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Reports

Psychoneuroimmunology and Postpartum Depression

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Abstract

Depression is the most common mental illness at the community level. It is estimated that annually 3-15% of the general population has a depressive episode. An increasing number of cases are identified among pregnant patients.

Thus, WHO has been recommending screening for pregnancy and pregnancy depression since 2015.

The causes of depressive pathology are not fully known. The most commonly identified factors are related to biochemical disorders in the brain, psychological or social causes or the administration of drugs with the potential to induce depressive phenomena: antihypertensives, oral contraceptives, hormones, anti-inflammatory drugs.

The association of hypertension with pregnancy can determine an increased risk of depression in pregnancy or childbirth. Hypertensive disorders in pregnancy cause an altered inflammatory response, with several studies identifying significant increased levels of IL-6, IL-8 and TNF-alpha in pregnant women with preeclampsia. Although hypertensive manifestations remit in approx. 6 weeks postpartum, studies have shown that the inflammatory syndrome persists for up to 3.5 months. Serum IL-6 levels are associated with preeclampsia severity and foetal status.

Inflammatory, neuronal and hormonal changes are found in both pathologies, thus explaining the causal links between hypertensive disorders in pregnancy and postpartum depression.

Current researchers have relied on the evaluation of a possible involvement of oxidative stress. Its association with depression is frequently identified, the severity of symptoms being directly proportional to the level of markers of oxidative stress.

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Postpartum depression is a potentially life-threatening mental disorder through suicidal ideation. It remains today a medical entity often neglected and underdiagnosed. While severe symptoms can be more easily identified by the patient, moderate or mild manifestations are often omitted, being considered normal aspects related to the physiology of the postpartum period. Multidisciplinary approach results to be indicated in the diagnosis, treatment and following dynamics related to psychopathological issues, considering different figures involved in the field (Balalau et al., 2021; Dimitriu et al., 2020; Iasevoli et al., 2012; Merlo et al., 2020; Settineri et al., 2019a, 2019b; Stewart & Vigod, 2019; Yang et al., 2022; Webber & Benedict, 2019).

Limited or absent access to educational and information tools, insufficient experience of the young mother in her first pregnancy, childbirth from a precarious socioeconomic environment and lack of medical care, are additional factors that contribute to the non-recognition of depressive symptoms. In addition, at the level of human communities, an exclusively positive representation of motherhood has been perpetuated over time, and this socio-cultural pressure, sometimes even family, which is associated with the stigma of a psychiatric pathology, ultimately determines poor addressability of the patient to medical care (Dennis & Chung-Lee, 2006; Rahaman et al., 2007).

The psychological dimension of motherhood and the postpartum period has been redefined as important and integrated into the medical act as a result of numerous studies that have shown not only the negative impact of postpartum depression on the mother, by dramatically decreasing quality of life, social interactions, physical and mental wellbeing, but also on the newborn, through short and long term effects in terms of intellectual development (Hay et al., 2008; Liu et al., 2017), language acquisition (Kaplan et al., 2014; Quevedo et al., 2012), increased risk of psychiatric disorders (attention deficit, hyperactivity, aggressive behavior , antisocial, anxiety disorders, depressive syndrome) (Barker et al., 2011; Nesti et al., 2018; Pawlby et al., 2008) and predisposition to poor physical health (Halligan et al., 2007; Letourneau et al., 2007; Pearson et al., 2013; Reposa et al., 2014; Stein et al., 2014).

Numerous authors have sought to identify predictive factors for postpartum depression in order to address a better prevention strategy and therapeutic intervention as early as possible.

One of the most formidable diseases associated with pregnancy due to the complexity of its manifestations and the severity of its complications is represented by hypertensive disorders.

