotnick C, O'Hara MW. Examination of premenstrual symptoms as a risk factor for depression in post-partum women. Archives of women's mental health, 2013 Jun; 16(3): 219-25.
50. Mayberry LJ, Horowitz JA, Declercq E. Depression symptom prevalence and demographic risk factors among US women during the first 2 years post-partum. Journal of Obstetric, Gynecologic& Neonatal Nursing, 2007 Nov 1; 36(6): 542-9.
51. Mathisen SE, Glavin K, Lien L, Lagerløv P. Prevalence and risk factors for post-partum depressive symptoms in Argentina: a cross-sectional study. International journal of women's health, 2013; 5: 787.
52. Gaillard A, Le Strat Y, Mandelbrot L, Keïta H, Dubertret C. Predictors of post-partum depression: Prospective study of 264 women followed during pregnancy and post-partum. Psychiatry Res., 2014; 215: 341-6.

53. Helle N, Barkmann C, Bartz-Seel J, Diehl T, Ehrhardt S, Hendel A, et al. Very low birth-weight as a risk factor for post-partum depression four to six weeks postbirth in mothers and fathers: Cross-sectional results from a controlled multicentre cohort study. J Affect Disord, 2015; 180: 154-61.
54. Figueiredo B, Canário C, Field T. Breastfeeding is negatively affected by prenatal depression and reduces post-partum depression. Psychol Med, 2014; 44: 927-36. Back to cited text no. 29
55. Corwin EJ, Murray-Kolb LE, Beard JL. Low hemoglobin level is a risk factor for post-partum depression. J Nutr, 2003; 133: 4139-42.
56. Choo, C. C., Harris, K. M., Chew, P. K. H., & Ho, R. C. What predicts medical lethality of suicide attempts in Asian youths? *Asian Journal of Psychiatry*, 2017; 29: 136– 141.
57. Nielsen NO, Strøm M, Boyd HA, Andersen EW, Wohlfahrt J, Lundqvist M, Cohen A, Hougaard DM, Melbye M. Vitamin D status during pregnancy and the risk of subsequent post-partum depression: a case-control study. PloS one, 2013 Nov 27; 8(11): e80686.
58. Ghaedrahmati M, Kazemi A, Kheirabadi G, Ebrahimi A, Bahrami M. Postpartum depression risk factors: A narrative review. Journal of education and health promotion, 2017; 6.
59. Huang T, Rifas-Shiman SL, Ertel KA, Rich-Edwards J, Kleinman K, Gillman MW, *et al. Pregnancy hyperglycaemia and risk of prenatal and post-partum depressive symptoms. Paediatr Perinat Epidemiol, 2015; 29: 281-9.*
60. Kk.
61. Jjj.
62. Ross LE, Murray BJ, Steiner M. Sleep and perinatal mood disorders: a critical review. Journal of Psychiatry and Neuroscience, 2005 Jul 1; 30(4): 247-56.
63. Zinga D, Phillips SD, Born L. Postpartum depression: we know the risks, can it be prevented?. Brazilian Journal of Psychiatry, 2005; 27: s56-64.
64. Dinas PC, Koutedakis Y, Flouris AD. Effects of exercise and physical activity on depression. Irish journal of medical science, 2011 Jun; 180(2): 319-25.
65. Gurber S, Baumeler L, Grob A, Surbek D, Stadlmayr W. Antenatal depressive symptoms and subjective birth experience in association with post-partum depressive symptoms and acute stress reaction in mothers and fathers: A longitudinal path analysis. Eur J ObstetGynecolReprod Biol., 2017; 215: 68-74.
66. Stewart DE, Vigod SN. Post-partum depression: pathophysiology, treatment, and emerging therapeutics. Annual review of medicine, 2019 Jan 27; 70: 183-96.

