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Perinatal major depression biomarkers: a systematic review

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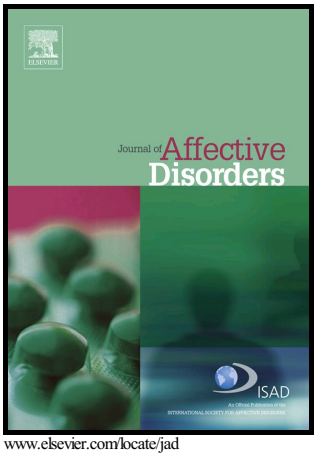

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Perinatal Major Depression Biomarkers: a systematic review

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Drs Buoli, Serati, Redaelli do not have any affiliation with or financial interest in any organization that might pose a conflict of interest with the present article.

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CONTENTS

List of abbreviations

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

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Highlight

1. Postpartum depression (PPD), now termed perinatal depression by the DSM-5, is a common medical complication associated with a poor outcome.
2. The majority of available data on the pathophisiology of PPD have been conducted in recent years. Most of them deal with endocrinological and immunological biomarkers, while only few biochemical/genetic biomarkers have been investigated showing interesting results.
3. Some robust associations with an increased risk of peripartum depressive symptoms have been reported with HPA axis, hormonal changes, IL-6, vitamin D, fatty acid, BDNF.
4. Affective disorders in pregnant women has to be detected as soon as possible and treated with focused therapies in order to reduce the impact of PPD on offsprings and promote the welfare of both mother and baby.

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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 have an impact on offspring: 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.

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1. Introduction

Perinatal depression, 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, perinatal depression 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 perinatal depression are commonly low mood, sadness, irritability, impaired concentration, feeling of guilt about the baby care and feeling overwhelmed. PPD seems to have several distinct phenotypes as recently reported by consortium Postpartum Depression: Action Towards Causes (PACT). 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). 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 and Dowswell, 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

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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 foetus/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.

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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 post-partum 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.

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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) identified estrogen mediated epigenetic changes associated with PPD, identifying two biomarkers, HP1BP3 and TTC9B, which predicted PPD in a sample of high risk women. In addition, the authors found a decrease in the ratio of monocytes to lymphocytes plus granulocytes in the antenatally depressed women in relation with HP1BP3 methylation status, thus supporting the hypothesis of a higher sensitivity to estrogens in women at risk for PPD. A cross-species translational study evaluating DNA methylation, confirmed the link of the two biomarker loci, HP1BP3 and TTC9B, with PPD onset with an area under the curve (AUC) of

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0.87 in antenatally euthymic women and 0.12 in a replication sample of antenatally depressed women, thus supporting the involvement of altered sensitivity to estrogen-mediated epigenetic alterations in PPD etiology (Guintivano et al., 2014). Recently Osborne and colleagues (2015) replicated Kaminsky/Guintivano findings (2014), in particular TTC9B and HP1BP3 DNA methylation have been associated with estradiol and allopregnanolone levels over the course of pregnancy, suggesting that epigenetic variation at these loci may be important for mediating hormonal sensitivity and possibly predicting PPD onset.

Maternal RNA was collected in order to analyse the pheripheral expression of glucorticoid receptor (GR) co-chaperone genes in women with a lifetime history of mood or anxiety disorder. This study reported that prenatal depressive symptoms appear to be associated with altered regulation of GR sensitivity, possibly being a biomarker for depressive symptoms during pregnancy (Katz et al., 2012). A prospective study found that PPD risk correlated significantly with 17β-estradiol (E2) induced DNA methylation change, suggesting an enhanced sensitivity to estrogen-based DNA methylation reprogramming in women at risk for PPD (Guintivano et al., 2014). A prospective study investigated the association of genetic variants in the glucocorticoid receptor (GR, NR3C1) and corticotropin releasing hormone receptor 1 (CRHR1) genes with increased risk for PPD, reporting a positive association in specific SNPs of genes, involved in 'stress' responses, that might contribute in the genetics of high-risk for depression during pregnancy and postpartum (Engineer et al., 2013). A case-control, prospective study analyzed steroid hormone function (NR3C1, FKBP5, ESR1, ESR2, PGR, AR, AKR1C2), neurotransmitter function (SLC6A4, MAOA, COMT, HTR2A), and neurotrophin function (BDNF), finding an association of three single nucleotide polymorphisms in the serotonin 2A receptor (HTR2A) with PPD (El-Ibiary and Cocohoba, 2008). A case-control study of oxytocin receptor gene (OXTR) DNA methylation (CpG site -934) and genotype (rs53576 and rs2254298) were assayed from DNA extracted during pregnancy: an interaction was found between rs53576 and methylation in the OXTR gene amongst women who did not have depression prenatally but developed PPD. Those women with GG genotype showed 2.63 greater odds of PPD for every 10% increase in methylation level, whereas methylation was unrelated to PPD amongst "A" carriers; OXTR could be a susceptible genotype play a contributory role in the etiology of PPD (Bell et al., 2015).

A prospective pregnancy cohort study examined associations between maternal depressive symptoms and placental expression of genes involved in glucocorticoid and serotonin transfer, reporting that altered placental function as a potential gestational-age-specific marker of PPD risk (Reynolds et al., 2015). A cohort study evaluated single nucleotide polymorphisms

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(SNPs) of tryptophan hydroxylase 2 (TPH2) gene in pregnant and postpartum women. The haplotype block in the promoter region of TPH2 showed significant associations with depression both in pregnancy and postpartum. Furthermore, a haplotype block in intron 8, had an influence on depression scores during pregnancy, but not after birth; the effect of TPH2 haplotypes on EPDS values was strongest during pregnancy and 6 months after birth (Fasching et al., 2012). Previously, Lin et al. (2009) investigated the role of TPH2 in the etiology of peripartum major depression and anxiety disorders, finding that TPH2 2755A allele increased 1.73 times the risk of peripartum major depression and anxiety disorders.

The serotonin-transporter linked polymorphic region (5-HTTLPR) S-allele carrier status was found to predict late postpartum depressive symptom severity only in case of negative life events (Mehta et al., 2012). An at-risk population sample was genotyped for 5-HTTLPR, reporting that the S-allele carrier status predicted the occurrence of a MDE in the early post-partum period (Binder et al., 2010). Previously, MAOA, COMT and 5-HTT polymorphisms were analysed, finding a significant interaction between these polymorphisms and the development of depressive symptoms in pregnancy; particularly, women carrying the combination of low activity variants of MAOA and COMT showed increased EPDS scores at the end of pregnancy and postpartum, but not during early pregnancy or 12-week postpartum (Doornbos et al., 2009a). A recent Chinese study reported the association between 5-HTTLPR allele LL and major depressive disorder in postpartum women (Zhang et al., 2014). Finally, an association between the COMT AA genotype (Met/Met) and PPD was reported by Alvim-Soares et al. (2013).

For a summary of the reviewed studied observing changes in genetic/epigenetic pathways in perinatal depression see Table 1.

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4. Biochemical studies

Depressive symptoms and serum zinc/magnesium levels were determined in antepartum and postpartum, revealing a relationship between severity of depressive symptoms and decreased serum zinc (but not magnesium) concentration in PPD (Wójcik et al., 2006). No relationship between maternal iron status and PPD was reported in a Chinese sample (Armony-Sivan et al., 2012). A prospective cohort study reported no significant associations between major depressive disorder (MDD) and nutritional biomarkers in mid-pregnancy (Bodnar et al., 2012). A recent cross-sectional Japanese study suggests that a higher intake of yogurt and calcium may be associated with a lower prevalence of depressive symptoms during pregnancy (Miyake et al., 2015b).

