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Review Article

A Molecular Survey of Postpartum Depression

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Received: May 14, 2024; **Published:** May 24, 2024

DOI: 10.31080/ECGY.2024.13.00976

Abstract

Postpartum depression (PPD) or baby blue refers to conditions in new mothers who experience depression, mood swings, and desperation. Affecting as many as 85% of mothers post-delivery, PPD is a serious health concern, especially in some vulnerable populations, precipitating postpartum psychosis leading to confusion, cognitive impairment, delusion, and disorganized behaviour. Left untreated, these may lead to suicidal episodes in some extreme situations. The first FDA-approved drug for PPD was brexanolone in 2019, which is infused over three days under medical supervision. A recent clinical trial using a single low dose of esketamine (0.2 mg/kg body weight), infused 40 minutes postdelivery, seems to significantly reduce symptoms in the treated groups. Affecting a large number of females, PPD is a major health concern that needs to be addressed promptly by healthcare professionals.

Keywords: *Postpartum Depression; Mood Swings; Baby Blue; Hormones; Drugs; Serotonin Receptors*

Abbreviations

PPD: Postpartum Depression; MDD: Major Depressive Disorder; GWAS: Genome-Wide Association Studies; TPH2: Tryptophan Hydroxylase-2; COMT: Catechol-O-Methyl Transferase; MAO: Monoamine Oxidase; BDNF: Brain-Derived Neurotrophic Factor; HPA: Hypothalamic-Pituitary-Adrenal Axis; 5-HTT: Serotonin Transporter Gene; MAOA: Monoamine Oxidase A

Introduction

"Postpartum" refers to the period after having a baby. While it's a joyful event and a milestone in a woman's life, some new mothers may also feel anxious, overwhelmed, tired, sad, or worried. These feelings, often termed the "baby blues", subside within a few days for many women. However, if a woman continues to experience feelings of hopelessness, sadness, or anxiety beyond two weeks after childbirth, it could be maternal postpartum depression (PPD).

According to the current literature, the burden of perinatal mental health disorders, including PPD, imposes a significant burden on low- and lower-middle-income countries [1]. Globally, the prevalence of PPD is estimated to range from 10 to 20% of new mothers, while in India, it affects about 22% of women postpartum [2,3].

Postpartum depression is a common mental health problem that affects one in 8 new mothers within the first year after birth. It differs significantly from the typical baby blues, with its symptoms being more severe and intense and mirroring those seen in major depression. However, PPD is understudied, underdiagnosed, and undertreated.

PPD is defined strictly in the psychiatric nomenclature as a major depressive disorder (MDD). It is a severe mental health condition that can profoundly affect the quality of life of both mother and child for years to come and potentially pose life-threatening consequences. Symptoms typically persist for more than two weeks following childbirth and can range from mild to severe. These include feelings of depressed mood, uncontrolled crying, irritability, loss of interest in daily tasks, insomnia or increased sleep, appetite disturbance, fatigue, difficulty bonding with the newborn, withdrawal from family and friends, feelings of worthlessness or guilt, diminished concentration, and death or suicidal ideation may also be present. Further, maternal depression can also have adverse effects on an infant's behavioural, emotional, and cognitive development. Therefore, understanding the underlying pathophysiological mechanisms contributing to postpartum depression is crucial for reducing the prevalence and making optimum treatment decisions.

Pathophysiological mechanisms

Several studies have identified the role of systemic hormonal fluctuations, neuroendocrine and neurotransmitter changes, neuroinflammation, neuronal circuit dysfunction and the involvement of genetics and epigenetics mediators in the pathophysiology of postpartum depression.

Based on twin and family studies and genome-wide association studies (GWAS), it has been identified that there is a genetic influence on PPD [4]. GWAS has also identified individual candidate genes and potential pathways associated with PPD [5]. Candidate gene studies in postpartum depression have primarily focused on genes previously associated with major depressive disorder, including the serotonin transporter, tryptophan hydroxylase-2 (TPH2), catechol-o-methyl transferase (COMT), monoamine oxidase (MAO), and brain-derived neurotrophic factor (BDNF). Notably, pathway analyses based on specific genes or unbiased screens have shown the involvement of estrogen signaling and the hypothalamic-pituitary-adrenal (HPA) axis in developing PPD [6].

