

Update on the Neurobiological Aspects of Postpartum Depression

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Abstract

Postpartum depression is the most frequent psychiatric complication during the postnatal period and, given its potential impact on the well-being of the mother and the baby, its correct management should be a public health priority. Regarding its etiology, there is more evidence concerning the psychosocial factors involved in the process, but considering the remarkable hormonal variability during pregnancy and postpartum, differences could be expected between women with this pathology, or there could also exist some causal relationship. However, the literature has not been consistent with these findings or with the influence of other neurobiological changes. Recent researches, including the evaluation of cytokines and neurotrophins (e.g. Brain-derived neurotrophic factor), has opened up new points of interest.

Keywords: Postpartum Depression; Risk Factors; Hormones; Cytokines; Brain-Derived Neurotrophic Factor

Introduction

Postpartum depression (PPD) is a prevalent pathology that can significantly affect women's well-being, their global functioning, family stability, and sometimes interfere with the development of their children [1]. The Diagnostic and Statistical Manual of Mental Disorders in its fifth edition (DSM-V) [2], modified from the previous version (DSM IV-TR) [3], now includes a major depressive disorder of onset in the peripartum, considering its development during pregnancy or in the first four weeks of postpartum. For PPD, the same time criterion was maintained, but this has been questioned in the clinical and research fields since the risk period could be extended three [4] to six [5] months after delivery.

Approximately 60 to 85% of women may manifest some symptoms of depression during the first few days of postpartum, known as postpartum blues that are usually mild and disappear within a short period of time. In contrast, PPD involves symptomatology typical of any major depressive episode. In addition, women experiencing PPD have obsessive ideas about the well-being of the newborn [6], anxiety, poor perception of motherhood, and greater motor or cognitive alterations as compared to other depressions [7].

The global prevalence of PPD is 10 - 20% [8,9], with higher values in adolescent mothers [10] and lower income families [11,12]. In the United States, there is sufficient information on prevalence, comorbidities and other aspects of PPD based on data from the 2001 - 2002 National Epidemiological Survey on Alcohol and Related Conditions (NESARC). The NESARC is a survey of 43,093 adults aged 18 years and older residing in households in the United States of whom 14,549 were women 18 to 50 years old with known past-year pregnancy status. Among pregnant and postpartum women, depression was associated with younger age, ethnicity other than Latin American, being widowed, divorced, separated or never married, traumatic events within the past 12 months, and pregnancy complication. Strong associa-

tions were found between major depressive episodes during pregnancy and postpartum and nearly all 12-month prevalence of psychiatric disorders. Pregnant women having depression within the past-year and postpartum women were more likely than non-depressed pregnant women to use substances such as alcohol, cigarettes, and illicit drugs [13].

Unlike other postpartum psychiatric disorders such as puerperal psychosis which has shown a stronger relationship with biological aspects, the factors related to PPD are more associated to psychosocial features [1]. In the last two decades, several meta-analyses have evaluated the level of risk associated with different predictors [12,14,15]. In 1996, O'Hara and Swain [12] reported that the strongest predictors of PPD were: (i) past history of psychopathology, (ii) psychological problems during pregnancy, (iii) poor marital relationship, (iv) low social support, and (v) stressful life events. Finally, indicators of low social status showed a small but significant predictive relation with this condition [12]. Five years later, Beck [14] found thirteen significant predictors of PPD, ten of these factors had moderate effect sizes while three predictors had small effect sizes. The mean effect size indicator ranges for each risk factor were: low self-esteem (0.45 to 0.47), childcare stress (0.45 to 0.46), prenatal depression (0.44 to 0.46), prenatal anxiety (0.41 to 0.45), life stress (0.38 to 0.40), social support (0.36 to 0.41), marital relationship (0.38 to 0.39), history of previous depression (0.38 to 0.39), infant temperament (0.33 to 0.34), maternity blues (0.25 to 0.31), marital status (0.21 to 0.35), socioeconomic status (0.19 to 0.22), and unplanned/unwanted pregnancy (0.14 to 0.17). And more recently, Robertson, et al. [15] found that the strongest predictors of PPD were: depression during pregnancy, anxiety during pregnancy, experiencing stressful life events during pregnancy or early puerperium, low levels of social support, and a previous history of depression.

Given the existence of adequate evidence for psychosocial predictors in PPD, the objective of this review is to update the information regarding neurobiological aspects related to peripartum, especially in relation to the hormonal hypothesis in this pathology.

Method

An information search in Spanish and English was made in the following electronic databases: Pubmed, Elsevier, ProQuest and Cochrane Library, during February and March in 2017. Keywords used for the search were: postpartum depression, risk factors, hormones, cytokines and brain-derived neurotrophic factor. A total of 60 references, published in the last 27 years, were selected. The criteria for inclusion of the articles (reviews, meta-analyses and clinical trials) were based on: the methodology used their results, the relevance of the publications, and the authors' experience in the PPD study. The diagnostic manuals were chosen as the result of an international consensus of experts.

