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The influence of Hypothalamic-Pituitary-Adrenal (HPA) axis dysregulation on postpartum mental disorders- literature review and new perspectives

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Abstract

Introduction and Purpose of work: Postpartum depression is a psychiatric disorder associated with the changes in the endocrine system as well as in neuroimmune signaling. The purpose of this review is to investigate the meaning of neurosteroids that are link between postpartum depression and changes in Hypothalamic-Pituitary-Adrenal (HPA) axis, as well as to highlight the therapeutic implications.

Review methods: This article is based on literature from PubMed, Google Scholar, and other databases. Observational studies, experimental studies, and meta-analyses on the HPA-axis and postpartum depression, including brain changes and neurosteroids as treatment options, were selected.

Abbreviated description of the state of knowledge:

Postpartum depression involves changes in the neuroendocrine and neuroimmune systems, often linked to HPA axis dysregulation affecting the CNS. Irregular GABAergic signaling is a key factor, influencing conditions like depression, anxiety, and PTSD. Neurosteroids have been used for treatment, and new options for postpartum depression are being explored. Hormonal shifts may also affect hippocampal and gray matter function.

Summary: This review explores the connection between postpartum depression and hormonal changes in the HPA axis, highlighting its clinical importance. It calls for deeper insight into the condition's pathophysiology, including hippocampal changes affecting memory and mood. Neurosteroid therapies show promise, but further research is needed on their role in HPA axis-related memory changes during postpartum. A comprehensive approach considering factors like sex, age, microbiome, stress, and diet is crucial.

Key words: postpartum depression, pregnancy and brain, postpartum amnesia, pregnancy and HPA axis, neuroimmune signalling, hormones, neurosteroids

Introduction

Changes in hormones during pregnancy allowing woman's body to promote growth and deliver a baby into the world and mental disorders that involve changes in neurotransmitters in the brain are seen as two different health conditions. Although the two are seen as separate, recent studies suggest there might be a connection between them.

The role of hormones in development of mental diseases, although widely investigated, still does not remain entirely clear and is underestimated in clinical work. Pregnancy causes significant physiological and hormonal changes that also affect the brain.

For instance, pregnancy causes a decrease in gray matter volume in the left putamen, showing that hormonal changes during this phase influence the female brain. Memory for verbal information decreases during pregnancy and continues after childbirth, with changes linked to prenatal glucocorticoids and estrogen levels.[2]

Hormonal changes during pregnancy can impact not only the brain in both the short and long term, including alterations in brain function, structure, and cognitive abilities. It has also great influence on mental health. As example, the study of 100 pregnant women shows that high levels of placental corticotropin-releasing hormone at 25 weeks of pregnancy strongly predicted postpartum depression around nine weeks after birth.[3]

Understanding this connection can be important because, as we already know, mental health and physical health are undeniably linked to each other and that is not often considered in clinical work. Stress experienced by mothers during pregnancy impacts the development of the fetal brain, increasing the likelihood of neurodevelopmental disorders in children.[4] In USA investigations have shown that providing somatic support for pregnant mothers to help their brain-dead babies lasted about 7 weeks on average, resulting in 77% of the babies that were born alive, and 85% were healthy at about 20 months old.[5]

In this review article, we will examine existing research on the relationship between Hypothalamic-Pituitary-Adrenal (HPA) axis dysregulation on postpartum mental disorders: postpartum depression and postpartum amnesia.

We are going to discuss the potential mechanisms underlying this relationship, as well as provide an update on the current state of knowledge on this topic. We will also address areas including clinical implications as well as implications for future research and clinical practice.

Postpartum depression (PPD)

It is a common condition, globally performing in 14 percent of women, that significantly affect the functioning of mother and may lead to negative effects for both the mother and baby.[6] [7]

There is no agreed-upon definition of the duration of the postpartum period. Taking into advance various definitions, we assume the postpartum period as the first 12 months after childbirth, but according to DSM-5, the start of postpartum major depression can happen either before or after childbirth as well, with "peripartum onset" occurring during pregnancy or the 4 weeks before delivery.[8]

About 50 percent of patients experience the onset of episodes before or during pregnancy.[9] In women with postpartum depression that starts after childbirth, symptoms typically begin within the first few months following delivery.[10]

The two main factors that strongly contribute to postpartum depression are: having depression during pregnancy and a history of depression, whether related to pregnancy or not[7],but finally the cause of postpartum depression remains not fully understood. It is also unclear to what extent the causes of postpartum depression differ from nonperinatal depression, or if it is a different subtype of depression.[11] Contributing factors may include genetic susceptibility, epigenetic phenomena, hormonal changes, and psychological or social issues.[12]

We are going to focus on discussing influence of hormonal changes during pregnancy to fully understand its relevance in developing postpartum depression and association with Hypothalamic-Pituitary-Adrenal (HPA) axis dysregulation.