It is known that vitamin D has regulatory functions in immune system, furthermore it has been suggested that vitamin D could act as a potential neurosteroid: the relationship between this vitamin and depressive symptoms has been explored in these years with inconsistent results. In 2010 Murphy et al. postulated that there may be a negative correlation between vitamin D levels and PPD, being women with lower vitamin D levels at higher risk of depression. A significant negative correlation between vitamin D levels in the first trimester of pregnancy and depressive symptoms in the second trimester was later reported in two different studies (Cassidy-Bushrow et al. 2012a; Brandenbarg et al. 2012). Data by Gur and collegaues (2014) pointed out that lower maternal 25-hydroxy vitamin D3 levels, measured in a large prospective cohort study during the second trimester of pregnancy, were associated with higher levels of PPD at all time points (1st week, 6^{th} week, 6 months) ($p=0.003$, $p=0.004$ and $p<0.001$, respectively): data confirmed in a prospective cohort study by Robinson et al. (2014), reporting a significant correlation between vitamin D levels in pregnancy and PPD. A cross-sectional study, by Miyake et al. (2015a), found that higher dietary vitamin D intake was significantly associated with a lower prevalence of depressive symptoms during pregnancy. A recent prospective study reported among women with higher levels of inflammatory markers, an association between lower prenatal log 25(OH) D and significantly higher PPD symptoms (Accortt et al., 2015).

A prospective cohort study evaluated the association between serum lipids and depressive symptom scores during pregnancy: HDL-c concentrations were inversely associated with changes in EPDS score (Teofilo et al., 2014). Long-chain polyunsaturated fatty acids (LC-PUFA), particularly DHA and AA, were found to have an important role in foetal and infant growth and development. Observational studies have suggested an association between low DHA status after pregnancy and PPD. A study by Otto et al. (2003), compared DHA contents in plasma at delivery and after 32 weeks and evaluated mood symptoms in relation to EPDS,

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reporting a lower availability of DHA in the postpartum period in women included in the "possible depressed" group. Since LC-PUFA required by the foetus is supplied by preferential placental transfer of preformed LC-PUFA rather than their precursor, it has been hypothesized that additional LC-PUFA maternal supply, especially DHA, during pregnancy may improve maternal and infant outcomes. Currently, there are not sufficient data proving that the consumption of enriched n-3 LC-PUFA oils during pregnancy reduces the risk for PPD (De Giuseppe et al., 2014). Lower plasma DHA concentration was significantly associated with prenatal depressive symptoms in a Japanese sample, however low dietary fatty acid intake was not associated with depressive symptoms (Shiraishi et al., 2015). DHA supplementation, perceived stress and higher cortisol rate in response to a stressor during pregnancy were studied in a sample of African American women: DHA supplemented group reported lower levels of perceived stress at 30 weeks of gestation, lower cortisol output and a more modulated reaction in response to stress (Keenan et al., 2014). PUFA status in late pregnancy was studied in a large sample of women only a slightly link between fatty acids status in late pregnancy and PPD risk was reported (Parker et al., 2015). A low omega-3 index in late pregnancy was associated with higher depression score three months after delivery in a community-based prospective cohort (Markhus et al., 2013). A study by Sallis et al. (2014) found a weak positive association between omega-3 FAs and PPD. Supplementation of low doses of DHA or DHA plus AA during pregnancy would not prevent PPD symptoms (Doornbos et al., 2009b). EPA-rich fish oil and DHA-rich fish oil supplementation did not prevent depressive symptoms during pregnancy or postpartum in a sample of pregnant women at risk for depression (Mozurkewich et al., 2013). A prospective cohort study evaluated the prevalence of suicide risk (SR) and MDE in early pregnancy, as well as the relationship of serum fatty acid status: it reported that women with higher serum AA and AdA levels had a greater likelihood of SR and MDE (Vaz et al., 2014). The mother-offspring cohort study "Growing Up in Singapore Toward healthy Outcomes" (GUSTO) evaluated plasma LC-PUFA status during pregnancy and perinatal period, finding that lower plasma total omega-3 PUFA concentrations and higher plasma omega-6 were associated with increased antenatal anxiety but not postpartum anxiety: in addition, no association between plasma PUFAs and PPD was found (Chong et al., 2015). Previously, the same group examined the relationships of plasma folate and vitamin B12 concentrations with perinatal depression in a sample of pregnant women: plasma folate concentrations were significantly lower in women with probable antenatal depression, whereas, no difference in folate concentrations was observed in those with and without probable PPD (Chong et al., 2014). A cross-sectional study, conducted in a sample of urban South Indian pregnant women, reported that blood concentrations of

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vitamin B12 and folate were not associated with depressive symptoms (Lukose et al., 2014). Omura et al. (2002) compared plasma biopterin, a co-factor involved in the fenilananine and triptofan metabolism, in pregnancy and early puerperal period with respect to a control group. They reported a correlation between Zung's depressive scores and the total biopterin levels; the authors hypothesed that a depressive state in pregnancy or in the early puerperal period could have the same neurochemical basis as in normal depression. Lewis et al. (2012) reported no strong evidence that folic acid supplementation reduces the risk of depression during pregnancy and up to 8 months after pregnancy. A Chinese study found significantly higher homocysteine level in women with PPD than that in the control group (Huang et al., 2015).

BDNF levels play a critical role in the pathophysiology of depression. A German study analysed maternal BDNF serum levels reporting a marked decrease both of serotonin (5-HT) and BDNF levels and significantly higher cortisol levels in case of maternal depression, thus, women, displaying marked decrease of BDNF serum levels before and after childbirth, could have an increased risk for PPD (Lommatzsch et al., 2006). Some years later, BDNF levels were quantified in women with three or more stressful life events and they were found to have lower BDNF levels; furthermore, serum BDNF levels in women with PPD and presenting suicide risk were significantly lower with respect to women without suicide risk (Pinheiro et al., 2010). In a recent study by Fung et al (2015) lower maternal serum BDNF levels in early pregnancy have been associated with antepartum depression.

For a summary of the reviewed studied observing changes in biochemical pathways in perinatal depression see Table 2.

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5. Immunological studies

Immune system may contribute to PPD onset, according to psychoneuroimmunology model, originally suggested by Chrousos in 1995 and recently expanded (Elenkov et al., 2005; Corwin et al., 2010; Ellsworth-Bowers and Corwin, 2012). Currently we know that prolonged or excessive proinflammatory immune system activation (IL-1, IL-6, and TNF-α) is one of the mechanisms involved in depression (Altamura et al., 2014: Raison et al., 2006; Schiepers et al., 2005), even in perinatal episodes (Osborne and Monk, 2013). In addition postpartum depressive episodes share etiological similarities with immune-related disorders. A very interesting cohort study, carried out through the Danish population registry, confirmed the association between pre-eclampsia and postpartum psychiatric episodes; primiparous women had a higher risk of first-onset psychiatric episodes during the first month postpartum when pre-eclampsia was diagnosed during pregnancy. Furthermore, having both pre-eclampsia and a somatic co-morbidity resulted in the highest risk of psychiatric episodes during the 3-month period after childbirth (Bergink et al., 2015). Similar data about primiparous women were reported in a retrospective study by Di Florio et al. (2014). It is known that ischemic placenta releases factors that provoke a generalized maternal endothelial dysfunction, being inflammatory cytokines (IL6, TNF α and CRP) elevated in severe preeclampsia (Udenze et al., 2015; Lambert et al., 2014).

