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REVIEW

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Conventional and new immunotherapies for immune system dysregulation in postpartum mood disorders: comparisons to immune system dysregulations in bipolar disorder, major depression, and postpartum autoimmune thyroid disease

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ABSTRACT

Introduction: Postpartum mood disorders are heterogenous disorders and comprise postpartum psychosis and postpartum depression. Evidence is accumulating that systemic monocyte/macrophage activation, low-grade inflammation and (premature senescence related) T cell defects increase the risk for mood disorders outside pregnancy by affecting the function of microglia and T cells in the emotional brain (the cortico-limbic system) leading to inadequate mood regulation upon stress.

Areas covered: The evidence in the literature that similar immune dysregulations are present in postpartum mood disorders.

Results: The physiological postpartum period is characterized by a rapid T cell surge and a mild activation of the monocyte/macrophage system. Postpartum mood disorder patients show a diminished T cell surge (including that of T regulatory cells) and an increase in low grade inflammation, that is, an increased inflammatory state of monocytes/macrophages and higher levels of serum pro-inflammatory cytokines.

Expert opinion: Anti-inflammatory agents (e.g. COX-2 inhibitors) and T cell boosting agents (e.g. low-dose IL-2 therapy) should be further investigated as treatment. The hypothesis should be investigated that postpartum mood disorders are active episodes (triggered by changes in the postpartum immuno-endocrine milieu) in ongoing, dynamically fluctuating aberrant neuro-immune-endocrine trajectories leading to mood disorders in women (inheritably) vulnerable to these disorders.

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Postpartum psychosis; postpartum depression; postpartum thyroiditis; monocytes; T cells; pathogenesis; therapy

1. Introduction to postpartum mood disorders

Mood disorders during pregnancy and the postpartum period have a large impact on mothers and their offspring, and timely diagnosis and treatment are therefore important. While depression can occur before pregnancy, during pregnancy, and at any point in the postpartum period, there is a period of increased vulnerability to more severe depression shortly after delivery [1]. Apart from postpartum depression, the postpartum mood disorders comprise a condition called postpartum psychosis. Both conditions put mothers at risk for suicide, and inpatient admission is often warranted [2].

Postpartum psychosis (PP) is a condition with relatively low prevalence (1 per 1000 childbirths, compared to approximately 150 per 1000 births for postpartum depression) (Table 1). In the majority of cases, the onset is rapid and within 2 weeks postpartum. Early symptoms include insomnia and mood fluctuation, followed by more severe mood symptoms such as mania, depression, or a mixed state, as well as psychotic and cognitive symptoms [3–5]. Postpartum psychosis is related to bipolar disorder and is considered an affective psychosis, not a primary psychotic disorder, since mood symptoms predominate. Moreover, after postpartum psychosis, women are at high risk of developing a lifelong bipolar disorder, but they are not at very high risk of schizophrenia or other psychotic disorders [6,7].

Postpartum depression is less severe than postpartum psychosis, but more common. Postpartum depression refers to a non-psychotic depressive episode that affects approximately 10–15% of mothers after childbirth [8]. Women with postpartum depression often experience symptoms of misery, apathy, irritability, social isolation, anxiety, failure to cope, and guilt. Postpartum depression is highly heterogeneous, and genetic and hormonal influences, psychosocial status, and stressful life events are important risk and modulating factors. The onset is highly variable; two thirds of women with postpartum depression have their onset during pregnancy or even before pregnancy [9]. The other one third of women have an onset or exacerbation of depressive symptoms in the weeks or months after childbirth. This broad definition of postpartum depression has greatly hampered efforts to identify causal mechanisms, which is why it

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Article highlights

- Postpartum mood disorders are heterogenous disorders of which part is caused by aberrancies in immuno-neuro-endocrine network interactions.
- Immuno-neuro-endocrine interactions determine the structure and function of the emotional brain, which is important in stress handling.
- Elements important in these immuno-neuro-endocrine network interactions are the microglia, intracerebral T cells, the fronto-limbic system, the hypothalamus-pituitary-adrenal axis, the sex steroids, oxytocin and prolactin.
- Acute postpartum psychosis and acute early onset severe postpartum depression belong to the bipolar spectrum and share with mania/bipolar depression immune abnormalities, such as inflammatory and chemotactic hyperactivity of monocytes/macrophages/microglia and reduced T helper cells (particularly T regulatory cells).
- Postpartum depression is a heterogenous condition and two-third occurs in a chronic process starting before childbirth; immune abnormalities are comparable to those found in major unipolar depression with T cell senescence and related inflammatory activation as key phenomena.
- Immuno-therapeutic approaches correcting T cell senescence, reduced T regulatory cells and inflammation hold promise as novel interventions.

might be beneficial to focus research efforts on more severe depression with a clear onset after childbirth.

Severe depression with an acute onset within the first month postpartum might be a more homogenous subtype and is characterized by a clear peak in incidence as well as prevalence. Depression with a clear onset after childbirth is clinically associated with bipolar disorder, just like postpartum psychosis [10,11]. In addition, there is some evidence for a shared genetic vulnerability between bipolar disorder and severe postpartum mood episodes [12–14]. There is also genetic evidence for the familiality of postpartum depression only when it is measured in the first 6–8 weeks postpartum, and not when it is measured later in the postpartum period [15].

We will first discuss the role of immune system dysregulation in severe mood disorders in general, thereafter we will highlight the peripartum period as a period of drastic fluctuating immuno-endocrine changes, followed by a discussion on immune dysregulations in the following postpartum mood conditions:

Postpartum Psychosis*.
Postpartum Depression that is severe and acute in first days/weeks after childbirth*.
* related to bipolar disorder
Postpartum Depression with onset weeks/months after childbirth.
Postpartum Depression with antenatal onset.
Postpartum Depression in combination with postpartum thyroiditis

2. A new concept in psychiatry: immune dysregulation as a causal factor for severe mood disorders

In the past decades, a new concept has been introduced that is additive to the accepted view that changes in the brain and the neuro-endocrine system elicited by stress and/or hormonal changes are playing a role in the pathogenesis of mood disorders. This novel concept places immune dysregulation at the center of attention [16] (Figure 1).