Postpartum depression-hormonal and neurotransmission changes

During the pregnancy serum levels of estrogen and progesterone decrease. There also occur significant changes in concentration of cortisol, melatonin, oxytocin and thyroid hormone. [13]
Women with a history of PPD are particularly vulnerable to hormonal changes and show mood changes in adverse to women lacking a history of PPD. We know that variations in the activity of specific genes in the hippocampus might heighten the risk of postpartum depression by increasing sensitivity to the drop in estrogen levels after childbirth.[14] It was also investigated that women who experience a major depressive episode after childbirth due to hormonal changes likely belong to a more genetically similar group.[12] These facts proof that women with a history of postpartum depression might be particularly more sensitive to sudden drops in gonadal steroid levels after giving the birth. Nowadays the statement that hormonal factors play a role in the development of postpartum depression seems to be very obvious, but mechanism underlying beyond them still need more investigation.

In addition to increased vulnerability to change in hormones in postpartum period, we could not forget about the role and activity of hormones itself.
When it comes to the role of steroids in developing the unipolar major depression, there are investigation on that placenta, an endocrine organ of embryonic origin, may contribute through dysregulated corticotropin-releasing hormone (CRH). Studies found that high placental CRH levels at 25 weeks predict postpartum depression around nine weeks after delivery.[3]The other investigation shows that elevated mid-gestational CRH is linked to depressive symptoms three months postpartum.[15]

The other significant role in development of postapartum depression plays dysregulated transmission in brain that showed elevated levels of monoamine oxidase-A, an enzyme that breaks down neurotransmitters like dopamine, norepinephrine, and serotonin.That means potentially faster neurotransmitter depletion.[16]

There is also promising evidence on the thesis that neuroimmune signaling impacts neuropsychiatric diseases.This involves dysregulation of inflammatory signaling in brain what is associated with neurosteroid deficiencies.[17]

We are going to investigate on some of these mentioned mechanisms leading in detail for the deep understanding of etiopathology of postpartum depression in the aspect of hormonal and neuroimmune changes.

HPA axis during pregnancy

After childbirth, cortisol levels generally decrease.[18] However, stressors such like recovering from delivery and caring for a newborn can disrupt the HPA axis. In women with postpartum depression (PPD), the HPA axis may stay imbalanced, resulting in abnormal patterns of cortisol release.

The HPA axis is a major neuroendocrine system that controls the body's response to stress. It involves the hypothalamus, the pituitary gland, and the adrenal glands. When the body perceives stress, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the pituitary to release adrenocorticotropic hormone (ACTH). ACTH, in turn, triggers the adrenal glands to release cortisol, a steroid hormone that prepares the body to respond to stress. Elevated cortisol levels result in the suppression of CRH and ACTH secretion through a negative loop mechanism.[19]

During pregnancy, the HPA axis undergoes significant changes, both to support fetal development and prepare the body for labor and delivery.

Cortisol helps regulate fetal growth and development, especially the development of the lungs, brain, and cardiovascular system. It plays a role in surfactant production in the lungs, which is critical for the fetus's ability to breathe after birth.[20]

Moreover pregnancy involves changes in immune function to protect the fetus from being rejected by the maternal immune system. Cortisol helps modulate the immune response to prevent excessive inflammation and supports immune tolerance to the fetus.[21]

This is why there occur necessary changes in the HPA axis during pregnancy.

Firstly, levels of cortisol during pregnancy, significantly increase in the second and third trimesters. This phenomenon occurs in order due to placenta's increased secretion of CRH, which prompts the mother’s pituitary to release ACTH, that increase the cortisol production.

Thus, the placenta’s CRH production regulates the maternal and fetal cortisol levels and contributes to the development of labor.[19]

On the other hand, the excessive activation of the HPA axis, due to chronic stress can have adverse effects on mother and fetum, crossing the placenta and affect fetal development.

The investigations regarding the health of placenta mention low birth weight, premature birth, alternations in brain development in areas of the brain involved in stress regulation,as well as increased susceptibility to mental health disorders later in life, such as anxiety and depression.[22] [23] [24] Regarding the health of mother the consequences include complications like gestational hypertension, preterm labor, and postpartum depression. [25] [26]

Dysregulation of the HPA axis, particularly with prolonged elevated cortisol levels, is associated with the development of postpartum depression.

As we have mentioned above, women with a history of depression may undergo more significant HPA axis imbalances during pregnancy, raising their likelihood of postpartum depression. After we have discussed the activity of HPA axis, we are going to discuss the mechanisms that undergoes with its influence on mental health.

Neurosteroids and neuroimmune effect

Neuroactive steroids are endogenous steroids synthesized in brain and in the peripheral.