Interestingly, the administration of atypical antipsychotics in animal models, such as clozapine, seems to prevent the neuropathological alterations induced by maternal immune activation during pregnancy (Piontkewitz et al., 2009, 2011). TNF-α and IL-6 were quantified in the postpartum: a positive association between cytokine levels and depressive mood was reported in a study by Boufidou et al. (2009). A study, examining the relationships among stress, fatigue, depression, and cytokines was carried on in late pregnant women and at 4-6 postpartum weeks. In this study, mothers experienced more depressive symptoms prenatally than postnatally; furthermore all analysed cytokines did not show significant change from late pregnancy to postpartum with the exception of Granulocyte Colony-Stimulating Factor (G-CSF), an anti-inflammatory cytokine, that resulted to be increased. Interestingly, only stress was related to macrophage inflammatory protein-1β (MIP-1β), a chemokine that has the ability to induce chemotaxis and that plays an important role in embryo implantation and labor (Cheng and Pickler, 2014). Depression and inflammation are associated with poorer birth outcomes: a study with African-American women reported higher levels of some inflammatory biomarkers (IL-6, IL-1), were directly associated with more depressive symptoms and a disparate burden of poorer birth outcomes (Cassidy-Bushrow et al., 2012b). Similar results were reported by Azar and

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Mercer (2013): early and midgestation women with mild to moderate prenatal depressive symptoms were found to have increased inflammatory markers, in particular IL-6 levels. A prospective study found an early increase of IL-1beta after delivery in depressed women with respect to healthy ones, suggesting that elevated IL-1beta early in the postpartum may increase the risk of PPD (Corwin et al., 2008).

Studies in humans and animals link maternal infection and imbalanced levels of inflammatory mediators with a lifetime increased risk for neuropsychiatric disorders. In particular, exposure to viral or bacterial agents is critical if happens during the second trimester of human gestation (Ashdown et al., 2006). Pregnant women were studied after receiving influenza virus vaccination and depressive symptoms were associated with sensitization to inflammatory response during pregnancy, thus women with greater depressive symptoms may be more vulnerable to negative sequelae of infectious illness during pregnancy (Christian et al., 2010). Previously, the same group (2009), reported that patients with higher depressive scores had higher levels of IL-6 and marginally higher TNF-alpha. In mothers with PPD, regulatory T cells were significantly increased both during pregnancy and postpartum, and their number predicted future development of PPD. Furthermore, after delivery the decrease of CXCR 1, a chemokine receptor expressed on the surface of neutrophils in mammals, was significantly higher in depressed mothers also having elevated neopterin levels, which are a biomarker of inflammation (Krause et al., 2014). Plasma pro- and anti-inflammatory cytokines were measured in pregnant and postpartum women, reporting higher cortisol in depressed women. Furthermore, a family history of depression, high cortisol levels and higher pro-inflammatory state as shown by IL8/IL10 ratio were all significant predictors of subsequent PPD symptoms. In particular, one unit increase each in the IL8/IL10 ratio and cortisol resulted respectively in 1.50 and 2.16 fold increased risk of PPD (Corwin et al., 2015).

Cord/maternal blood IgG ratio was decreased in depressed women compared to controls; thus major depression during pregnancy could reduce prenatal transfer of IgG from mother to neonate (Kianbakht et al., 2013).

A longitudinal preliminary study with high risk PPD women measured serum C-reactive protein and IL-6, as well as tryptophan, kynurenine, and the kynurenine/tryptophan ratio. C-reactive protein levels were found to be positively related to atypical and total depression scores in the prepartum period and with atypical depression scores in the early postpartum period, while tryptophan was found to be negatively associated with total depression scores (Scrandis et al., 2008).

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For a summary of the reviewed studied observing changes in immunological pathways in perinatal depression see Table 3.

6. Endocrinological studies

Maternal hypothalamic-pituitary-adrenal (HPA) axis becomes gradually less responsive to stress as pregnancy progresses, being pregnancy a transient, physiologic, period of hypercortisolism (Mastorakos and Ilias, 2003). Alteration of HPA axis is considered as a robust biomarker of anxiety and depression: mid-pregnancy depression has been significantly associated with increased cortisol (O'Connor et al., 2014). In a prospective study by Glynn and Sandman (2014) depressive symptoms at 3-month postpartum were associated with elevated midgestational placental CRH (pCRH), whereas pCRH was not predictive of PPD symptoms at 6-month postpartum, and prepartum cortisol/corticotrophin levels did not increase the risk of developing PPD. Meltzer-Brody et al. (2011) failed to find an association between midpregnancy pCRH levels and risk of PPD; similar data were reported by Zaconeta et al. (2015) measuring CRH levels in cerebrospinal fluid (CSF).

A prospective study evaluated maternal self-report psychosocial distress at mid- and late gestation: cortisol levels were found to be directly correlate with maternal depression, anxiety and stress (Parcells, 2010). Maternal psychological well-being, parity status and birth weight were studied in relation to cortisol diurnal rhythm in pregnant women group: severe trait anxiety was associated with a flatter afternoon decline of cortisol (Kivlighan et al., 2008). A recent population-based longitudinal study of psychological wellbeing during pregnancy and the postpartum period assessed the association between evening salivary cortisol levels and depressive symptoms in the peripartum period. Women with postpartum EPDS score ≥ 10 had higher salivary evening cortisol at six weeks postpartum compared to healthy controls. Additionally, women with postpartum depressive symptoms had higher postpartum cortisol levels compared to both women with depressive symptoms antenatally and controls (Iliadis et al., 2015). Salivary cortisol and chromogranin A/protein concentration changes were studied as stress markers during pregnancy: the elevation of cortisol and chromogranin A/protein in the saliva was found to be suppressed in the chronic high stress group during pregnancy (Tsubouchi et al., 2011). A recent study reported than women with depressive symptoms in late pregnancy had elevated awakening salivary alpha-amylase (sAA) levels compared with non-depressed controls, highlighting that symptoms of depression during late pregnancy are associated with

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increased maternal sympathetic nervous system (SNS) activity (Braithwaite et al., 2015) A previous follow-up study reported higher ACTH levels in patients with postpartum thoughts of harming the infant, while no variations were found in CRH/cortisol levels (Labad et al., 2011).

A longitudinal study assessed salivary cortisol awakening response (CAR) at the 36th week of gestation and 6 weeks postpartum in order to analyse the association of maternal HPA activity during pregnancy with maternal HPA responsiveness to stress after parturition. CAR in late pregnancy negatively predicted maternal ACTH, plasma cortisol and salivary cortisol, but not emotional stress reactivity at 8 weeks postpartum, whereas CAR at 6 weeks postpartum failed to predict ACTH, plasma cortisol, salivary cortisol or emotional stress responses at 8 weeks postpartum (Meinlschmidt et al., 2010).

Yim et al. (2010), found that women developing PPD symptoms had higher beta-endorphin levels throughout pregnancy than healthy pregnant women.