Brain immune dysregulation in severe mood disorders. It has become evident that microglia and T cells are not only brain sentinel and gatekeeper cells for defense against microbial intruders, but in resting state (defined as not involved in defense processes and activated by danger signals) are supporting anabolic processes for growth and function of the frontal brain-limbic system. This brain system regulates, in a physiological way, mood and behavior under stressful and life-threatening conditions. Microglia are paramount for the growth and interconnectivity of neurons in the limbic system during embryogenesis and later in life, and play a role in synaptic pruning, regulate neurotransmitter balances in the synapses, and remove apoptotic and necrotic cells [17]. Moreover, microglia support the proper myelination of white matter tracts [17]. In a preclinical mouse model, absence of microglia induces obsessive-compulsive-like behavior, while reintroduction of the microglia restores normal behavior [18]. T cells play an important role in the function of the frontal brain-limbic system too. Mouse models characterized by an absence of T cells show an anxious behavior, while reintroduction, particularly of the CCR6+ Th17 cells, restores normal behavior [19]. There exists a specific route of entry of CCR6+ T cells into the brain via the choroid plexus [20].

In severe mood disorders, such as major depressive disorder (MDD) and bipolar disorder (BD), pro-inflammatory activated microglia and diffuse accumulations of macrophages and T cells in the perivascular spaces have been observed in post mortem and PET studies of (amongst other areas) the frontal brain-limbic system [21]. Pro-inflammatory activation of microglia was found to be associated with cognitive dysfunctions, severity of depression, and suicide, in agreement with postmortem findings of higher density of activated microglia in patients with mood disorders who died of suicide [22]. Prolonged microglial pro-inflammatory activation induces pathological neuronal apoptotic mechanisms destroying functional neuronal pathways and inhibiting the construction of new pathways, which may manifest in reduced neural plasticity and brain connectivity, leading to suboptimal brain

Table 1. Mood symptoms and syndromes during the postpartum period.

	Estimated incidence	Onset	Frequent symptoms	Management
'Baby blues'	50%	3–5 days postpartum	Emotional lability, mood swings, anxiety	Self-limited, emotional support
Postpartum depression	15%	Variable window: during pregnancy up to the first months postpartum	Low mood, feelings of guilt, anhedonia, impaired bonding with the child	Psychotherapy, antidepressant medication, mother-baby therapy
Postpartum psychosis*	0.1–0.2%	Within first weeks postpartum	Agitation, irritability, euphoric mood, depression, delusions, hallucinations, confusion, cognitive symptoms	Hospitalization, medical workup, lithium, antipsychotics, ECT

*Including postpartum psychosis, mania, and postpartum depression with psychotic features.

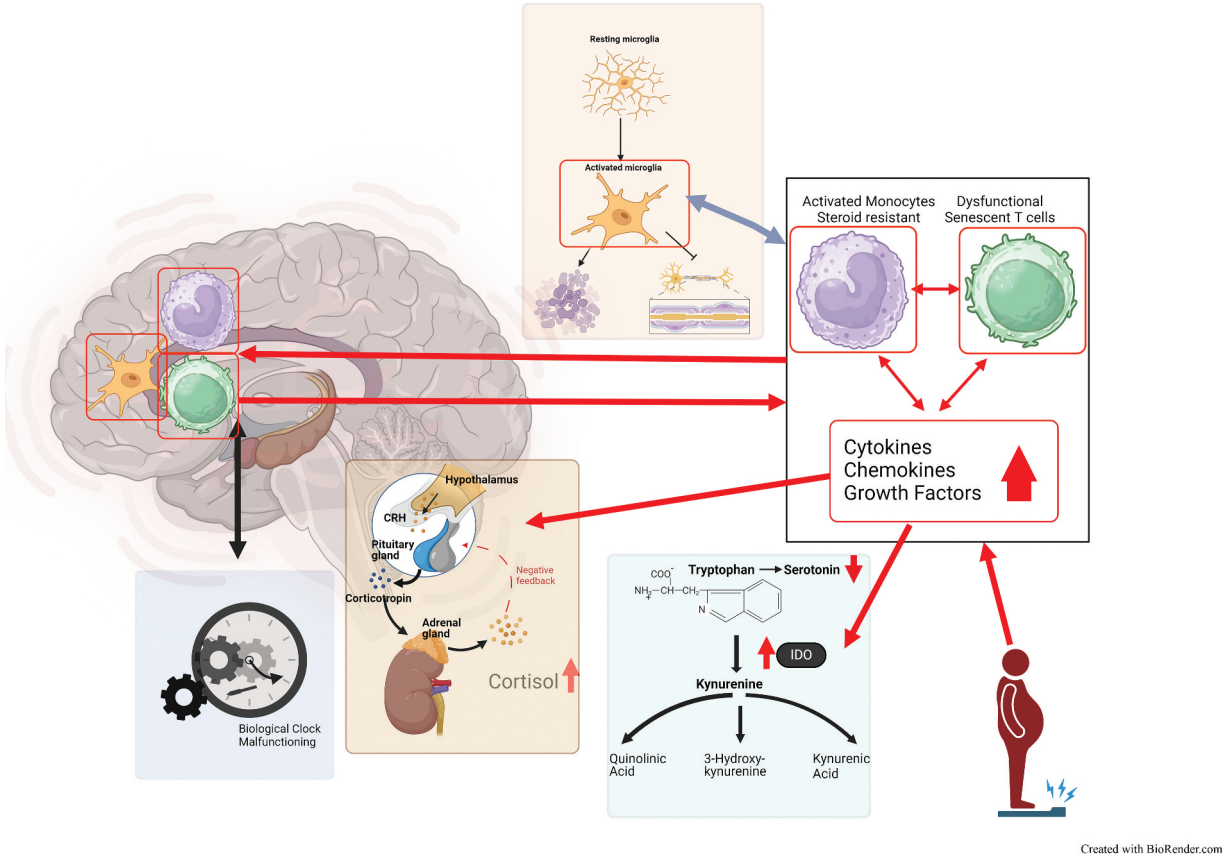

Figure 1. Immune pathological mechanisms involved in mood disorders.

