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Review article

Perinatal Major Depression Biomarkers: A systematic review

M. Serati *, M. Redaelli, M. Buoli, A.C. Altamura

Department of Psychiatry, University of Milan, Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Via F. Sforza 35, 20122 Milan, Italy

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ABSTRACT

Postpartum depression, now termed perinatal depression by the DSM-5, is a clinically relevant disorder reaching 15% of incidence. Although it is quite frequent and associated with high social dysfunction, only recently its underpinning biological pathways have been explored, while multiple and concomitant risk factors have been identified (e.g. psychosocial stress). Peripartum depression usually has its onset during the third trimester of pregnancy or in the postpartum, being one of the most common medical complications in new mothers.

Purpose of the present review is to summarize the state of art of biological biomarkers involved in the pathogenesis of perinatal depression, in view of the fact that suboptimal prenatal milieu can induce permanent damage in subsequent offspring life and have a negative impact on mother–child relationship. Furthermore, parents' biological changes due to medical/psychiatric disorders or stress exposure could influence offspring life: a concept known as 'intergenerational transmission', acting by variations into gametes and the gestational uterine environment.

Given the evidence that perinatal mental disorders involve risks for the mother and offspring, the search for reliable biomarkers in high-risk mothers actually represents a medical priority to prevent perinatal depression.

Contents

Abbreviations: PPD, Postpartum Depression; EPDS, Edinburgh Postnatal Depression Scale; CES-D, Center for Epidemiological Studies Depression Scale; BDI, Beck Depression Inventory; MADRS-S, Montgomery–Asberg Depression Rating Scale Self-rated version; PHQ-9, Patient Health Questionnaire; SAS, Self-Rating Anxiety Scale; SDS, Self-rating Depression Scale; RDC, Research Diagnostic Criteria; HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Rating Scale for Depression; STA-Y, State-Trait Anxiety Inventory; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale; TSST, Trier Social Stress Test; GHQ, General Health Questionnaire; MINI, Mini International Neuropsychiatric Interview, Postpartum Blues Questionnaire, Kessler Psychological Distress Scale; RMD, Recurrent Major Depression; MDE, Major Depressive Episode; PMDD, Premenstrual Dysphoric Disorder; MDD, Major Depressive Disorder; DHA, Docosahexaenoic acid; AA, Arachidonic acid; HPA, Hypothalamic Pituitary and Adrenal axis; BDNF, Brain Derived Neutrophic Factor

* Corresponding author.
E-mail address: martaserati@libero.it (M. Serati).

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1. Introduction

Perinatal depression (PND), which includes major and minor depressive episodes, is one of the most common medical complications during pregnancy and postpartum (Committee on Obstetric Practice, 2015). As for other psychiatric disorders, PND is a complex condition, having a multi-dimensional phenotype and involving psychological/social factors beyond biological aspects (Martini et al., 2015; Di Florio and Meltzer-Brody, 2015; Weobong et al., 2014; O'Hara and Wisner, 2014; Yim et al., 2015). The clinical symptoms associated with PND are commonly low mood, sadness, irritability, impaired concentration, feeling of guilt about the baby care and feeling overwhelmed. Postpartum depression (PPD) seems to have several distinct phenotypes as recently reported by consortium Postpartum Depression: Action Towards Causes (PACT, 2015). Women in class 1 had the least severe symptoms (mean EPDS score 10.5), followed by those in class 2 (mean EPDS score 14.8) and those in class 3 (mean EPDS score 20.1). The most severe PPD symptoms were significantly associated with poor mood (mean EPDS score 20.1), increased anxiety, onset of symptoms during pregnancy, obstetric complications, and suicidal ideation. In class 2, most women (62%) reported symptom onset within 4 weeks postpartum and had more pregnancy complications than in other two classes (69% vs 67% in class 1 and 29% in class 3) (PACT, 2015). The need of efficacious treatments is justified by high-risk suicidality, near to 20% of all postpartum deaths and reduced maternal sensitivity (Lindahl et al., 2005; Meltzer-Brody and Jones, 2015).