A prospective study found no associations between progesterone levels and mood symptoms in postpartum, whereas lower levels of evening cortisol in the immediate peripartum period were associated with PPD (Harris et al., 1996). Bloch et al. (2000) provided direct evidence in support of the involvement of the reproductive hormones estrogen and progesterone in the development of PPD, being women with a history of PPD more sensitive to mood-destabilizing effects of gonadal steroids. In contrast, some years later, data by Klier et al. (2007) did not support the hypotheses of a role of sex hormones in the etiology of PPD. An Italian study evaluated serum allopregnanolone, progesterone, cortisol, prolactin, and estradiol in blood samples of primiparous women: serum allopregnanolone levels were significantly lower in women experiencing postpartum "blues" with respect to euthymic women, whereas progesterone levels were not significantly different (Nappi et al, 2001). Serum estradiol, progesterone and testosterone concentrations were measured upon admission for delivery and daily until the fourth postpartum day, without finding an association between the occurrence of postpartum mood disorders and sex steroid hormone levels, whereas preterm labour may be associated with a higher risk of postpartum mood disturbances (Chatzicharalampous et al., 2011).

A prospective observational study evaluated whether the presence of thyroperoxidase antibodies (TPOAbs) during pregnancy can be regarded as a marker for depression in the first year postpartum: it reported a positive correlation between TPOAbs presence during early pregnancy and the development of PPD (Kuijpens et al., 2001). A previous pilot study measured thyroid and adrenal hormones and mood symptoms at the end of pregnancy and postpartum in 12 women with major depression history and 14 women with negative psychiatric history. Subjects

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with prior depressions had significantly higher T3, T4, TSH and cortisol levels during the puerperium, while subjects with higher levels of postpartum dysphoria had lower T4 and free T4 levels as well as higher T3 uptake at 38 weeks of pregnancy, higher cortisol levels during the puerperium (Pedersen et al., 1993).

Oxytocin (OT) system contribute to parental, romantic and filial attachment in humans. Skrundz et al. (2011) measured plasma OXT in a prospective study during pregnancy reporting that OXT concentration in mid-pregnancy significantly predicted PPD symptoms at 2 weeks postpartum.

For a summary of the reviewed studied observing changes in endocrinological pathways in perinatal depression see Table 4.

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7. Conclusions

In 1998 The National Institutes of Health Biomarkers Definitions Working Group defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, that has to be reproducible and objective in indicating a medical state observed and has to repeatedly show to correctly predict clinical outcomes (Strimbu et al., 2010). In the last decades, several biomarkers have been investigated in relation to PPD, but only some of them have being associated with increased risk of depressive symptoms during pregnancy and postpartum. With regard to biochemical studies, maternal iron status was not associated with PPD onset while biopterin, homocysteine, zinc, vitamin B12 levels have been reported to have a positive association with PPD onset although in single studies having small sample size, thus needing replications. It is interesting to underline that five non-controlled studies with a total number of more than 5,000 women, found a relation between vitamin D levels during pregnancy and risk of future PPD. From these studies it seems that vitamin D levels could be a possible useful biomarker for PPD early detection, being low vitamin D levels in pregnancy associated to higher EPDS scores (Murphy et al., 2010; Cassidy et al., 2012a; Brandenbarg et al., 2012; Robinson et al., 2014; Gur et al., 2014; Accortt et al., 2015; Miyake et al., 2015a). BDNF serum levels may predict the development of mood disorders in the perinatal period (Pinheiro et al., 2010; Fung et al., 2015). Cochrane reviews (Miller et al., 2013; Dennis and Dowswell, 2013) conclude that there is insufficient evidence to state that selenium, DHA or EPA supplementation prevent PPD: most studies have been judged to be of low-to-moderate

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quality for small sample sizes and failure to adhere to Consolidated Standards of Reporting Trials guidelines (Larqué et al., 2012). However a recent review by Shapiro et al. (2012) seems to partially support a link between n-3 PUFAs, the 5-HTT genotype, and PPD.

In line with previous studies reporting higher antibody levels against viruses in pregnant mothers of patients with psychotic disorders, a very recent case- control study investigated the potential association between viral infections during pregnancy and progeny with psychotic disorders, finding a significantly lower viral prevalence in the pregnant mothers of offspring with schizophrenia, thus confirming that a more prominent maternal immune activity during pregnancy can be considered a risk factor for future psychotic disorders (Canuti et al., 2015). As gestation progresses, placenta becomes increasingly resilient to maternal inflammation, but there is a narrow window in gestation when the placenta is still vulnerable to immune challenge, with implications on early cortical neurogenesis in foetal brain (Burton and Fowden, 2015).

With regard to immunological and endocrinological studies, regulatory T cell count seems to predict PPD (Krause et al., 2014), having women with a history of depression an amplified sensitized inflammatory response (Azar and Mercer, 2013; Scrandis et al., 2008). Most studies found an association between cytokines and PPD (see below) while only two small studies have found no association (Cheng et al., 2014; Kianbakht et al., 2013).

Abnormal HPA axis function is frequently found in pregnant women affected by MDD, who have high levels of cortisol that can pass through the placenta, determing preterm labor and reducing birth weight. Most studies measuring cortisol levels in relation to PPD found an association however some did not (Kivlinghan et al., 2008; Meinlschmidt et al., 2010; Meltzer-Brody et al., 2011; Zaconeta et al., 2015). Endocrinological studies show that TPOAbs presence during gestation is associated with the occurrence of subsequent depression during the postpartum period but further studies are necessary to draw sound conclusions (Kuijpens et al., 2001). Women with PPD seem to display 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; Guintivano et al., 2014). In line with such data a recent review postulated that reproductive hormones may influence every biological system especially in a subgroup of women constituting a "hormone-sensitive" PPD phenotype, as estrogen are closely tied to HPA axis and inflammation, all these factors may contribute to the etiology of PPD (Schiller et al., 2015).

Regarding genetic studies a recent systematic review by Figueiredo and colleagues (2014) summarize available data on PPD, reinforcing the idea of a pathophysiological role of the hormonal changes. Without cytokine glucocorticoid feedback, a pregnant woman's ability to

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regulate inflammation is limited, potentially contributing to adverse maternal and infant outcomes. In particular, IL-6 seems to be a reliable and useful biomarker of risk in perinatal depression as confirmed in different studies (Boufidou et al., 2009; Christian et al., 2009, 2010; Krause et al., 2014; Cassidy-Bushrow et al., 2012b; Azar et al., 2013). PPD magnetic resonance studies are limited in number and design, a recent systematic literature search yielded only eleven studies in which findings appear to replicate those obtained in MDD (Fiorelli et al., 2015). As for other mental disorders, we have to take into account that PPD is a complex disorder involving gene-environment interactions (GEI). Moreover it is important to underline that some of the cited biomarkers, possibly predictive of PPD onset, have been previously linked to MDD (e.g vitamin D, IL-6, PUFA), supporting a common etiopathogenetic pathways. Future studies should focus on specific PPD biomarkers that could represent an early marker of disease, thus modifying PPD natural course. Prospective and controlled studies are needed to better explore for example the supplementation with micronutrients that, in the last years, have shown a role in the synthesis and absorption of neurotransmitters and in epigenetic modifications.

Affective disorders in pregnant women have to be detected as soon as possible and treated with focused therapies in order to prevent deleterious effects and promote the welfare of both mother and baby. Although it was not in the aim of this review we have to underline how a woman's good mental health status can contribute to the infant's future well being, as some studies have shown. More longitudinal and interventional studies, are needed to increase our knowledge about etiology, development and management of maternal distress, being a priority the search for reliable biomarkers for at-risk mothers in the next future.

Searching: clinical trial, pregnancy, depression, biomarker, immune system, endocrinology, biochemical, postpartum, peripartum, genetic.