It has become evident that microglia and T cells are not only brain sentinel and gatekeeper cells for immune defense, but in resting state (defined as neither involved in defense processes nor activated by danger signals) are supporting anabolic processes for growth and function of the frontal brain-limbic system, a system regulating mood and behavior under stressful and life-threatening conditions. In patients with a severe mood disorder an abnormal inflammatory activation state, and a higher presence in the brain have been found. The abnormal state of the cells impacts nerve fiber function and synapse transmitter composition.

These local microglia and T cell abnormalities are part of systemic monocyte, macrophage, and lymphocytic abnormalities found in these psychiatric conditions and detectable in the blood. Systemic immune abnormalities comprise an activation and raised inflammatory state and a dysfunctionality and a premature senescence of the cells, and these immune abnormalities are also a characteristic of postpartum psychosis depression patients (see text).

Cytokines produced by the systemic immune cells (but also to a certain extent by other cells like neurons, astrocytes, endothelial cells and adipocytes in obese individuals) contribute to high systemic and brain concentrations of the compounds and influence the catabolism of tryptophan, important for the production of downstream serotonin and kynurenine catabolites, such as quinolate and kynurenic acid, which play a role in neurotransmission, neuroprotection, and neurotoxicity.

The cytokines also activate the HPA axis to produce more cortisol to dampen the immune activation, but on the long run steroid resistance kicks in (activated monocytes become steroid resistance and cytokines downregulate steroid receptors) to lead to even higher cortisol levels.

The cells of the immune system are also markedly affected by sleep and disruption of the biological clock (a characteristic of severe psychiatric disorders), leading to even higher levels of cytokines.

function and maladaptive behavior. Currently it seems that the dualistic classification of microglia activation (resting versus pro-inflammatory) is not fully representative of the wide repertoire of microglial states and functions in development, plasticity, aging and disease [23].

Systemic immune dysregulation of immune cells in severe mood disorders. The local microglia, perivascular macrophage, and T cell abnormalities are part of systemic monocyte, macrophage, and lymphocyte abnormalities found in severe MDD and BD and detectable in the blood [24–27].

Systemic immune abnormalities comprise a premature aging and inflammaging of circulating monocytes and T cells in MDD, the inflammatory state of the cells being even higher in individuals with childhood trauma and cardiovascular disease [28]. An increased inflammatory state of monocytes has also been found in active bipolar mania and depression [26]. Similar immune cellular abnormalities are also present in postpartum psychosis and postpartum depression [29,30]. This review will focus in particular on these immune cell abnormalities found in the peripheral blood of postpartum psychotic or depressed patients.

Systemic immune dysregulation of inflammatory cytokines in severe mood disorders. It is already known for a considerable period of time (since the 1990s) that increases in the levels of pro-inflammatory compounds in the serum of patients is part of the systemic immune abnormalities. Recent meta-analyses confirm that both MDD and active bipolar mania and depression must indeed be considered as pro-inflammatory conditions.

In MDD the increase of a variety of more than 10 pro-inflammatory compounds was shown in a recent meta-analysis including over 5000 patients and controls [31]; CRP,

IL-1β, IL-6 and TNF-α being studied the most. In another meta-analysis [32] childhood trauma and obesity were found to be important drivers of these increases. Also inflammation (measured by CRP or IL-6) predicted future depression in another meta-analysis among children and adolescents [33], while results suggest that bidirectional associations existed between depression and the pro-inflammatory state.

In BD patients the importance of peripheral pro-inflammatory compound have been confirmed too in a recent meta-analysis [34]. In the study, CRP and TNF-α were considered to represent state markers, as they were only elevated during mood episodes, while IL-6 appeared to be a trait marker for BD.

It is important to note that we and others [35] have found that the increases in pro-inflammatory compounds in the circulation of mood disorder patients are associated with reduced cortical thickness and white matter microstructure alterations, phenotypes linking the pro-inflammatory compound elevations to poor responsiveness to antidepressant treatment, cognitive impairment and severe depressive psychopathology.

The inflammatory compounds measured in the circulation do only poorly correlate with the gene expression of the compounds in circulating immune cells [26,36], and therefore must have other sources. It is known that endothelial cells, adipocytes, but also brain glial cells and even neurons are capable of producing these inflammatory compounds [37,38], making local vicious circles of interaction possible. Indeed neuronal interaction networks have been described involving reactive microglia and astrocytes, inflammatory cells and cytokines and TLR2, TLR3 and TLR 4 pathways in various neurologic disorders, including those with a mood component [39,40].

HPA axis disturbances. In response to the raised serum levels of pro-inflammatory compounds (especially of IL-1β, IL-6 and TNF-α), there is increased secretion of corticotrophin releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol. Normally, glucocorticoids then act as negative feedback on the inflammatory response to avoid the deleterious effects of excessive production of inflammatory mediators. However, in case of prolonged low grade inflammation in mood disorders monocytes become glucocorticoid resistant [29], thus allowing pro-inflammatory signaling pathways to avoid normal feedback inhibition. The pro-inflammatory cytokines decrease the expression, translocation and downstream effects of glucocorticoid receptors, thereby blunting the negative feedback loop of the HPA axis allowing for further elevation of cortisol levels. Accordingly, increased cortisol levels that are resistant to regulatory feedback by the HPA axis are among the most consistently replicated markers of mood disorder [41].

Tryptophan catabolic abnormalities in severe mood disorders. Cytokines produced by the abnormally functioning monocytes, macrophages and T cells also influence the catabolism of tryptophan, important for the production of downstream serotonin and kynurenine catabolites, such as quinolate and kynurenic acid, which play a role in neurotransmission, neuroprotection, and neurotoxicity.