These steroids are synthesized from cholesterol and are classified into three types: pregnane, androstane and sulfated neuroactive steroids.

They have pleotropic effects on organism regulating mood, behavior, and neural activity. Pregnanes (allopregnanolone, pregnenolone) act as positive modulators of GABA receptors, enhancing inhibitory neurotransmission. This leads to effects such as anxiolysis, sedation, anti-convulsant activity, and the enhancement of inhibitory brain circuits. Distinct to these GABAergic influence, pregnanes also have anti-inflammatory actions that we are going to discuss below.[18]

There is evidence that many brain disorders involve dysregulated pro-inflammatory immune signaling.

Allopregnanolone (ALLO) and pregnenolone role is both to inhibit pro-inflammation in macrophages and brain and to enhance anti-inflammatory and trophic transmission.[27]

Inflammation happens when pathogens activate Toll-Like Receptors (TLR) , starting a process that leads to the production of molecules that cause inflammation: chemokines and cytokines. Allopregnanolone and pregnenolone inhibit inflammatory signaling by blocking protein-interactions that are required for TLR activation. These neurosteroids inhibit proinflammatory

neuroimmune pathways on the body's perimeter and in the brain. This is important to underline again that mechanism is independent of GABAergic mechanisms.

Neurosteroids, which inhibit these inflammatory pathways, show decreased levels in conditions like depression. Thus, supplementing neurosteroids has demonstrated therapeutic benefits in managing this condition. One example is brexanolone, an Food and Drug Administration (FDA)-approved intravenous form of allopregnanolone, which has been shown to effectively suppress TLR-mediated inflammatory pathways, leading to symptom improvement in PPD. [28]

To sum up, neurosteroid deficiencies may trigger excessive pro-inflammatory responses, creating a self-perpetuating cycle that impairs brain networks responsible for stress, emotion, and motivation regulation. More and more evidence is found to prove that pathological immune reactions contribute to development of neurological and psychiatric conditions.

HPA axis and neurosteroids- bridging the gap between hormones and the brain

For many years neurosteroids have been used for therapy of postpartum depression, depression, PTSD, anxiety and diseases associated with overuse of stimulants in order to restore GABAercic transmission. All of these disorders are characterized by a dysregulation in hypothalamic–pituitary–adrenal (HPA) axis activity that is most likely resulting from irregular GABAergic signaling.

Elevated cortisol levels, as a result of chronic stress or dysregulation of the HPA axis, can reduce the synthesis of these neurosteroids, potentially contributing to mood disorders, anxiety, and depression.

Several studies concludes on situations where corticotropin-releasing factor-CRF levels are high, multiple neurosteroids are reduced, and stress responses are diminished.

Major depressive disorder (MDD) often involves dysregulation of the HPA axis, with individuals typically showing low levels of allopregnanolone in both plasma and CSF. The same applies to women with PPD, showing changes in GABA and allopregnanolone levels, along with HPA axis. In animal studies, mice with disrupted GABA receptors, represented increase in CRH during postpartum period. [29] Moreover, both allopregnanolone and 3α,5α-THDOC have been shown to prevent stress-induced increases in adrenocorticotropic hormone (ACTH) and corticosterone levels when administered prior to stress induction in rats.[18]

Importantly, treatment with allopregnanolone and other neurosteroids could be a promising approach for treating disorders linked to dysregulation in the HPA axis and GABAergic signaling. The mechanism involves allopregnanolone that modulates GABA receptors in the brain, affecting the hypothalamus and reducing CRH secretion, which helps lessen the stress response and regulates the HPA axis through a feedback loop.
Additionally, given the research on the anti-inflammatory effects of neurosteroids in the brain and peripheral tissues, they should be considered as a therapeutic option for neuropsychiatric diseases that are associated with neuroinflammation.
It is important to notice that both of mechanisms- GABAergic influence and anti-inflammatory work independently.

The relationship between the HPA axis and neurosteroids is a complex. It is also worth to notice that there are significant sex differences in HPA axis reactions to stress, shaped by gonadal hormones. Women generally show a quicker and more intense release of stress hormones than men. Androgens tend to boost HPA activity, while estrogens reduce it. These variations may play a role in gender-specific susceptibilities to stress-related conditions and to the pathogenesis of postpartum depression as we know the HPA axis may stay imbalanced and cortisol decreases after women give a birth.[30] Moreover, we know that the the levels of neuroactive steroids and the enzymes that produce them are different in male and female rodents and change during the estrous cycle.[31]

In addition recent studies also suggest that the levels and actions of neurosteroids can differ not only based on factors like sex and age, but also neuroimmune effect. They have been shown to produce sex-differentiated neuroprotective effects in various animal models, indicating a possible approach for sex-specific treatment in the future. [32]

Neurosteroids and physiological effects on brain postpartum

Pregnancy causes major physical and hormonal changes that also affect the brain. Studies indicate these changes can impact brain structure, function, and thinking abilities both temporarily and over the long term. During postpartum time changes include regions such the hippocampus and the cortex (gray matter) .
This may be in part related to the high concentration of steroid and peptide hormone receptors in the hippocampus, particularly glucocorticoid receptors, and to a lesser extent

estrogen,progesterone,oxytocine and prolactine receptors.We will focus on mechanism that involves the influence of transmission associated with neurosteroids.