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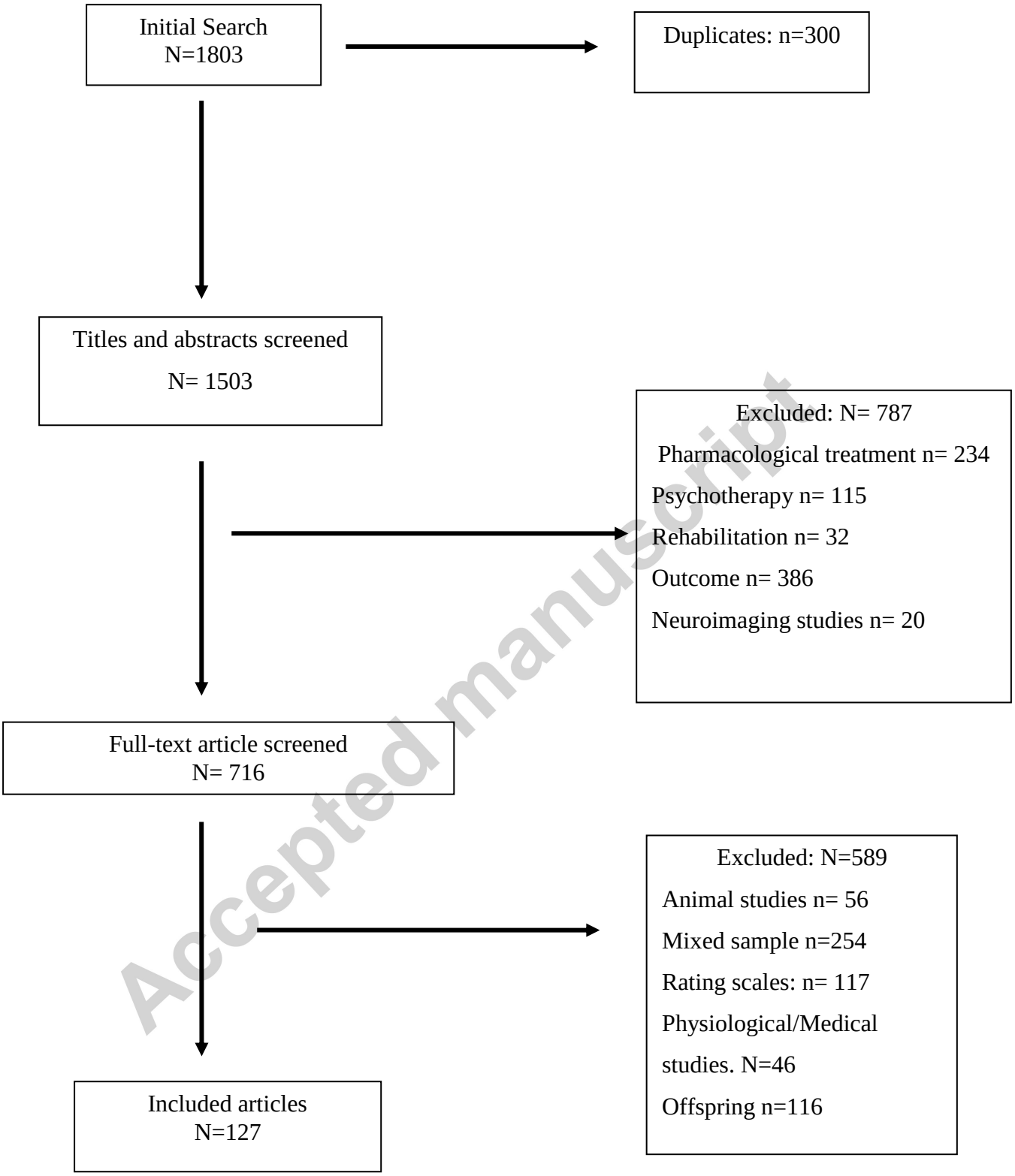

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Tab. 1 Genetic studies

Author, year Sample size	Methods	Results
Figueira et al., 2010 227 mothers	EPDS, biological, psychiatric and environmental assessment and PPD risk.	No difference in BDNF genotype distribution between depressed/non-depressed women. No association between BDNF polymorphisms and PPD.
Comasco et al. 2011 275 mothers Case-control study	Genes encoding for BDNF, serotonin transporter (5-HTT) and Period2 (PER2). EPDS, stressful life events (SLEs) and maternity stressors assessment	Significant association between BDNF Met66 carrier status and development of PPD symptoms. A cumulative effect was detected with carriers of a greater number of 5-HTTLPR S and BDNFVal66Met Met alleles reporting higher EPDS scores, if delivered during autumn/winter.
Segman et al., 2010 19 women case-control design	Blood mononuclear cells	A distinctive gene expression signature was observed after delivery among mothers with an emergent PPD.
Xie et al., 2009 69 pregnant women Pilot study	Genotyping rs174553, rs99780, rs174575, and rs174583 in FADS1/FADS2, blood lipid fatty acids and EPDS.	Association between rs174575 and PPD risk. SNPs in FADS1/FADS2 are associated with higher blood lipid LA and lower ARA and PPD risk.
Mehta et al., 2014 62 women	Gene expression and plasma estradiol and estriol measure.	Women with PPD displayed an increased sensitivity to estrogen signalling.
Pinsonneault et al., 2013 257 postpartum women	SCID, MINI, EPDS, MADRS. Genomic DNA extraction for nine *ESR1* variants and detection of a significant association with EPDS scores.	Role for *ESR1* in the etiology of PPD, possibly through the modulation of serotonin signalling.
El-Ibiary et al., 2008 case-control, prospective study	Steroid hormone function, neurotransmitter function and neurotrophin function (BDNF)	Association of three single nucleotide polymorphisms in the serotonin 2A receptor (HTR2A) with PPD
Bell et al., 2015 545 pregnant women case-control study	OXTR DNA methylation (CpG site -934) and genotype (rs53576 and rs2254298).	Evidence of an interaction between rs53576 and methylation in the OXTR gene amongst women who did not have depression prenatally but developed PPD. GG genotype showed 2.63 greater odds of PPD for every 10% increase in methylation level.
Lin and collegues, 2009 200 postpartum	Schedule for Affective Disorders and Schizophrenia (CM-SADS)—Six single nucleotide polymorphisms were selected	The TPH2 2755A allele was found only in women with peripartum major depression and anxiety disorder and exhibited a dominant gene action with