A key idea in this hypothesis is that the increased inflammatory compounds increase the conversion of tryptophan to kynurenine by activating the enzyme indolamine 2,3-dioxygenase (IDO-1) [42]. This mechanism causes depletion of tryptophan and subsequent decrease in serotonin levels. Moreover, kynurenine degradation leads to the formation of 3-hydroxykynurenine (3-HK) and quinolinic acid (QUIN) or kynurenic acid (KA). While KA shows a neuroprotective effect, competitively antagonizing NMDA glutamate receptors, 3-HK and QUIN seem to exert neurotoxic effects. Furthermore, IL-6 and TNF-α have been shown to directly increase serotonin turnover by facilitating its release and conversion into 5-hydroxyindoleacetic acid [43]. Of note, serotoninergic abnormalities are a well-established feature of mood disorders pathophysiology, with a relative decrease in cortical serotonin stimulation during depression, and an excessive activation of the kynurenine pathway, which seems to be shifted toward its neurotoxic branch (3-HK, QUIN) and contribute to lower the availability of serotonin. However, it must be noted that in recent studies of our group [42] on the tryptophan metabolism in a large group of severely depressed patients we did not find higher kynurenine levels, a higher expression of IDO and a stimulation of the neurotoxic branch, although we did find low tryptophan levels linked to the increased pro-inflammatory monocyte state of the patients. More experiments are needed to clarify the tryptophan catabolism in mood disorder patients, also taking into account a possible heterogeneity and the stage of the disorder (see later).

Disruption of the biological clock. Dysfunction of the circadian timing system is considered as a transdiagnostic contributor to several psychiatric disorders, by disrupting sleep and the circadian rhythmicity of physiological processes including neurotransmitter and hormone release and immune function. In turn, the mood disorders behavioral psychopathology deepens circadian disruption, thus leading to a circle of progressive symptomatologic worsening. The immune system is also markedly affected by sleep and circadian disruption, leading to higher levels of cytokines also involved in depression, such as IL-1, IL-6, and TNF-α [44]. In turn, the circadian timing system plays a key role in inducing and sustaining sleep, and in promoting the core brain homeostatic processes which take place during sleep.

3. The peripartum period as a time of extensive and dynamic physiological changes in the immune-endocrine milieu

Neuro-endocrine milieu. The peripartum period is a period in which the endocrine milieu is physiologically, but drastically and dynamically, changing, with increases in levels of Human Chorionic Gonadotropin (HCG), estrogens, and progesterone derivatives during pregnancy, with sharp decreases after parturition. The physiology of the hypothalamic-pituitary-adrenal (HPA) axis also undergoes substantial changes [45]. Cortisol levels increase substantially toward parturition, mainly due to the production of placental CRH (pCRH), to decrease sharply after childbirth. Several reports suggest a causal relationship between these gonadotropic and HPA axis alterations and the occurrence of postpartum mood disorders, yet clear correlations and explanations do not exist [46,47].

Oxytocin and prolactin also play a role in the changing endocrine milieu during and after childbirth [48,49]. Prolactin levels rise as of the first trimester and increase linearly. The dramatic drop in progesterone following delivery releases its inhibitory effect on milk protein production, allowing lactation to proceed in the presence of abundant, unopposed prolactin. Frequent suckling then becomes the primary stimulus for continued prolactin release during breastfeeding. Oxytocin is increasingly produced during the process of parturition and is implicated in childbirth and uterus contraction; later it is involved in milk ejection and breastfeeding. With regard to behavior, the brain oxytocin system has been implicated in decreasing maternal levels of fear, pain, and stress during childbirth, but also in cuddling and empathy behavior thereafter, while prolactin-driven brain adaptations are crucial for regulating maternal emotionality, well-being, and stress responses [50,51]. These peripartum changes in oxytocin and prolactin milieu have been discussed as important triggering factors for mood disorders occurring in the peripartum period, yet again clear correlations and explanations do not exist and seem to be contextual.

Immune system milieu. But there are not only considerable changes in the neuro-endocrine milieu during pregnancy and in the postpartum period, that are thought to be responsible for changes in mood and behavior in the peripartum period. There are also considerable immune changes, which can be considered as physiological adaptations to the pregnancy and postpartum conditions [52,53]. These immune changes can also be viewed as important factors in the development of mood disorders (see following chapters).

The pregnancy related immune changes are a dampening of the parts of the immune system that specifically react to the new semi-foreign (fetal) antigens to protect the (semi-foreign) fetus from rejection. More specifically there exist in the placenta at the decidua-fetal interface an immune suppressive and tolerogenic milieu for paternal antigens (e.g. production of immune suppressive cytokines/factors, non-attraction of effector T cells, proliferation of T regulator cells). Local antigen-presenting macrophages are set at a tolerogenic setpoint (so-called tolerogenic dendritic cells) to locally support this immunosuppressive/tolerogenic state [54–57]. Systemic monocytes and macrophages are immune-metabolically activated, particularly in the first trimester, most likely to be able to combat foreign intruders in this T cell tolerogenic milieu of pregnancy (Supplementary material and Figure 2, left panel). Trophoblastic factors, high levels of HCG and progesterone are thought to play important roles in the induction of these T cell tolerance mechanisms and monocyte/macrophage alterations ([58] Supplementary material). That these local placental immunosuppressive/tolerogenic mechanisms have systemic tolerogenic consequences is illustrated by the fact that autoimmune diseases often improve during pregnancy with decreases in the level of autoantibodies [59].

In the postpartum period, there is a 'rebound' activation of the pregnancy-suppressed/tolerogenic T cell system [29,60]. Prolactin might play a role here as a T cell stimulator [61]. Our research team found systemic T cell increases in the circulation of healthy postpartum women, particularly of T cytotoxic cells, Th1 cells and T regulatory cells [30]. We assume that the latter plays a role in controlling an over activation of the postpartum activated immune system. The postpartum immune activation lasted several months, with the increases in T regulatory cells staying the longest, probably providing an immune milieu combatting a high chance of auto-inflammation [62].