Two large-scale studies that have been carried out over a period of 30 years and 24 years, respectively, have found an increase in the incidence of this pathology in recent decades (Ananth et al., 2013; Auger et al., 1016). The epidemiological study published in May 2021 by Wang et

al. (2021), which assessed the global evolutionary trend of hypertensive disorders from 1990 to 2019, reports an increase in the total number of new cases of 10.92% with a standardized incidence rate according to age, decreasing by 0.68% per year, the discrepancy between the two indices being probably due to population growth and multiple pregnancies. Regarding mortality, the results obtained identified a decline of 30.05%. The authors conclude that, although the epidemiological trend is a downward one, mainly due to medical education, prevention programs, technological developments that have allowed better monitoring of the pregnant woman and the implementation of stronger health policies, this pathology remains continue a major public health problem (Wang et al., 2021).

Hypertensive disorders in pregnancy come in several clinical forms. Hypertension identified at more than 20 weeks of pregnancy, which is not accompanied by damage to the target organs and which resolves within a maximum of 12 weeks after birth is defined as gestational hypertension. When it is identified before the 20th week of pregnancy and persist beyond 12 weeks postpartum is called chronic hypertension. Preeclampsia is a multisystemic syndrome that involves high blood pressure accompanied by proteinuria or damage to the target organs +/- proteinuria. Triad consisting in haemolysis, hepatic cytolysis, thrombocytopenia, which may be associated with, but not necessarily, hypertension and / or proteinuria characterize HELLP syndrome. Eclampsia involves seizures. What is important to remember is that this pathology can persist even after birth.

Certain inflammatory, neuronal, hormonal and genetic factors that are found to some extent in both pathologies have raised the hypothesis of a common biological link and a possible causal link between the spectrum of hypertensive disorders in pregnancy and postpartum depression.

The maternal organism develops in normal pregnancy a specific immunological and inflammatory environment that favours the implantation process of the blastocyst, placental and maternal immunological tolerance towards the semialogenic foetal graft (Poterasu et al., 2020). Early pregnancy is a proinflammatory stage, followed during foetal growth and development by an anti-inflammatory phase, culminating in birth when the myometrium is invaded by immune system cells and inflammatory factors. Hypertensive disorders in pregnancy are characterized by an altered inflammatory response, by overproduction of proinflammatory cytokines and decreased anti-inflammatory cytokines. Indeed, several studies have identified significant increases in IL-6, IL-8 and TNF-alpha in preeclamptic pregnant women compared to those with normal pregnancy (Bălălău et al., 2019; Jonsson et al., 2006; Sharma et al., 2007). The inflammatory process has been associated with the progression of symptoms and remains

persistent in the postpartum period, even up to 12-14 weeks postpartum, even if all other manifestations have subsided (Bean et al., 2016; Coskun, 2020; LaMarca et al., 2013). Serum levels of IL-6 correlate positively with the severity of preeclampsia and negatively with foetal weight and condition at birth (van Rijn et al., 2016). Attention on neurobiological domains related to depression and related outcomes is widely increasing (Dell'Osso et al., 2011; Piccinni et al., 2012), highlighting several risk factors linked to subthreshold symptomatologic presentation.

The molecular mechanisms underlying postpartum depression have not yet been fully elucidated. The researcher efforts were focused on evaluating a possible involvement of oxidative stress, inflammatory process, neurobiological factors, disorders of the hypothalamic-pituitary-adrenal axis.

Inflammation as an etiological factor of postpartum depression has been evaluated by several authors. Boufidou et al. (2009) demonstrated an association between elevated levels of TNF-alpha and IL-6 harvested at birth from serum and cerebrospinal fluid and depressive symptoms in the first 4 days after birth (Boufidou et al., 2009). Elevated levels of Hs-CRP and IL-6 were correlated with an increased risk of depression in the first 6 months postpartum (Liu et al., 2016). IL-6 and near-term IL-10 have been identified as strong predictors of postpartum depressive symptoms. In the same study, however, the authors found no association between the evolution of changes in inflammatory factors and that of depressive symptoms, assessed during pregnancy and in the first 12 weeks after birth (Schetsche et al., 2021). Bränn et al. (2020) identified in women with postpartum depression versus those without, an increased peripheral level of 5 inflammatory biomarkers, TRANCE, HGF, IL - 18, FGF - 23 and CXCL1, but without obtaining statistically significant differences in IL-6, IL-8, IL-10 and IL-1 (Bränn et al., 2020).