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women (117 major depression and/or anxiety disorder; 83 healthy controls)	from previously profiled genetic information of TPH2.	an estimated disease risk of 1.73.
Mehta et al.,2012 419 non-psychiatric pregnant women	Depression assessment EPDS. Genotype of the 5-HTTLPR assessment.	The 5-HTTLPR S-allele carrier status predicted late postpartum depressive symptom severity only in the presence of negative life events.
Binder et al., 2010 274 women with a history of MDD prospective observational study	Assessment (SCID), HAM-D 5-HTTLPR genotyping and evaluation	5-HTTLPR S-allele carrier status predicted the occurrence of a MDE in the early post-partum period only.
Doornbos et al. 2009a 89 pregnant women	Depressive symptoms assessment EPDS. MAOA, COMT and 5-HTT polymorphisms were analyzed	A significant interaction between the development of depressive symptoms and polymorphisms in 5-HTT; MAOA and COMT and MAOA x COMT. Women carrying the combination of low activity variants of MAOA and COMT showed increased EPDS scores.
Fasching, 2012 361 pregnant women Cohort study	EPDS assessment. Genotyping of single nucleotide polymorphisms (SNPs) in TPH2 and SNPs.	Significant associations between the haplotype block in the promoter region of TPH2 and depression. Influence of a haplotype block in intron 8 on depression scores during pregnancy.
Zhang et al. 2014 192 women with MDD	BDI, HAMA, HRSD, SAS, PSQI, and EPDS, PHQ-9. SLC6A4 promoter VNTR polymorphism genotyping.	5-HTTLPR is strongly associated with MDD in postpartum women. Women who carry the long allele when experiencing maternal pregnancy complications showed higher prevalence ratios for symptoms of postpartum depression.
Engineer, 2013 200 pregnant women prospective study	EPDS assessment Genotyping of the BclI and ER22/23EK single nucleotide polymorphisms (SNPs) of the GR and the haplotype-tagged rs1876828, rs242939 and rs242941 SNPs of the CRHR1.	Evidence that specific SNPs of genes involved in 'stress' responses might contribute in the genetics of high-risk for depression during pregnancy and postpartum.
Alvim-Soares et al., 2013 116 women	COMT Val158Met SNP was evaluated, EPDS collected	An association was found between the COMT AA genotype (Met/Met) and PPD
Kaminsky and Payne 2014 cross-species translational design	DNA methylation profiles cross-referenced with syntenic locations, which demonstrated murine hippocampal DNA methylation changes in response to long-term treatment with 17b-estradiol.	Decrease in the ratio of monocytes to lymphocytes and granulocytes in the antenatally depressed women that correlated with HP1BP3 DNA methylation status.

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Licinio, 2010	Gene expression from peripheral blood mononuclear cells	Downregulation of transcription after delivery, with differential immune activation, decreased transcriptional engagement in cell proliferation, and DNA replication and repair processes
Osborne et al., 2015	TTC9B and HP1BP3 DNA methylation association to the change in estradiol and allopregnanolone over the course of pregnancy	Epigenetic variation at these loci may be important for mediating hormonal sensitivity and possibly predicting PPD onset.

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Tab. 2 Biochemical studies

Author, year Sample size	Methods	Results
Armony-Sivan et al., 2012 567 pregnant women	A complete blood count, ZPP (zinc protoporphyrin), serum ferritin, and sTfR (soluble transferrin receptor) assessment. EPDS.	No relations between maternal iron status and maternal symptoms of PPD.
Omura et al., 2002 14 normal pregnant and 15 normal puerperal women	Plasma total biopterin and tetrahydrobiopterin levels measure.	Plasma biopterin levels in pregnancy and the early puerperal period closely resembled those of patients with mood disorders who show depressive symptoms.
Huang et al., 2015 43 women	Homocysteine level.	Homocysteine levels in women with PPD was significantly higher than that in the control group.
Wojcik et al., 2006 66 women	Depressive symptoms and serum zinc and magnesium level in antepartum and postpartum women. BDI.	Relationship between severity of depressive symptoms and decreased serum zinc (but not magnesium) concentration in postpartum depression.
Lukose et al., 2014 365 pregnant women cross-sectional study	Kessler Psychological Distress Scale (K-10). Nutritional, clinical and biochemical factors assessment.	No association between blood concentrations of vitamin B12, folate and depressive symptoms.
Murphy et al., 2010 97 postpartum women exploratory, descriptive study	Serum 25(OH)D samples collection and EPDS.	Negative correlation between vitamin D levels and PPD, being women with lower vitamin D levels at higher risk of depression.
Cassidy-Bushrow et al., 2012a 178 women	Vitamin D dosage and depression symptoms measure with CES-D.	Increased depressive symptoms in African American women with lower vitamin D.
Brandenbarg et al., 2012 4236 women	Maternal serum vitamin D. CES-D	Women with high levels of depressive symptoms (28%) had lower vitamin D concentrations than women with low levels of depressive symptoms.
Robinson et al., 2014	Serum collection of 25(OH)-vitamin D.	Women in the lowest quartile for 25(OH)-vitamin D status were more

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796 pregnant women		likely to report a higher level of PPD symptoms than women who were in the highest quartile for vitamin D.
Gur et al., 2014 179 pregnant women	Serum 25(OH)D3 levels Maternal PPD assessment with EPDS.	Significant relationship between low 25(OH)D3 levels in mid-pregnancy and high EPDS scores. Negative correlation between vitamin D levels and EDPS.
Accortt et al., 2015 91 women Prospective study	Vitamin D status (serum 25-hydroxyvitamin D, 25[OH]D, inflammatory markers dosage	An inverse association between prenatal log 25(OH) D and PPD symptomatology approached significance, IL-6 and IL-6/IL-10 ratio significantly moderated the effect. Among women with higher levels of inflammatory markers, lower prenatal log 25(OH)D was associated with significantly higher PPD symptoms.
Miyake et al., 2015a 1745 pregnant women Cross-sectional study	CES-D assessment. Dietary intake assessment during the preceding month using a self-administered diet history questionnaire.	Significant association between higher dietary vitamin D intake and a lower prevalence of depressive symptoms during pregnancy, independent of potential dietary and nondietary confounding factors.
Otto et al., 2003 112 women	DHA and its status indicator n-6 docosapentaenoic acid (n-6DPA, 22:5n-6) in the plasma phospholipids. EPDS.	The postpartum increase of the functional DHA status, expressed as the ratio DHA/n-6DPA, was significantly lower in the 'possibly depressed' group compared to the non-depressed group.
Teofilo 2014 238 pregnant women cohort study	EPDS Assessment. Serum concentrations of triglycerides, total cholesterol, and low- and high-density lipoproteins were the main exposures.	Lower EPDS scores in women classified in the 3rd tertile of the distribution of HDL-c concentrations during pregnancy, when compared to those classified in the first or second tertile. Inverse association between HDL-c concentrations and changes in EPDS score.
Mozurkewich EL 2013 126 pregnant women	EPA-rich fish oil, DHA-rich fish oil, or soy oil placebo random intake. BDI and MINI	No differences between groups in BDI scores. Significant increase of post supplementation concentrations of serum EPA and serum DHA respectively in EPA- and DHA-rich fish oil groups. Inverse association between serum DHA-concentrations at 34-36 weeks and BDI scores in late pregnancy.
Shiraishi M., 2015 329 pregnant	EPDS, plasma EPA and DHA concentrations assayed.	Significant association between lower plasma docosahexaenoic acid concentration and prenatal depressive