Monocytes and macrophages also stay at a somewhat altered immune-metabolically activated setpoint (supplementary

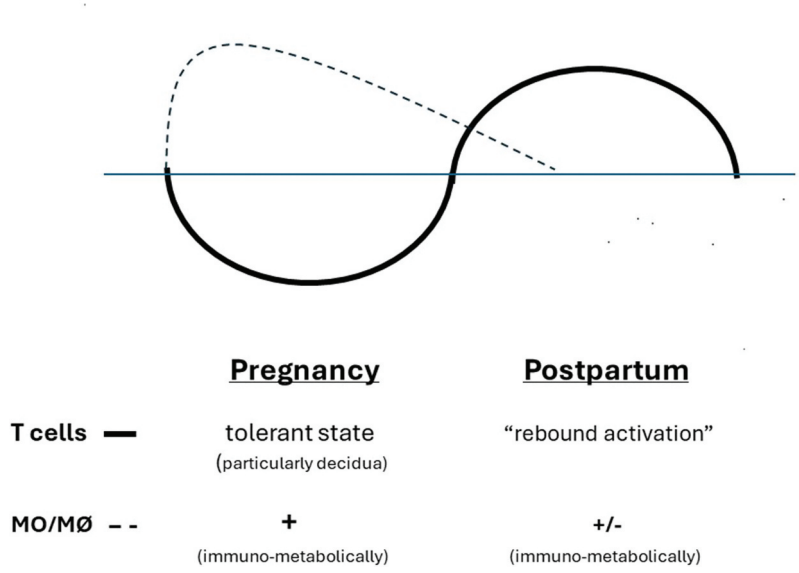

Figure 2. Dynamic and fluctuating immune changes during pregnancy and postpartum in the general population.

The T cell system is in a tolerogenic mode during pregnancy, particularly at the maternal-placenta interface to accept the semi-foreign fetus. T regulator cells play a prominent role in this. In the postpartum period there is a 'rebound' activation: Numbers of particularly Th1 and T cytotoxic cells increase. Also, T regulator cells increase, probably to control the activation of the effector T cells.

The monocyte/macrophage (Mo/Mø) system is immuno-metabolically activated particularly in the first trimester to decrease during pregnancy and early postpartum (see for details text and supplementary material).

material, and Figure 2, left panel), but it is debated whether levels of inflammatory compounds produced by these macrophages are raised in serum [29,63,64]. The T cell and monocyte activation after childbirth is thought to be beneficial to resist the higher chance of infections in this vulnerable period for the young mother.

Tryptophan metabolism. The first two months of the physiological postpartum period were also characterized in our studies by low tryptophan levels [62]. Tryptophan is the precursor of serotonin, an important neurotransmitter combatting depression. In the postpartum period we also found a preferential breakdown of tryptophan toward kynurenine and an increased breakdown of kynurenine toward neurotoxic 3-hydroxykynurenine away from neuroprotective kynurenic acid [62]. The above-described postpartum immune activation is thought to be the driver of these tryptophan catabolic alterations. The decrease of the serotonin pathway and increase in neurotoxic catabolites is thought to contribute to the postpartum blues.

In conclusion: The pregnancy period is a period of immune acceptance of the semi-foreign fetus (with heightened T cell tolerance mechanisms, particularly at the decidua-fetal interface), while the postpartum period is a period of controlled physiological immune activation of both the T cell and monocyte/macrophage system (Figure 2).

In the following chapters, it is discussed that the control over this immune suppression/activation might be lost in situations of a preexisting liability to a dysregulated immune responsiveness (genetically or environmentally determined). This would lead to enhanced states of low grade inflammation and an accelerated premature monocyte and T cell senescence with consequences for an altered regulation of mood and behavior in the peripartum period.

4. Postpartum psychosis and severe postpartum depression starting shortly after childbirth

4.1. Immune profile of postpartum psychosis and severe postpartum depression starting shortly after childbirth

We found patients with postpartum psychosis and with an early onset severe postpartum depression to be deficient of the physiological postpartum increase in circulating CD3+ T cells and lacking in particular increases in CD4+ T-helper cells, CD8+ T-cytotoxic cells, and CD4+ T regulatory cells [30] (Figure 3).

Patients did, however, show a significant elevation of circulating monocyte levels and a significant and strong monocyte inflammatory and adhesive/chemotactic activation (Figure 3) as compared to general population controls and postpartum healthy females who had limited increases in immune-metabolic activation (Figure 2) [29]. Also, the glucocorticoid receptor α to β gene ratio was decreased in the inflammatory activated monocytes of postpartum psychosis patients, and this sign of glucocorticoid resistance correlated strongly to the monocyte inflammatory activation state [29]. This suggests that the over activated monocytes are resistant to the anti-inflammatory effect of raised cortisol levels and stress in the postpartum period of patients with postpartum psychosis [65,66]. Therefore, our data underscore the dysfunctional link between the endocrine and immune systems during postpartum psychosis.