Results

Hormones

The hormonal changes inherent in pregnancy and their abrupt modification immediately after postpartum have generated interest in their implication in the onset of PPD. Studies in animals and humans have confirmed the ability of estrogens to regulate serotonin pathways at different points, especially by increasing their availability. Therefore, a reduction in their levels during early postpartum could increase the probability of having a depressive condition [16]. One of the most important actions of estrogens includes an increase in the synthesis of tryptophan-hydroxylase enzyme, a limiting step in the synthesis of serotonin, and also a decrease in the synthesis of the transporter for serotonin reuptake, finally acting as serotonergic agonists [17]. In addition to clinical evidence, these biological findings may support the recommendation to use antidepressants in women with moderate to severe PPD [18,19] as first-line pharmacotherapy. Even with breastfeeding, the use of selective serotonin reuptake inhibitors, especially sertraline and paroxetine, is considered safe because they do not show detectable levels in the baby, unlike fluoxetine and citalopram that are able to pass into the breast milk [20,21].

Postpartum changes in other hormones such as progesterone, corticotropin, oxytocin, and thyroid function have also been evaluated. Despite this, consistent endocrine differences between women with and without PPD have not been found [22]. The poor association

between hormonal variations and PPD may be due to (i) limitations in establishing the correlation between peripheral and central hormone levels; (ii) the alterations represent a pathological reaction to the hormonal changes during this period [18] and these women could constitute a “vulnerable subgroup” [23] or “hormone-sensitive PPD phenotype” [24] that should be studied independent of other PPD phenotypes to identify underlying pathophysiology and develop novel treatment targets [24]; and (iii) the most generalized explanation is that this disease is made up of multiple variables, with a greater emphasis on the psychosocial aspects that interact with the biological components at different postpartum stages.

Bloch, *et al.* [22] attempted to simulate postpartum hormonal changes in a double-blind trial developed in non-pregnant women given leuprolide to induce a hypogonadal state followed by supraphysiological doses of estradiol and progesterone, which were eventually discontinued. In 62.5% of the women with a history of postpartum depression, mood alterations were detected except in eight women with a history of depression not related to postpartum. Based on these results, the authors suggested that women with a history of PPD would be more vulnerable to a reduction in gonadal hormones.

The effectiveness of hormone therapy has not been conclusive; estrogen therapy may be of modest value for the treatment of severe postpartum depression [18,19,25,26], but given at high doses it is useful in women with low levels of estradiol [25,26]. Fitelston, *et al.* [19] found that estrogen administration favored women with severe PPD when assessed three months after treatment (RR = 0.30, 95% CI, [0.14 - 0.66]). However, its role in the prevention of recurrent postpartum depression has not been rigorously evaluated [24].

For its part, progesterone withdrawal [27] and lower allopregnanolone levels (metabolite) [28] were related with postpartum blues in a study which found that the peak postpartum score for maternity blues was associated with low progesterone concentrations in saliva [27]. In PPD, findings have been less consistent with data showing unchanged [29] or increased [30,31] progesterone levels. Abou-Saleh, *et al.* [31] detected that hormone levels also predicted the occurrence of depression 6 - 10 weeks after delivery, observing higher progesterone and lower prolactin levels in these women. Additionally, progestogen administration during the immediate postpartum period increased the risk of PPD [32].

The relationship between cortisol levels as an expression of the impact of stress during pregnancy and postpartum and the risk of PPD have also been evaluated with regards to the normal increase in their values from week 25 of gestation and a return to baseline values two weeks after postpartum. During the third trimester, maternal cortisol levels reached approximately three-times that of nonpregnant subjects not taking contraceptive pills [33]. The hypothesis that dysfunction in the immune system or the hypothalamic-pituitary-adrenal (HPA) axis, or that both may contribute to the development of PPD is conceptually based on the psychoneuroimmunology model suggested by Chrousos and Gold [34] and expanded upon more recently [35-37]. The physiological excess production of corticotropin-releasing hormone (CRH) at the end of pregnancy leads to a transient downregulation of hypothalamic CRH postpartum, which could possibly lead to an elevated risk for depression [38-41]. Jolley, *et al.* [40] reported high levels of adrenocorticotropin (ACTH) and low levels of cortisol in women with PPD at 6 and 12 weeks postpartum, as opposed to non-depressed women who showed adequate regulation of this hormonal axis. Also, Urizar and Muñoz [42] found that women with higher scores for gestational depressive symptoms had a significantly higher perception of stress and a higher frequency of past depressions, and those who presented this antecedent exhibited significantly higher levels of cortisol in their saliva at 18 weeks postpartum.