Neurosteroids, through their pleiotropic effects, affect brain function at the level of physiology but also structural changes, what we are going to discuss now.

It is known how stress, which contributes to the development of depression through dysregulation of the HPA axis[14], can affect the hippocampus. The hippocampus plays a key role in different types of learning and memory, such as contextual memory and spatial memory.[31] During research on a prenatal stress animal model, along with an in vitro study it was shown a substantial decrease in miRNAs of hippocampal stem cells that were exposed to cortrisol.MiRNA target gene FKBP5, which is a stress-related gene influenced by glucocorticoids. This discovery underscores the essential role of these miRNAs in influencing the long-term effects of early-life stress.[33] As mentioned at the beginning, we also know that variations in the activity of genes in the hippocampus might heighten the risk of postpartum depression by increasing sensitivity to the drop in estrogen levels after childbirth.[14]

Other research showed that pregnenolone raised brain-derived neurotrophic factor-BDNF levels in the hippocampus and hypothalamus, while allopregnanolone boosted BDNF levels in the amygdala but reduced them in the hippocampus.[17]
BDNF helps with the growth, development, and changeability of synapses (connections between nerve cells) that use glutamate and GABA. It also affects how neurons develop, impacting serotonin and dopamine signals. It supports the adult neurogenesis by development of dendritc spines in hippocampus.[34]
In rodents, prenatal stress reduces the number of GABA-ergic neurons in the hippocampus and prefrontal cortex and lowers GABA receptor levels in the hippocampus and amygdala.[35] Changes in how new nerve cells are formed in adults can affect learning, memory, and can lead to behaviors like depression.

Additionally, allopregnanolone supports neurogenesis and has demonstrated regenerative potential in animal models of Alzheimer’s disease. Estrogens have also possible significance in slowing the progression of Parkinson disease as there is higher prevalence of it in men.[17]

There are more studies that proof comprehensiveness of neurosteroids. Study from Tufts University found that reduced levels of allopregnanolone in the brain's amygdala, a region critical for processing emotions, are associated with depressive behaviors in mice subjected to chronic stress. [36] This neurosteroid may be significant in function in the nucleus accumbens that is responsible for reward and motivation system, although its role has not been clearly explored in this area.[22]

In other studies it has been shown that change in memory abilities are associated with a decrease in ALLO levels in the hippocampus,but also with oxidative stress,neuroinflammation, chanoxidative stress, impaired mitochondrial function, and changes in gut microbiome balance. The study was investigating on experimental model of type 2 diabetes mellitus. That only confirms the widespread nature that neurosteroids have and also the need for further research in understanding the complicated network of hormones in the body.[37]
Allopregnanolone as the controller of anti-inflammation and GABA-ergic neurotransmmision in brain provide a crucial foundation for its application in pathophysiology of postpartum depression. In future investigations it seems to be the right direction to consider its effect on brain changes that can also contribute to the development of postpartum depression and other mental disorders such as amnesia. To sum up, the significant changes in steroid hormone levels during the postpartum period may coincide with some of the alterations in hippocampal function. Further research is required to determine whether these hormonal fluctuations mediate the significant changes in memory postpartum.[31]

Conclusions

Based on the studies analyzed in this paper, it can be concluded that there is a correlation in changes in Hypothalamic-Pituitary-Adrenal (HPA) Axis and postpartum depression.
Further research is required to determine whether there are significant changes in brain responsible for memory as some studies say that pregnancy mostly causes tissue loss, and a few say this loss is mostly permanent. On the other hand, most studies show that during the postpartum period, there is a lot of tissue growth throughout the whole brain.[38]

An important finding in the etiopathogenesis of postpartum depression draws attention to the neuroimmune signaling that impacts neuropsychiatric diseases. This creates a new approach to the problem and creates the potential to implement new treatments.

More and more studies also indicate other crucial factors responsible for development of this pathology such like: sex, age, changes in gut microbiome balance, stress and diet.
In consequence, postpartum depression can lead to poor health and nutrition in the baby. It may also make breastfeeding, bonding with the baby, caring for children, and maintaining a good relationship with the partner harder. We need a multidisciplinary approach to the problem, which will allow more effective help for depression, including post-depression.
Moreover, effective treatment for postpartum depression ,with consideration of new potential treatments, could potentially alleviate the symptoms of amnesia, but more evidence is needed.

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