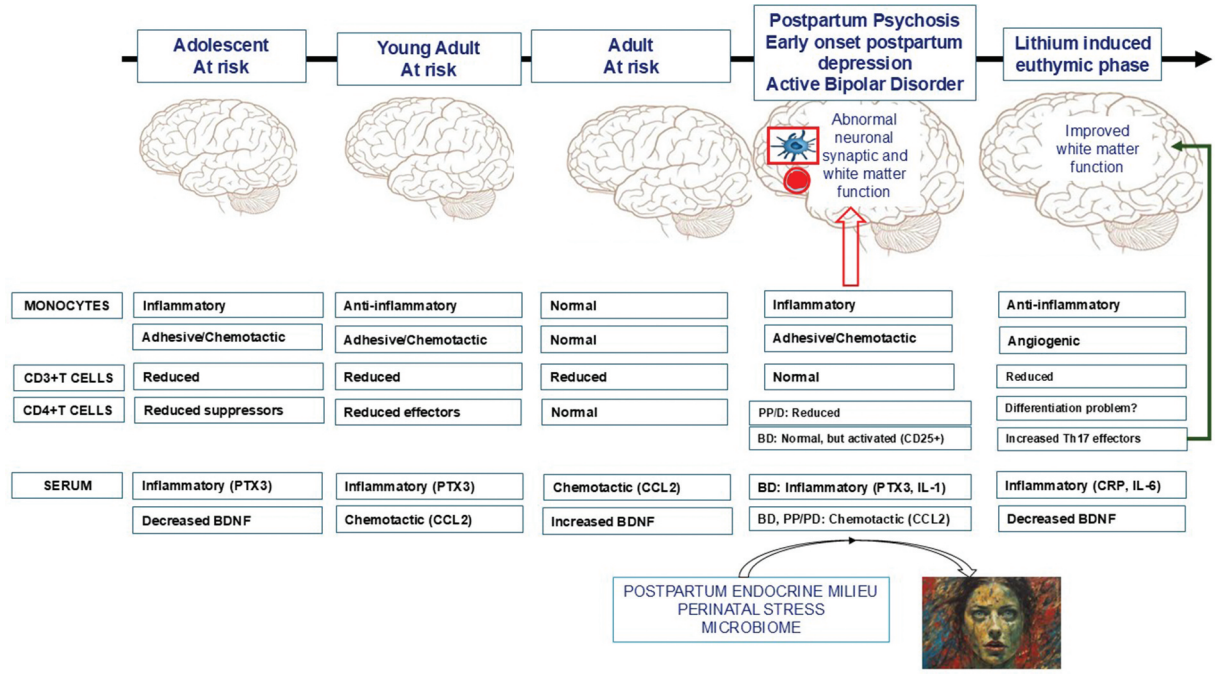

Figure 3. A dynamic view of the immune profiles of pre-phases of bipolar disorder, the acute phases of postpartum psychosis, early onset postpartum depression and active bipolar disorder, and the relative quiescent phase of (lithium induced) euthymic bipolar disorder.

See text for the explanation of the various immune profiles in these phases. Due to the similarities of the immune abnormalities in the different phases it is tempting to view that the immune abnormalities of postpartum psychosis and early onset postpartum depression are a derailment of an already existing and dynamic and fluctuating immune dysregulation linked to a liability for bipolar disorder development starting in childhood in individuals genetically at risk. Such an acute derailment in the postpartum period would be elicited by changes in the peripartum endocrine, microbiome and stress milieu of childbirth.

MiR-146a expression was significantly down-regulated in the monocytes of the postpartum psychosis patients as compared to postpartum and non-postpartum healthy controls [67]. MiR-146a is a microRNA dampening the inflammatory state of the cells. In a correlation study, the decreased expression of miR-146a in patient monocytes was related to the decreased natural T regulatory cells in the circulation of the patients; indicating that the lower the T regulatory cells in postpartum psychosis the higher the inflammatory activation of the monocytes.

In addition, we found that CCL2 was increased in the serum of postpartum psychosis patients (Figure 3).

With regard to the tryptophan catabolism we found the tryptophan levels reduced and the breakdown pathway to serotonin de-activated, similar to the situation in healthy puerperium women [40]. Surprisingly, however, considering the strong monocyte/macrophage activation in the postpartum psychosis women, we did not find the tryptophan catabolism into the kynurenine pathway to be activated and levels of downstream products such as those of neurotoxic 3-hydroxy kynurenine and neuroprotective kynurenic acid were not changed from those of healthy controls. However, data of other groups on the metabolites of kynurenine in postpartum mood disorders are conflicting with ours [68] and this thus needs further research.

In sum, postpartum psychosis was characterized by an increased state of low grade inflammation with pro-inflammatory and steroid resistant monocytes/macrophages and a defective T cell system, not responding to the drivers of the physiological postnatal T cell surge, as illustrated in Figure 2. We assume that these immune aberrancies influence the cortico-limbic system in such a way that women become vulnerable to react to stressors with an abnormal mood regulation (Figures 1 and 3).

4.2. Comparison of the immune profile of postpartum psychosis and severe postpartum depression starting shortly after childbirth with the immune profile of active and inactive bipolar disorder

In the *active phase (mania or depression)* of BD outside the peripartum period, we found that the inflammatory gene expression of monocytes, as well as the serum inflammatory compounds PTX3 and IL-1β and the chemokine CCL2, were strongly increased [26]. Elevated pro-inflammatory cytokines in serum correlated to the hampered structural white matter connectivity in critical cortico-limbic networks in BD patients [69]. Circulating T cells showed a high expression of the activation marker CD25 and sCD25 levels [70], but abnormal percentages of CD4+Th1 cells, CD4+Th2 cells, CD4+Th17cells, or CD4+T regulatory cells were not present in our studies [26] (Figure 3).

In the *inactive* (*euthymic) phase*, induced by treatment (in the majority by lithium), we found the monocyte inflammatory gene expression normal to even decreased [71] (Figure 3).

Total T cell percentages in blood were low [71]. With regard to the peripheral differentiation of T cells, populations of CD4+ and CD8+ central memory cells were high, while effector memory cells were reduced [27]. Also the T cell growth factor IL-7 was found reduced in serum [27]. These aberrancies suggest a peripheral T cell differentiation abnormality in bipolar disorder.

The proportion of CD4+Th17 cells within the lymphocyte population was increased in two of our studies [27,71], and the literature on CD4+Th17 cells in BD confirms these increases [72]. We found the increased Th17 levels to correlate to CMV antibody positivity [27]. Interestingly, high levels of Th17 cells correlated positively to the structural and functional integrity of the brain in both bipolar patients and healthy controls [73]. Thus, counterintuitively, the rises in Th17 cells might be beneficial and contributing to euthymia. Lithium is known as a stimulator of T cell differentiation [74].

With regard to CD4+T regulatory cells we found increased levels in one study [27] and near decreased levels in the other study [71], Maes et al [75] explains these fluctuations by staging of the disorder and by chronic CMV infection.

In sum, postpartum psychosis shares with active bipolar disorder an increased inflammatory, adhesion, diapedesis, and chemotactic state of monocytes (Figure 3). CCL2 levels are also raised in both disorders in the active phase.