Numerous studies have shown an association between the hypothalamic-pituitary-adrenal (HPA) axis dysfunction and PPD. Stress and a strong history of adverse life experiences are also associated with PPD, as these two factors, in turn, are related to neuroendocrine changes, including HPA axis reprogramming and epigenetic modifications, thereby influencing HPA function [5].

Additionally, recent research suggests a positive connection between mutations in the serotonin transporter gene (5-HTT) and PPD [7]. Studies have found that variations in 5-HTT are linked to depression symptoms, particularly in the early post-partum phase [8]. However, recent studies suggest that variations in 5-HTT only predispose to PPD symptoms in those individuals with a history of adverse life events [9].

Other investigations have identified a correlation between polymorphism in the genes encoding for enzymes like monoamine oxidase A (i.e. MAOA, the enzyme involved in the oxidative deamination of amines, such as dopamine, norepinephrine, and serotonin) and catechol-o-methyltransferase (i.e. COMT, enzyme that degrades catecholamines, including dopamine, epinephrine and norepinephrine) and PPD. Few studies suggest that elderly women with alterations in MAOA and adverse life events were highly susceptible to developing PPD and also showed increased cortisol levels [5].

The neuroendocrine mechanisms underlying postpartum depression (PPD) involve complex interactions between reproductive hormones, stress hormones, and mood-regulating pathways [10,11].

Studies investigating neuroendocrine mechanisms of postpartum depression suggest that during the peripartum phase, a woman goes through dramatic changes in hormonal levels, including increased cortisol levels [5].

Additionally, the peripartum is a sensitive period for the development of mood disorders. Both these factors are linked with significant fluctuations in reproductive hormones that could affect the brain in ways that lead to mood disorders. This may play a role in the neurobiology of postpartum mood disorder, a concept that led to the "ovarian-steroid-withdrawal hypothesis".

Further, the role of reproductive and lactogenic hormones like estrogen and oxytocin has been studied to understand the underlying neurobiology of postpartum depression [12,13].

During the secretory phase, plasma levels of total estrogen are approximately 300 pM, which subsequently increases to about 1000 pm during the proliferative phase. As gestation advances, there is a significant rise in these levels. During parturition, estrogen levels increase drastically, peaking at levels more than 1000 times their usual baseline [14]. However, following delivery, these levels drop sharply. Although there is no consistent finding regarding changes in absolute estradiol levels in postpartum depression (PPD), in patients across different studies, some evidence suggests that women with PPD may have increased sensitivity to estrogen signaling [5].

Additionally, estrogen signaling impacts various mood-related pathways, including the hypothalamic-pituitary-adrenal (HPA) axis. Studies on oxytocin show mixed results [15].

It has received attention in PPD with its role in lactation. Few studies suggest that women facing difficulties related to breastfeeding may develop PPD, while others show a negative association between higher oxytocin levels during breastfeeding and symptoms of depression [16].

Therefore, pathophysiological mechanisms underlying postpartum depression are complex and do not play a role in isolation; however, there is an interplay between several potential pathways, including polymorphism in genetic and epigenetic mechanisms, fluctuations in reproductive/lactogenic hormones, history of adverse events/stress and HPA axis dysfunction, neuroinflammatory processes, altered synaptic transmission, and circuit-level changes in network communication in brain regions related with mood.

Early diagnosis and treatment of PPD are essential; however, it can be challenging to identify them due to their overlapping symptoms with typical post-delivery experiences. Changes in sleep patterns, changes in appetite, and excessive fatigue are common during postpartum, which can make it challenging to identify PPD symptoms. Hence, all healthcare providers need to educate the new mothers and their partners regarding the signs of an actual depressive disorder and encourage them to contact their medical provider in case a significant concern arises [17].

Immune network and dysfunction in PPD

During pregnancy, implantation of the semi-allogenic fetus in the maternal endometrium is primarily executed by a balanced interplay between pro and anti-inflammatory cytokines such that the developing fetus is accepted. PPD is a complex multi-system disorder involving the hypothalamic-pituitary-adrenal (HPA) axis, endocrine, and neurotransmitter imbalance [18]. Genomic and epigenomic alterations also play a strong role in this process.