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women cross-sectional study		symptoms.
Keenan K., 2014 64 pregnant women randomized controlled trial	Cortisol response to a controlled stressor, the TSST was measured from saliva samples collected upon arrival to the laboratory and after the completion of the TSST.	Women in the DHA supplementation had lower cortisol output and a more modulated response to the stressor.
Parker G., 2015 911 pregnant women	EPDS assessment Blood collection to generate data on nine PUFA variables.	Univariate associations between pre-natal depression and measures of blood fatty acids. Such associations were not found post-natally, but different associations were quantified between EPDS-diagnosed depression and total omega-6, total omega-3 and EPA omega-3.
Markhus MW 2013 72 pregnant women prospective cohort study	Fatty acid status Screening for PPD using the EPDS.	Association between a low omega-3 index in late pregnancy and higher depression score three months postpartum. Inverse correlation between DPA content, DHA content, omega-3 index, omega-3/omega-6 ratio, total HUFA score, omega-3 HUFA score with the EPDS score.
Sallis, 2014	Association between levels of two omega-3 FAs (DHA and EPA) and perinatal onset depression, antenatal depression and postnatal depression.	A weak positive association was found with FAs and PPD.
Vaz, 2014 234 pregnant women prospective cohort study	Suicide risk and MDE defined according to the MINI. Fatty acid compositions determined	Higher likelihood of suicide risk among women with higher AA levels and adrenic acid levels. Higher likelihood of MDE among women with higher AA levels and AdA levels.
Chong, 2015 cohort study	Plasma LC-PUFAs measure. STAY and EPDS assessment.	Lower plasma total omega-3 PUFA concentrations and higher plasma omega-6: omega-3 PUFA ratios, were associated with increased antenatal anxiety, but not postpartum anxiety.
Doornbos et al. 2009b 119 pregnant women	Women were supplemented daily with placebo, DHA (220 mg) or DHA+AA (220 mg each). Fatty acid analyses. EPDS	The supplementation groups did not differ in mean EPDS scores or changes in EPDS scores, nor in incidence or severity of postpartum blues. Red blood cell DHA, AA and DHA/AA ratio did not correlate with EPDS or blues scores.
Lommatzch, 2006, 40 pregnant and	EPDS assessment Blood collection, measure BDNF serum concentrations, 5-HT and	Maternal serum levels BDNF were markedly decreased, both before and after childbirth. BDNF correlated with

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40 non pregnant women	Transforming growth factor b1 (TGF-b1)	decreased 5-HT levels in serum. There were significantly higher cortisol levels in cases of maternal depression than in cases without depression.
Pinheiro, 2010 968 pregnant women cross-sectional study	PHQ-9 assessment. Maternal serum BDNF levels were measure.	Maternal early pregnancy serum BDNF levels were significantly lower in women with antepartum depression compared to women without depression. Lower BDNF levels were associated with increased odds of maternal antepartum depression. Women whose serum BDNF levels were in the lowest three quartiles had 1.61-fold increased odds of antepartum depression as compared with women whose BDNF levels were in the highest quartile.
Fung, 2015 968 pregnant women	PHQ-9assessment. Maternal serum BDNF levels	Significantly lower maternal early pregnancy serum BDNF levels in women with antepartum depression compared to women without depression.
Miyake et al., 2015b 1745 pregnant women Cross-sectional study	CES-D assessment. Dietary intake assessment during the preceding month using a self-administered diet history questionnaire.	Higher intake of yogurt and calcium may be associated with a lower prevalence of depressive symptoms during pregnancy
Lewis et al., 2012 6809 pregnant women	EPDS Methylenetetrahydrofolate reductase (MTHFR) C677T genotype on change in depression scores, and carried out our analysis of folic acid supplementation and depression stratifying by genotype.	No strong evidence that folic acid supplementation reduces the risk of depression during pregnancy and up to 8 months after pregnancy. Low folate as a risk factor for depression outside of pregnancy, especially among women with the MTHFR C677T TT genotype.
Bodnar 2012 135 pregnant women Prospective cohort study	HRSD; fatty acids, plasma folate was measured, maternal plasma ascorbic acid concentrations were determined.	No association between Essential Fatty Acid or Micronutrient patterns and MDD.
Chong, 2014 709 pregnant women	Measure of plasma folate and vitamin B12. EPDS assessment.	Plasma folate concentrations significantly lower in women with probable antenatal depression than those without. No difference in folate concentrations in women with and without probable PPD.

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Tab. 3 Immunological studies

Author, year Sample size	Methods	Results
Scrandis et al., 2008 27 pregnant women Longitudinal, preliminary study	Serum C-reactive protein and IL-6, tryptophan, kynurenine, and the kynurenine/tryptophan ratio.	C-reactive protein levels were found to be positively related to atypical and total depression scores in the prepartum period and with atypical depression scores in the early postpartum period. Negative association between tryptophan and total depression scores.
Boufidou et al., 2009 56 women	A blood sample and a CSF sample TNF-a and IL-6 were quantified with an ELISA assay, EPDS	Cytokine levels were positively associated with depressive mood during the first four days postpartum and also at sixth week postpartum.
Christian, 2009 60 pregnant women	PSS and CES-D. Measure of serum levels of IL-6 and TNF-alpha.	Higher scores on the CES-D were related to significantly higher levels of IL-6 and marginally higher TNF-alpha. Perceived stress was not significantly related to serum levels of IL-6 or TNF-alpha.
Krause et al., 2014 100 women prospective study	Immune parameters (neopterin, regulatory T cells, CXCR1, CCR2, MNP1 and CD11a) MADRS, EPDS	Regulatory T cells were significantly increased prenatal and postnatal in mothers with postnatal depressive symptoms. Mothers with postnatal depressive symptoms showed already prenatal significantly elevated neopterin levels.
Cheng et al., 2014 46 pregnant women	Set of questionnaire and a 1 ml of blood at both data collection point	All cytokines analysed except for G-CSF, an anti-inflammatory cytokine that increased, did not showed significant change from late pregnancy to postpartum.
Kianbakht et al., 2013	Peripheral venous blood from depressed women and cord venous blood from their neonates. Evaluation serum levels of immunoglobulins IgG, IgM and IgA and complements C3 and C4 were determined.	Immune parameters of depressed women were not significantly different from controls. Lymphocyte counts in neonates of women with major and minor depression were increased, whereas ratio of the cord blood level of IgG to the maternal blood level of IgG in neonates of women with major depression were decreased compared to controls.
Cassidy-Bushrow et al., 2012b 187 women	CES-D scale and inflammatory biomarkers (high-sensitivity C-reactive protein [hs-CRP], IL-6, IL-10, IL-1β, and TNF-α	Depressive symptoms are associated with increased inflammation among pregnant African-American women
Azar et al.,	PHQ-9 assessment	Association between proinflammatory

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2013 27 pregnant women prospective pilot study	Serum inflammatory markers.	markers and prenatal depressive symptoms.
Christian et al., 2010 22 pregnant women	CES-D; cytokine blood collection, serum levels of macrophage migration inhibitory factor (MIF) were assayed	Depressive symptoms predicted exaggerated MIF production following influenza virus vaccination during pregnancy
Corwin, 2015 152 pregnant women	Measure of plasma pro- and anti-inflammatory cytokines. EPDS assessment.	Cortisol AUC was higher in symptomatic women on Day 14. Family history of depression, day 14 cortisol AUC, and the day 14 IL8/IL10 ratio were significant predictors of PPD symptoms.