With regard to circulating T cells, levels tend to be reduced in postpartum psychosis/early depression and bipolar disorder: In postpartum psychosis and early onset postpartum depression there is a lack of the physiological postpartum T cell surge, while there are signs of a T cell differentiation problem in bipolar disorder (i.e. reduced IL-7 levels and an abnormal apportioning between central and effector memory populations).

4.3. Comparison of the immune profile of postpartum psychosis and severe postpartum depression starting shortly after childbirth with the immune profile of individuals at risk to develop bipolar disorder

One of us (HD) was involved in a series of investigations studying individuals prone to develop BD, that is, children of a bipolar parent who have a high risk of developing episodes of severe depression and mania [76–78].

Intriguing was the fact that monocyte and T cell abnormalities were found in the at-risk subjects years before the development of depression and mania. Figure 3 summarizes the data. A constant abnormality was the slightly reduced T cell number throughout the period of observation. Slightly reduced T cell numbers are also found in the euthymic phase of BD (Figure 3 and text before).

However, remarkable were the strong dynamic and fluctuating courses of monocyte inflammatory abnormalities and T cell subsets from adolescence onwards (average age 16 years, the time when we started the observations), until adulthood (average age 28 years) [76–78].

Adolescence was characterized in particular by T regulatory cell deficits and a strong monocyte inflammatory activation (Figure 3). Of the pro-inflammatory serum factors PTX3 was increased, supporting the pro-inflammatory state of monocytes. A cluster of T cell growth factors (IGF-BP2, IL-7, SCF and sCD25) was increased in the serum, while a cluster of neurotrophic factors (amongst which BDNF and S100B) was decreased. In sum, extensive

abnormalities were found in the neuro-immune network of adolescents of bipolar parents consisting of low grade inflammation, T cell growth factor disturbances, low levels of T regulatory cells, and a low expression of neurotrophic factors in serum. In fact we found an activated inflammatory profile similar to that found in active mania and bipolar depression, but of note: in adolescent at-risk individuals without signs of depression/mania. However, the majority of children were characterized by ADHD-like symptoms, although they did not suffer from the specific mood dysregulations of BD.

After adolescence, monocyte inflammatory activation vanished, with even an anti-inflammatory state of the monocytes in *young adulthood* (average age 21 years) (Figure 3). However, a set of chemotaxis and adhesion molecules stayed over-expressed in the monocytes. As another sign of active monocyte chemotaxis, CCL2 levels in serum were increased. Percentages of Th17 cells and Th1 cells were decreased. In sum, young adulthood was characterized by an anti-inflammatory state of circulating immune cells, with signs of increased monocytes adhesion and chemotaxis activity.

In our last observation in *late adulthood* (average age 28 years), the monocyte inflammatory state and the Th1, Th17, and T regulatory cells were at normal levels, comparable to those of healthy controls (Figure 3). Of the cytokines, only the CCL2 level was raised in serum, indicating that the increased monocyte chemotactic and adhesive endothelial interaction still existed, be it to minor extent.

Although some of the children developed depressive episodes over time, a clear link with the above listed monocyte, T cell, and serum factor abnormalities could not be established, apart from a trend of high IGFBP-2 levels at adolescence and a trend of low T regulatory cells at adulthood being linked to future depression/mania.

In sum, activation phases with high inflammatory signs were seen in adolescence in individuals with an inherited risk of BD and in active phases of the disorder. De-activation phases with reduced inflammatory signs were seen in adulthood in at-risk individuals and in euthymic phases after treatment. We hypothesize that these immune activation and deactivation phases in at risk individuals are risk factors and upbeats to BD development and that changes in the sex hormone milieu (adolescence) and the microbiome (in active disease, see [79,80] are playing a role in the activation phases of the inflammatory response system (Figure 3). Reasonable constant immune abnormalities found in all phases were the slightly reduced levels of CD3+T cells (as measured in FACS analysis in our studies) (a sign of a T cell differentiation problem?) and an activation of monocyte chemotactic and adhesion activity (as measured in our gene expression studies).

4.4. Conclusion

Postpartum psychosis and severe depression shortly after childbirth are immunologically characterized by the absence of the physiological T helper cell surge after childbirth and a strong inflammatory activation of the monocyte/macrophage system correlating to reduced levels of T regulatory cells.

It is tempting to view these immune aberrancies as a derailment of an already existing and dynamic immune dysregulation linked to a liability for bipolar disorder development starting in childhood in individuals genetically at risk (Figure 3). In such a view, an acute derailment would be elicited by changes in the peripartum endocrine, microbiome and stress milieu connected to the birth of the child and the period thereafter. Arguments in favor of such a view is first the clinical relationship of the postpartum disorders with bipolar disorder (see introduction) and second the similarity of the immune abnormalities of the postpartum disorders with the immune abnormalities found in active bipolar mania and depression and in individuals at risk for bipolar disorder (particularly in adolescence). In both postpartum disorders and in the trajectory leading to bipolar disorder T cell defects are present (signs of T cell differentiation problems, slightly reduced CD3+ T cell numbers in most phases, variable reductions in CD4+ T effector and suppressor populations), as well as an activation of monocyte chemotactic and adhesion activity, and an episodic activation/de-activation of the monocyte/macrophage inflammatory response system.

5. The immune state of patients with an antenatal and postpartum depression

5.1. A heterogenous group of disorders needing more studies into the underlying neuro-immuno-endocrine abnormalities

Antenatal and postpartum depression is heterogeneous and has various causal backgrounds [81]. Genetic and hormonal influences, psychosocial status, and stressful life events are important risk factors for antenatal and postpartum depression, and timing of onset may be crucially related to etiology.