The role of T cells, especially an imbalance between Treg and activated T cells, along with a surge in inflammatory cytokines like IL1beta, IL-6 and reduced anti-inflammatory cytokines like TGFbeta, IL10 contributes to PPD. Reports also indicate the involvement of Nod-like receptor protein (NLRP) inflammasomes contributing to PPD, mostly NLRP3 inflammasomes [19]. NLRP3 also contributes to IL1beta release via the caspase-1 pathway. Further, increased inflammation increases the production of indoleamine 2,3-dioxygenase

(IDO) as a result of the activation of tryptophan 2,3-dioxygenase (TDO) [20]. These enzymes produce tryptophan (Trp) into kynurenine (Kyn), which may, in turn, damage neurons, leading to some PPD-related changes [19]. These findings indicate that anti-inflammatory approaches might be beneficial in PPD.

Treatment measures for PPD

Treatment measures for postpartum depression include anti-depressants, psychotherapy, and the use of anxiolytics in case of significant anxiety [21,22].

Other practical options for managing postpartum depression include complementary and alternative treatments like exercise, yoga, and breastfeeding [23,24].

Exercise and PPD

Exercise emerges as a promising strategy to reduce depression, offering numerous benefits over traditional treatments. It is cost-effective, suitable for overall health, and has minimal side effects. The beneficial effects of exercise on depression come from its impact on biochemical and physiological pathways, including enhanced sleep quality, mood regulation, and cognitive function [25,26].

Mechanisms such as increased circulation of endorphins, norepinephrine, and serotonin and cerebral blood flow contribute to the positive outcomes of exercise. Research suggests that exercise can be as effective as antidepressants in treating major depression, with systematic reviews indicating its efficacy in preventing and treating antenatal depression [27]. According to the American College of Obstetrics and Gynaecology, pregnant and postpartum women without complications should indulge in at least 30 minutes of moderate intensity physical activity on most days of the week [28].

Yoga and PPD

Yoga is an ancient mind-body practice involving three main components: physical postures (asanas), breath control (pranayama), and meditation (dhyana). Though research in this area is still in its early stages, preliminary evidence suggests that prenatal and postpartum yoga interventions lead to more significant improvements in depression from pre- to post-intervention [28].

However, further exploration through more extensive randomized controlled trials is necessary to understand these interventions' efficacy better.

Breastfeeding and PPD

Breastfeeding has also been reported to reduce postpartum depression [24].

The advantages of breastfeeding are linked with various hormonal and psychological processes that protect the mother against PPD [29]. The mechanisms behind these positive effects need to be studied more extensively, yet current literature suggests that this protective effect is because lactation attenuates stress responses, particularly cortisol [30].

Incorporating these strategies during the postpartum period can reduce postpartum depression and can prove to be beneficial for both the mother and the infant.

Conclusion

Postpartum depression (PPD) is a complex mix of emotional, physical, and behavioral changes affecting some mothers post-delivery. The symptoms are more severe than the typical baby blues and similar to those of major depressive disorder (MDD), persisting

beyond two weeks after birth. The pathophysiology of PPD involves the interplay of several factors, including neuroendocrine and neurotransmitter changes, neuroinflammation, neuronal circuit dysfunction, and the involvement of genetics and epigenetics mediators. One aspect contributing to PPD involves the systemic hormonal fluctuations occurring postpartum. After birth, there is a sharp decline in hormones as part of the chemical changes. Though not clear, how this decline may lead to depression is not known. It is possible that during pregnancy, the levels of the female reproductive hormones, progesterone, and estrogen, increase several-fold, followed by an abrupt decline in their level post-delivery, which might lead to mood swings, as seen in PPD. Understanding these underlying mechanisms is crucial for early diagnosis and effective management of PPD.

Pharmacological interventions, psychotherapy and counselling, complementary therapies, and multidisciplinary approaches are among the few treatment modalities for postpartum mood disorders. Additionally, engaging in regular exercise and adopting breastfeeding practices can reduce PPD symptoms.

Recently, healthcare and alternative therapies like ayurveda, yoga, and nature-therapy are gaining traction in treating PPD. By providing education about PPD and its treatment interventions, healthcare providers can support new mothers navigate the challenges of the postpartum phase, promoting better maternal mental health and optimal development of the infant.

Authors Contribution

SG drafted the manuscript with assistance from IG, RD, and SK. RD and SK conceptualized and oversaw the entire work.

Acknowledgements

SK thanks the Indian Council of Medical Research (ICMR) for supporting the research.

Conflict of Interest

None.

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Volume 13 Issue 6 June 2024