Other authors recently reviewed several data on the psychoneuroimmunology of postpartum depression. These authors concluded that, although there is a lack of consistency between the results of the studies, the need for further evaluation of the involvement of inflammatory factors in the pathophysiology of postpartum depression remains relevant (Myles et al., 2021). The heterogeneity of the studies, the variability of the measurements of the biological markers, and the way of quantifying the depressive symptomatology require the performance of studies on larger cohorts and the observance of a consistency in the choice of the measured factors and of the clinical evaluation method of depression.

A chronic inflammatory status is interconnected with the production of free radicals, the two processes taking place in a vicious pathological cycle that consumes more and more antioxidant factors and amplifies the harmful tissue effects.

Oxidative stress is involved in inflammatory processes, insulin resistance, endothelial dysfunction, the development of atherosclerosis and plays an important role in the pathogenesis of many diseases, such as cardiovascular disease, neurodegenerative diseases, cancer, obesity, DM II, psychiatric diseases. In a meta-analysis which reviewed 33 studies involving a total of 4,980 subjects, depression is associated with increased oxidative stress and a possible link between the severity of symptoms and the level of oxidative stress markers is suggested (Alamolhoda et al., 2020). Hirose et al published in 2020 a prospective analysis reporting a higher level of oxidative stress and lower antioxidant activity in pregnancy and immediately after birth. The novelty of this study is the association between antioxidant activity immediately after birth and the symptoms of postpartum depression (Hirose et al., 2020). Another article published in 2020 correlates the total antioxidant capacity in the serum of pregnant women of 38-40 weeks with postpartum depression (Bălălău et al., 2020).

Regarding hypertensive disorders in pregnancy, some authors attribute to oxidative stress a central role in the initiation and progression / evolution of this obstetric pathology and emphasize the potential predictors of factors that modulate the production of reactive oxygen species (antithrombin-1, TNF alpha) in for the early detection of their overexpression in pregnancy (Jordan, 2020). Oxidative stress is markedly higher than normal pregnancy (Mohanty et al., 2006), and its level in weeks 24-26 has been associated with preeclampsia and intrauterine growth restriction (Hsieh et al., 2012).

Another possible link between hypertensive disorders in pregnancy and postpartum depression may be related to disruption of the brain's self-regulatory mechanism, which, under physiological conditions, allows cerebral blood flow to remain relatively constant even under conditions of perfusion brain fluctuations. This process is disrupted in women with preeclampsia (Janzarik et al., 2019; van Veen et al., 2015) and may lead together with endothelial dysfunction and proinflammatory status to an increase in blood-brain barrier permeability, neuroinflammation, neuronal degradation, impaired synaptic plasticity, neurotransmitter function and neurocircuits responsible for mental state (Capuron & Miller, 2011).

The study of genetic factors involved in hypertensive disorders in pregnancy and postpartum depression has brought new perspectives to explore the link between the 2 pathologies. A meta-analysis that evaluated 7398 patients with preeclampsia and 11230 pregnant women with normal

pregnancies concluded that the MTHFR C677T genotype was associated with an increased risk of preeclampsia (Wu et al., 2015). In another study, MTHFR C677T was identified as an independent risk factor for postpartum depression (Lewis et al., 2012).

Hypertensive disorders as a pathology that occurs in pregnancy are a stressor in itself both through the effects on the mother, but especially through the foetal complications it can generate: prematurity, low birth weight newborn, foetal death in utero, newborn born who needs care in the intensive care unit. Data concerning stressors and their role in the onset of pathological issues represent a well-known phenomenon in literature (Frisone et al., 2021; Suárez-Rico et al., 2021), with particular reference to psychological dynamics related to medical conditions (Barchetta et al., 2021; Conversano & Di Giuseppe, 2021; Dekel et al., 2020; Hutchens & Kearney, 2020; Marchini et al., 2021; Martino et al., 2021; Shahar, 2021). In the study of Furuta et al. (2014), severe maternal morbidity, which included cases of severe preeclampsia, eclampsia, and HELLP syndrom, was independently associated with posttraumatic stress disorder at 6-8 weeks postpartum (Furuta et al., 2014), and another study correlated severe preeclampsia with low quality. of life, as a result of a precarious psycho-emotional balance, at 12 weeks after birth, especially in the context of a foetal / neonatal death or the hospitalization of the newborn in the intensive care unit (Hoedjes et al., 2011).