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Tab. 4 Endocrinological studies

Author, year Sample size	Methods	Results
Pedersen et al., 1993 12 pregnant women with major depression history and 14 women with negative psychiatric history Pilot study	Measure of thyroid, adrenal hormones and mood	Subjects with prior depressions had significantly higher T3, T4, TSH and cortisol levels during the puerperium. Lower T4 and free T4 levels as well as higher T3 uptake at 38 weeks of pregnancy, higher cortisol levels during the puerperium in subjects with higher levels of postpartum dysphoria.
Kuijpens, 2001 310 pregnant women prospective observational study	TSH, free thyroxine and TPOAb testing, depression assessment according to the Research Diagnostic Criteria (RDC).	After the exclusion of women who were depressed at 12 weeks gestation, the presence of TPOAbs during early pregnancy was still found to be associated with the development of PPD; after exclusion of women who had had depression in earlier life, TPOAb during early gestation was still associated with PPD.
Bloch, 2000	Gonadotropin-releasing hormone agonist leuprolide acetate, adding back supraphysiologic doses of estradiol and progesterone for 8 weeks, and then withdrawing both steroids under double-blind conditions.	Five of the eight women with a history of PPD (62.5%) and none of the eight women in the comparison group developed significant mood symptoms during the withdrawal period. Increase in depressive symptoms in women with a history of PPD.
Bloch, 2006 1800 women	EPDS.	Significant risk factors for early postpartum depressive symptoms were a history of mental illness including past PPD, premenstrual dysphoric disorder, and mood symptoms during the third trimester.
Nappi 2001, 40 primiparous women	Serum allopregnanolone, progesterone, cortisol, prolactin, and estradiol. HAM-D	Serum allopregnanolone levels were significantly lower in those women experiencing postpartum "blues" with respect to euthymic women; progesterone levels did not differ significantly.
Klier et al., 2007 192 pregnant women	EPDS Levels of estrogen and progesterone.	Results in contrast to the current hypotheses of estrogen withdrawal or hypogonadal levels as an etiological factor for PPD.
Pařízek, 2014	Samples of maternal blood, mixed umbilical cord blood collection.	Changes in androgens levels correlating with postpartum mood

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44 pregnant women	HAM-D.	disorders. After childbirth both testosterone, most likely of maternal origin and estrogens from the fetal compartment played the main role.
Guintivano, 2014 prospective study cross-species translational design	Estrogen-mediated epigenetic reprogramming events, DNA methylation profiles and risk PPD	PPD risk correlated significantly with 17β-estradiol (E2) induced DNA methylation change.
Chatzicharalampous et al., 2011 57 post partum women	PBQ and EPDS. Measure of serum estradiol, progesterone and testosterone concentrations upon admission for delivery and daily until the fourth postpartum day..	No association between the occurrence of postpartum mood disorders and sex steroid hormone levels. Preterm labour may be associated with a higher risk of postpartum mood disturbances.
Harris, 1996 120 primiparous women prospective study	Saliva collection for characterisation of cortisol and progesterone profiles.	Association between lower levels of evening cortisol in the immediate peripartum period and PPD.
Kivlinghan, 2008 98 low-risk pregnant women (51 primiparae)	Saliva collection cortisol Assay. STA-Y; PSS	Regulation of the HPA axis may differ by parity status with downstream implications for fetal growth and development. Higher trait anxiety was associated with a flatter afternoon decline for all mothers.
Meinlschmidt et al., 2010 22 pregnant women Longitudinal study	Assessment of the salivary cortisol awakening response (CAR) to a psychosocial laboratory stressor	CAR in late pregnancy negatively predicted maternal ACTH, plasma cortisol and salivary cortisol, but not emotional stress reactivity at 8 weeks postpartum. CAR at 6 weeks postpartum failed to predict ACTH, plasma cortisol, salivary cortisol or emotional stress responses at 8 weeks postpartum.
Meltzer Brody, 2011 1230 pregnant women prospective cohort study	The relationship between pCRH Maternal depression assessed CES-D and EPDS	No association between higher midpregnancy pCRH and an increased risk of PPD
Tsubouchi, 2011 69 pregnant women	Salivary cortisol levels and chromogranin A/protein Zung self-rating depression scale and GHQ-28.	Cortisol levels in the saliva of pregnant women showed biphasic change during pregnancy. Chromogranin A/protein levels in the saliva of pregnant women increased in the second and the early third trimesters and decreased to the puerperal period. Salivary cortisol concentrations of the chronic high stress group were

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		significantly lower compared with those of the normal group. Salivary chromogranin A/protein concentrations of the chronic high stress group were also significantly lower than those of the normal group.
Labad et al., 2011 132 post partum women	Assessment for trait anxiety, social support, peripartum or postpartum anxiety or depression, stressful life events and obstetric variables, Postpartum thoughts of harming the infant. Measure of serum cortisol, and plasma CRH and ACTH levels.	Higher ACTH levels in women with postpartum thoughts of harming the infant. No significant differences in CRH or cortisol levels.
Katz, 2012 106 pregnant women with a lifetime history of mood or anxiety disorders	Maternal RNA from whole blood, plasma and the BDI were collected. The expression of 16 genes in whole blood involved in glucorticoid receptor (GR). Plasma concentrations of progesterone, estradiol and cortisol were measured.	mRNA expression of a number of GR-complex regulating genes was up-regulated over pregnancy. Women with depressive symptoms showed significantly smaller increases in mRNA expression of four of these genes - FKBP5, BAG1, NCOA1 and PPID. GR sensitivity diminished with progression of pregnancy and increasing maternal depressive symptoms. Plasma concentrations of gonadal steroids and cortisol did not differ over pregnancy between women with and without clinically relevant depressive symptoms.
Glynn, 2014 170 pregnant women	Blood samples were obtained and assayed to determine maternal cortisol, adrenocorticotropic hormone, and pCRH concentrations.	Depressive symptoms at 3 months postpartum were associated with elevated midgestational pCRH and also accelerated trajectories of pCRH. Placental CRH was not predictive of PPD symptoms at 6 months postpartum. Prepartum cortisol and corticotrophin profiles were not associated with PPD symptoms.
O'Connor, 2014 101 women at mid-pregnancy and early third trimester.	Links between diurnal cortisol and mood symptoms from self-report questionnaire and diagnostic interview.	There were modest but significant associations between depression and elevated cortisol, indexed by a decreased morning level and diminished diurnal decline.
Reynolds, 2015 54 healthy pregnant women with singleton pregnancies and without pregnancy complications	CES-D term placental mRNAs of 11beta-hydroxysteroid dehydrogenase type 2 (HSD2B11), type 1 (HSD1B11), glucocorticoid (NR3C1), mineralocorticoid receptors (NR3C2) and serotonin transporter (SLC6A4).	Higher placental NR3C1 mRNA partly mediated the association between maternal depressive symptoms during pregnancy and infant regulatory behaviors.

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Parcells, 2010 59 pregnant women	Maternal depression, anxiety and stress assessment and an estimate of the stress hormone cortisol from maternal saliva samples.	High incidences of prenatal depression, anxiety and stress across the 3rd trimester.
Braithwaite et al., 2015 76 pregnant women	EPDS. Saliva samples, to be assayed for alpha-amylase activity.	Women with depressive symptoms in later pregnancy had elevated awakening sAA levels compared with non-depressed controls, and continued to have raised sAA throughout the day.
Iliadis et al., 2015 365 pregnant women population-based longitudinal study	EPDS Evening salivary samples for cortisol analysis.	Higher salivary evening cortisol in women with postpartum EPDS score ≥ 10 compared to healthy controls.
Zaconeta et al., 2015 107 healthy pregnant women 22 nonpregnant healthy women prospective cohort study	CRH in CSF was measured in pregnant and nonpregnant women The association between CSF CRH concentration EPDS.	CRH concentration in the CSF was significantly higher in pregnant than in nonpregnant women. No difference in CRH concentration between women without depressive symptoms and women showing such symptoms during pregnancy or in the postpartum period.
Skrundz, 2011 100 pregnant women	Blood samples for the OXT assessment. EPDS.	An increased occurrence of depressive symptoms in the first 2 weeks after delivery in individuals with low plasma OXT concentrations in pregnancy, also after controlling for prepartal EPDS scores.
Yim, 2010 307 pregnant women	Blood samples pre and postpartum for assessment of beta-endorphin. CES-D and the EPDS.	Women developping PPD symptoms had higher levels of beta-endorphin throughout pregnancy compared to women without PPD symptoms.

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