Lifetime occurrence of perinatal mood episodes was analysed in a large sample of women with bipolar I disorder, bipolar II disorder and RMD and rates of perinatal episodes per pregnancy/postpartum period were recorded. More than two-thirds of all diagnostic groups reported at least 1 lifetime episode of illness during pregnancy or the postpartum period, being mood episodes significantly more common in the postpartum period in bipolar I disorder and RMD; the risk of a perinatal major affective episode per pregnancy/postpartum period was lower in women with RMD (Di Florio et al., 2013). Currently we know that significant risk factors for early postpartum depressive symptoms are a history of mental illness including past MDE, PMDD, mood symptoms during the third trimester and low partner support (Bloch et al., 2006; Milgrom et al., 2008; Stuart-Parrigon and Stuart, 2014). A large prospective cohort study in perinatal mental health-the beyondblue National Postnatal Depression Program- conducted in all six states of Australia reported that antenatal depressive symptoms appear to be as common as postnatal depressive symptoms, thus confirming clinical reports. A very interesting study by Patton et al. (2015) – the Victorian Intergenerational Health Cohort Study (VIHCS) assessed the extent to which women with perinatal depressive symptoms had a history of mental health problems before conception. They reported that perinatal depressive symptoms are mostly preceded by mental health problems that begin before pregnancy, in adolescence or young adulthood, being women with a history of persisting common mental disorders before pregnancy a high-risk group. In light of their study they conclude that the window for considering preventive intervention for perinatal depression should be extended to the time before conception. A recent prospective mother–child study conducted in Greece analysed the relation between maternal trait anxiety and depression during pregnancy and the association with PPD, reporting the importance of antenatal maternal mental health and well being in identifying women at risk for PPD (Koutra et al., 2014).

The effects of prenatal maternal stress impact mother and fetus/child bonding and infant growth in utero, furthermore, prolonged stress may result in hyperactivity of the stress system, altering glucocorticoid feedback, creating a vulnerability to addictive and mood disorders in offsprings (Brittain et al., 2015). In the light of significant personal and social burden of PPD, purpose of the present review is to evaluate the state of art of the available biological biomarkers that could be useful in early detection of perinatal depression.

2. Methods

In order to provide an update overview, a research in main databases (Pubmed, ISIWEB of Knowledge, PsycINFO) was performed. Suitable articles were sourced from a comprehensive literature search and from references identified through other studies. All articles, concerning major/minor depression in pregnancy and postpartum were included. Keyword were "depression" matched with "pregnancy", "post partum", "perinatal" "biomarkers", "biochemistry", "immunology" "endocrinology", "genetic", "epigenetic", "clinical trials". Exclusion criteria were: animal studies, studies with different diagnosis (e.g. bipolar disorder), physiological studies, studies assessing rating scales, studies assessing the impact of pathological pregnancy on offsprings, neuroimaging studies.

The review covers findings from 1969 to 2015, last search was conducted on November 2015, even though most of articles have been produced in the last 10 years. After applying the inclusion and exclusion criteria, a total of 127 papers were included in the review, the majority of data being represented by endocrinological and immunological studies, while less studies have analysed biochemical and genetic pathways.

3. Genetic studies

As for other psychiatric disorders, PPD is, at least, partially genetic determined. The gene encoding BDNF is a strong candidate for PPD pathogenesis: its polymorphism (Val66Met) alters the regulated protein secretion (the Methionine variant is associated with insufficient secretion compared to the Valine variant). A study by Figueira et al. (2010) evaluated BDNF gene Val66Met polymorphism and the association with PPD, however no difference in BDNF genotype distribution was observed between the depressed and non-depressed women. A case-control study evaluated whether functional polymorphic variants, BDNF Val66Met, 5-HTTLPR, or Period2 (PER2) SNP 10870, are associated with PPD symptoms without revealing any statistically significant association between such polymorphisms and PPD symptoms. Interestingly, a significant association between BDNF Met66 carrier status and development of PPD symptoms was found at 6 weeks postpartum among mothers delivering during autumn/winter (Comasco et al., 2011). A case-control study found a distinctive gene expression signature of mononuclear cells after delivery in mothers with an emergent PPD with respect to healthy mothers, bringing initial evidence that early cell mapping may harbor valuable prognostic information to identify PPD onset (Segman et al., 2010; Licinio, 2010). SNPs in FADS1/FADS2, encoding Delta-5 and Delta-6 desaturase, rate-limiting enzymes in metabolism of LA to ARA and alpha-linolenic to eicosapentaenoic and DHA have been associated with higher PPD risk (Xie and Innis, 2009).

A genome-wide association study found that women with PPD displayed an increased sensitivity to estrogen signaling, confirming the previously proposed hypothesis of increased sex-steroid sensitivity as a susceptibility factor for PPD (Mehta et al., 2014). Nine polymorphisms in estrogen receptor alpha gene (ESR1) were studied in postpartum women supporting a role for ESR1 in the etiology of PPD, possibly through the modulation of serotonin signaling (Pinsonneault et al., 2013). Recently, Pařízek et al. (2014) found that androgen levels correlated with postpartum mood disorders. A prospective study by Kaminsky and Payne (2014)