67. Langan RC, Goodbred AJ. Identification and management of peripartum depression. American family physician, 2016 May 15; 93(10): 852-8.
68. Dennis, C. L., Ross, L. E. &Herxheimer, A. Oestrogens and progestins for preventing and treating post-partum depression. *Cochrane Database Syst. Rev.*, 2008; 4: CD001690.
69. Deligiannidis, K. M. & Freeman, M. P. Complementary and alternative medicine therapies for perinatal depression. *Best Pract. Res. Clin. Obstet. Gynaecol*, 2014; 28: 85–95.
70. Molyneaux E, Howard LM, McGeown HR, Karia AM, Trevillion K. Antidepressant treatment for postnatal depression. *Cochrane Database Syst Rev*., 2014; (9): CD002018.
71. Sharp DJ, Chew-Graham C, Tylee A, et al. A pragmatic randomised controlled trial to compare antidepressants with a community-based psychosocial intervention for the treatment of women with postnatal depression: the RESPOND trial. *Health Technol Assess*, 2010; 14(43): iii-iv.
72. Wisner KL, Parry BL, Piontek CM. Clinical practice. Post-partum depression. *N Engl J Med*, 2002; 347(3): 194-199.
73. Lam, R. W. et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder. Section 1. Disease Burden and Principles of Care. *Can. J. Psychiatry*, 2016; 61; 510–523.
74. Orsolini, L. &Bellantuono, C. Serotonin reuptake inhibitors and breastfeeding: a systematic review. *Hum. Psychopharmacol*, 2015; 30, 4–20.
75. Payne JL, Maguire J. Pathophysiological mechanisms implicated in post-partum depression. Frontiers in neuroendocrinology, 2019 Jan 1; 52: 165-80.
76. Wójcik J, Dudek D, Schlegel-Zawadzka M. Antepartum, post-partum depressive symptoms and serum Zn and Mg levels. *Pharmacol Rep.*, 2006; 58: 571–576.
77. Roomruangwong C, Kanchanatawan B, Sirivichayakul S, Mahieu B, Nowak G, Maes M. Lower serum zinc and higher CRP strongly predict prenatal depression and physio-somatic symptoms, which all together predict prenatal depressive symptoms. *Mol Neurobiol*, 2016.
78. Eyles D, Burne T, McGrath J. Vitamin D: a neurosteroid affecting brain development and function; implications for neurological and psychiatric disorders. InVitamin D Jan 1 (pp. 565-582). Academic Press, 2011.
79. Christesen HT, Falkenberg T, Lamont RF, JØrgensen JS. The impact of vitamin D on pregnancy: a systematic review. *Acta ObstetGynecol Scand*, 2012; 91: 1357–67. doi: 10.1111/aogs.12000.

80. Brandenbarg J, Vrijkotte TGM, Goedhart G, van Eijsden M. Maternal early-pregnancy vitamin d status is associated with maternal depressive symptoms in the amsterdam born children and their development cohort. *Psychosom Med*, 2012; 74: 751–7. doi: 10.1097/PSY.0b013e3182639fdb
81. Gur EB, Gokduman A, Turan GA, Tatar S, Hepyilmaz I, Zengin EB, et al. Mid-pregnancy vitamin D levels and post-partum depression. *Eur J ObstetGynecolReprod Biol.*, 2014; 179: 110–6. doi: 10.1016/j.ejogrb.2014.05.017.
82. Robinson M, Whitehouse AJO, Newnham JP, Gorman S, Jacoby P, Holt BJ, et al. Low maternal serum vitamin D during pregnancy and the risk for post-partum depression symptoms. *Arch WomensMent Health*, 2014; 17: 213–9. doi: 10.1007/s00737-014-0422-y
83. Miyake Y, Tanaka K, Okubo H, Sasaki S, Arakawa M. Dietary vitamin D intake and prevalence of depressive symptoms during pregnancy in Japan. *Nutrition*, 2015; 31: 160–5. doi: 10.1016/j.nut.2014.06.013.
84. Accortt EE, Schetter CD, Peters RM, Cassidy-Bushrow AE. Lower prenatal vitamin D status and post-partum depressive symptomatology in African American women: preliminary evidence for moderation by inflammatory cytokines. *Arch WomensMent Health*, 2016; 19: 373–83. doi: 10.1007/s00737-015-0585-1
85. Fu C-W, Liu J-T, Tu W-J, Yang J-Q, Cao Y. Association between serum 25-hydroxyvitamin D levels measured 24 hours after delivery and post-partum depression. *BJOG.*, 2015; 122: 1688–94. doi: 10.1111/1471-0528.13111
86. Maes M, Verkerk R, Bonaccorso S, Ombelet W, Bosmans E, Scharpé S. Depressive and anxiety symptoms in the early puerperium are related to increased degradation of tryptophan into kynurenine, a phenomenon which is related to immune activation. *Life Sci.*, 2002; 71: 1837–48. doi: 10.1016/S0024-3205(02)01853-2
87. Slykerman RF, Hood F, Wickens K, Thompson JMD, Barthow C, Murphy R, et al. Effect of lactobacillus rhamnosus HN001 in pregnancy on post-partum symptoms of depression and anxiety: a randomised double-blind placebo-controlled trial. *EBioMedicine*, 2017; 24: 159–65. doi: 10.1016/j.ebiom.2017.09.013
88. Papadopoulou Z, Vlaikou AM, Theodoridou D, Komini C, Chalkiadaki G, Vafeiadi M, et al. Unraveling the serum metabolomic profile of post-partum depression. *Front Neurosci*, 2019; 13: 1–9. doi: 10.3389/fnins.2019.00833.
89. Lin L, Chen XM, Liu RH. Novel urinary metabolite signature for diagnosing post-partum depression. *Neuropsychiatr Dis Treat*, 2017; 13: 1263–70. doi: 10.2147/NDT.S135190

90. Zhang L, Zou W, Huang Y, Wen X, Huang J, Wang Y, et al. A preliminary study of uric metabolomic alteration for post-partum depression based on liquid chromatography coupled to quadrupole time-of-flight mass spectrometry. *Dis Markers*, 2019; 2019: 1–9. doi: 10.1155/2019/4264803.