On the other hand, the literature suggests that failed or early discontinued lactation is associated with postpartum depressive symptoms. However, the direction of this association remains unclear [43]. Stuebe, *et al.* [44] postulated an association between PPD and difficulties in breastfeeding due to a shared hormonal dysfunction. In this study, 39 of 52 women completed a follow-up until the eighth week postpartum and the data revealed an inverse relationship between oxytocin values according to area under the curve and symptoms of anxiety and depression ($p \leq 0.01$). These results were also associated with a negative perception of breastfeeding [44,45].

Immune system

The etiology of depression as a dysfunction of the immune system suggests that prolonged or excessive activation of proinflammatory cytokines may be an explanatory mechanism for this condition [46-48]. Chronic stress acts as a trigger for anxiety and depression, initiating changes in the hypothalamic-pituitary-adrenal axis and the immune system. The mechanism whereby psychological stress influences both the peripheral and central inflammatory cascade is coordinated by the autonomic nervous system [49]. Thus, the release of noradrenaline and adrenaline results in the activation of adrenoceptors (alpha and beta) on immune cells in the peripheral blood, initiating the release of proinflammatory cytokines via activation of the nuclear factor-kappa-beta (NF-kB) cascade [50]. In the brain, these cytokines activate both neuronal and non-neuronal cells in a similar manner to that occurring in the peripheral inflammatory response [51]. Puerperal women are especially vulnerable because their inflammatory response increases significantly during the last trimester of pregnancy, when they are also at high risk for depression. Moreover, psychological stress, sleep disturbance, postpartum pain, and trauma also increase inflammation [52]. For some women, PPD might represent a psychoneuroimmunological disorder which arises from amplification of this response that normally accompanies labor and delivery, while the HPA-axis function is not adequately suppressed [43]. In addition, IL-6 interacts with the HPA axis and increased IL-6 levels have been reported in women with PPD early in the perinatal period and in women with a past history of depression [53,54]. It was also found that lower serum levels of interferon-gamma (IFN-gamma) and a lower IFN-gamma/interleukin-10 (IL-10) ratio in both serum and in whole blood stimulated cultures, suggesting a decrease in the ratio of Th1/Th2 T-helper (Th) lymphocytes [39].

Neurotrophins: Brain-derived neurotrophic factor

Current evidence highlights the role of the brain-derived neurotrophic factor (BDNF) and its binding to tyrosine-kinase receptor type B (TrkB) in the pathogenesis of affective disorders, and specifically depression. This neurotrophin in conjunction with the serotonin system has synergistic effects on the development and plasticity of neurons in affective related circuits [55].

Modifications in plasma BDNF levels have also been associated with gonadal sex hormones [56,57] and show a circadian fluctuation in women analogous to diurnal cortisol changes that vary according to the ovarian function [57]. Women with PPD also have lower BDNF levels in comparison with control mothers [58]. Comasco, *et al.* found that the season during which the child is born modulated the association between PPD and the Val66Met polymorphism of the BDNF gene. For example, when delivery occurred during autumn/winter, women with BDNF Met66 alleles had significant association with PPD symptoms at 6 weeks postpartum [59]. It should be noted that pre- and post-partum environmental risk factors were controlled. This study investigated a genetic aspect of PPD that could serve as an example for future studies in this field and be useful for preventive treatment of this condition.

Discussion and Conclusions

Biological hypothesis on the etiology of PPD are similar to those of other psychiatric disorders. However, postpartum women represent a specific group, with both hormonal and psychosocial factors that have no comparison to any other stage in a woman's life time [43]. There is sufficient evidence for epidemiological data and psychosocial predictors of PPD, and relatively few studies have examined the biological aspects of this disorder. The stress model poses a plausible pathway for explaining the interaction of biological factors (eg. variation in hormonal levels) and psychosocial factors in PPD. The other interesting aspect of this model to explain depression is vulnerability, considering that stress in early stages (eg. abuse, neglect, trauma) coupled with factors related to genetic predisposition (family history) contributes to a greater risk for depressive and anxious disorders [60]. Concerning PPD, it was shown that the presence of stressors and the personal history of depression were associated with greater vulnerability [12,14,15].

The difficulty in finding consistent hormonal differences in women with PPD may also be due to the lack of adequate techniques for the correlation between central and peripheral hormonal levels, similar to what occurs with the measurement of neurotrophic factors such

as BDNF. Even so, postpartum hormonal assessment should include, in addition to estrogen, progesterone, oxytocin or prolactin levels, precisely those corresponding to the adrenal axis, which may be suggestive of the physiological response to stress as evaluated by some researchers [40-42].

In recent years, progress has been made in the understanding of depression, and in particular PPD, as a psychoneuroimmunological disease, and in alterations in the levels of neurotrophins such as BDNF. These aspects open new avenues for research, especially for the use of neurotrophins as biomarkers in the prevention and treatment of depression.

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Conflicts of Interest

None.

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