Premature birth and IUGR have been significantly associated with posttraumatic symptoms and a higher level of distress (Baecke et al., 2009). A recently published meta-analysis provides some evidence of an increased risk of postpartum depression in women with premature babies (de Paula et al., 2019). A group of 685 women were investigated at 3 months postpartum for the evaluation of psychiatric comorbidities. The authors noted that the vast majority also experienced manifestations of severe post-traumatic stress and major depressive symptoms in obstetric complications associated with childbirth (Dekel et al., 2020).

Another direction that some researchers have taken has been the correlation between the treatment administered in gestational hypertension and the risk of postpartum psychiatric disorders. Methyldopa is the first-line drug for pregnant women with high blood pressure and has a mild depressive disorder (De Muth et al., 1983; Oren et al., 1994). Nayak and Nachane (2018) found in their study of a group of women with no history of psychiatric illness or endocrinopathy that patients who used antenatal methyldopa were at risk of developing postpartum depression (Nayak & Nachane, 2018). Wicińskia et al. (2020) developed this theory and sought to explain the mechanisms involved. The authors concluded that methyldopa can be considered an inducer of postpartum depression by altering the level of neurotrophic factors,

reducing cerebral blood flow, neurotoxicity by increasing NO concentration, reducing the level of dopamine that causes hyperprolactinemia and altering the reward system (Wiciński et al., 2020).

The currently available literature provides little, and some contradictory, data on postpartum depression that occurs as a result of tasks complicated by hypertensive disorders. Blom et al. (2010) analyzed the occurrence of psychiatric symptoms 2 months after birth in the context of obstetric complications and reported a significant association between preeclampsia and postpartum depression, the risk of the latter increasing with the severity of the hypertensive disorder (Blom et al., 2010). Similar conclusions were presented by some authors (Bălălău et al., 2020; Chen et al., 2019) while in other studies the results were not statistically significant (Stramrood et al., 2011). Several reviews / systematic analyzes and meta-analyzes have suggested that hypertensive disorders in pregnancy increase the likelihood of developing postpartum depression, subject to several factors that did not allow a definitive conclusion. Given the variations in the studied populations, cultural, behavioral aspects and beliefs related to psychoemotional health, differences in access to obstetric, psychiatric and psychological care, relatively small patient groups, lack of coherence on assessment tools, the authors emphasize the need to continue this scientific approach (Caropreso et al., 2020; Delahaije et al., 2013; Roberts et al., 2019). Caropreso et al. (2020) also discuss studies to investigate the response to pharmacotherapy and psychotherapy in patients with preeclampsia versus those without (Caropreso et al., 2020).

Women with hypertensive disorders, especially those with severe forms, should be monitored equally from the perspective of the mental component. In fact, ACOG recommends in 2015 the evaluation of depressive symptoms at least once during pregnancy and in the postpartum period with the help of a validated screening tool (ACOG, 2015; Stănescu et al., 2018). Collaboration among obstetrician, psychologist and psychiatrist is essential in this direction. The psychoeducation measures have the role both to help the patient to recognize the symptoms of depression as early as possible but also to raise awareness and overcome a negative mentality / preconception associated with mental illness. Screening, diagnosis and early therapeutic intervention will improve the quality of life and mental health not only of the mother but of the whole family.

High oxidative stress and low antioxidant activity in pregnancy and immediately after birth are closely related to the severity of depression. Obstetric complications associated with birth and foetal prematurity are factors that cause major depressive symptoms.

Hypertensive pathologies in pregnancy increase the probability of developing postpartum depression, its risk being proportional to the severity of the hypertensive disorder. Methyldopa in pregnancy causes mild depressive disorders.

ACOG recommends evaluating depressive symptoms at least once during pregnancy and the postpartum period. It is important to diagnose depression early and immediately initiate proper management to prevent progression to severe forms.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any potential conflict of interest.

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