Two thirds of women with postpartum depression have their onset before or during pregnancy [9], and antenatal depression is a strong predictor of postnatal depressive symptoms [82,83]. Therefore, many studies have taken the prenatal mental and immune state into account to predict the presence of postpartum depression. Studies vary, however, in pregnancy trimester and postpartum week studied, in immune and/or endocrine tests carried out, in ways of measuring depression, and in types of immune markers studied. In addition, many studies conflate antenatal and postpartum depression. Therefore, clear conclusions cannot be drawn, but existing reviews do conclude that it is worthwhile to focus on the immune-endocrine background to unravel the causes for postpartum depression [84]. Indeed, a genome-wide gene expression study [85] interrogated the transcriptomic landscape during pregnancy and tested its association with postpartum depression and found altered immune genes and estrogen pathway as important pathogenic factors for postpartum depression: The 71 found PPD related genes in whole blood predominantly represented immune processes such as humoral immune responsiveness and innate immune system pathways, with the TNF receptor TNFRSF17 as an important gene, suggesting that an altered immune profile during pregnancy played a role in postpartum depression vulnerability. The found genes were also for a large part associated with

those found due to estradiol changes among women with a GnRHa-induced depression and therefore the results of this study emphasize the role of estrogen signaling in the immune activation of postpartum depression.

There is also considerable debate on the time definition of postpartum depression. The DSM classification strictly limits depressions with an onset starting during pregnancy or within 4 weeks postpartum. This poses problems for understanding postpartum depression both from a biological perspective (as pregnancy and the postpartum represent different immune-endocrine environments, and the early postpartum is also distinct from later postpartum) and also from a clinical perspective.

5.2. Pro-inflammatory cytokines, chemokines and growth factors in antenatal and postpartum depression

Studies on postpartum depression have concentrated on levels of circulating cytokines, chemokines and growth factors in late pregnancy throughout the postpartum period to predict or explain the depression. These studies have delivered substantial evidence implicating dysregulated immune activity in perinatal depression, yet little clarity regarding a consistent growth factor and cytokine profile [86].

In a study [87] profiling serum proteins, screening was conducted at two time points, namely in the third trimester and at 3 months postpartum, to detect proteins related to postpartum depression. A unique 20-protein signature in the third trimester differentiated patients with perinatal mood and anxiety disorders from controls. This protein signature included CXCL11, CXCL6, MIC-B, and beta 2 microglobulin, proteins that regulate leucocyte migration, inflammation, and immune function, and NCAM1, NRCAM, and NTRK3, proteins that converge around neuronal signaling pathways regulating axonal guidance, astrocyte differentiation, and maintenance of GABAergic neurons, illustrating abnormal neuro-immune interactions in peripartum depression.

A study of Brann et al. [88] measured inflammatory markers in the postpartum period only, and found elevated levels of five inflammatory markers (TRANCE, IL-18, HGF, FGF-23, and CXCL-1) in depressed women after correction for multiple comparisons.

Another study of the group [89] compared inflammatory marker levels between women with healthy pregnancies, and women with antenatal depression, and showed that women with antenatal depression around week 25 show higher levels of IL-6, IL-10, TNFα, and VEGF. Other studies have also replicated the finding that levels of IL-6 are increased in association with antenatal depressive symptoms in the last trimester of pregnancy [90]. Indeed, the mainstream view is that the serum level of IL-6 in women with peripartum depression is increased, compared to healthy women [91]. IL-6 has a special route of entry into the brain, inducing local inflammatory cascades, and is also considered an important pro-inflammatory cytokine in major depression outside the pregnancy/puerperium period [92]. There are, however, also studies that refute an important role for IL-6 in peripartum depression [93], and studies finding even reduced levels of inflammatory compounds in antenatally depressed women [93]. This has been explained by ascribing these phenomena to the antidepressant medication taken by the affected women.

However, it is also possible that complex dynamic trajectories exist for pro-and anti-inflammatory cytokines in the peripartum period for both healthy individuals and patients, with different trajectories for the two groups [91]. Indeed, the study of Brann et al. [89] investigated also the trajectories of various cytokines and growth factors in pregnancy (38 weeks), at delivery, and 8 weeks postpartum; they found that for IL-8, IL-18, TNF-alpha, M-CSF, and fractalkine pregnancy was associated with higher levels compared to non-pregnant controls, with delivery being the most prominent time-point and return to non-pregnant state at 8 weeks postpartum for M-CSF and IL-18. An effect of perinatal depressive symptom trajectory groups on cytokine levels was found for VEGF-A: Women with ante- and post-partum depression had lower levels of VEGF-A throughout the study period compared to women with persistent depression, and women with postpartum depression had lower levels compared to non-depressed women. VEGF-A levels were back to the non-pregnant state at 8 weeks postpartum.

5.3. Immune cells in antenatal and postpartum depression

Studies on the inflammatory state of monocytes/macrophages are lacking in antenatal studies predicting postpartum depression, but mothers with postnatal depressive symptoms show prenatally already significantly elevated serum neopterin levels, a sign of monocyte/macrophage inflammatory activation [94]. Also, regulatory T cells were measured in the study on neopterin, and raised levels of T regulatory cells in pregnancy staying raised into the postpartum period strongly predicted postnatal depressive symptoms. This is an interesting observation regarding the above described trajectory of reduced VEGF-A, since VEGF-A signaling pathways have been shown to reduce regulatory T cells [95]. One study [96] measured immune cell differences in pregnant women with anxiety, a major risk factor for postpartum depression, and found elevations in the cytotoxic T cell to helper T cell ratio and a decrease in the Th17 to regulatory T cell ratio in those with anxiety compared to healthy controls.

Other signs of altered T regulatory cell function were found in Latin female immigrants into the US who experienced excessive stress due to adaptation to the country of residence way of live (acculturation stress) [97]. Stress in these immigrants predicted shorter telomere length, especially among participants with high methylation of the FOXP3 promotor region (a sign of suppression of FOXP3 expression). The shorter telomere length during pregnancy predicted greater postpartum depression symptom severity. Telomere length is a measure of aging of immune cells and premature aging of T cells fosters low-grade inflammation and is also a hallmark of major depression outside the pregnancy/puerperium period [25] (Figure 4). The results in the Latin female immigrants thus highlight an impact of stress and a potential interactive role of premature aging and epigenetic immune regulatory alterations in the risk for postpartum depression.

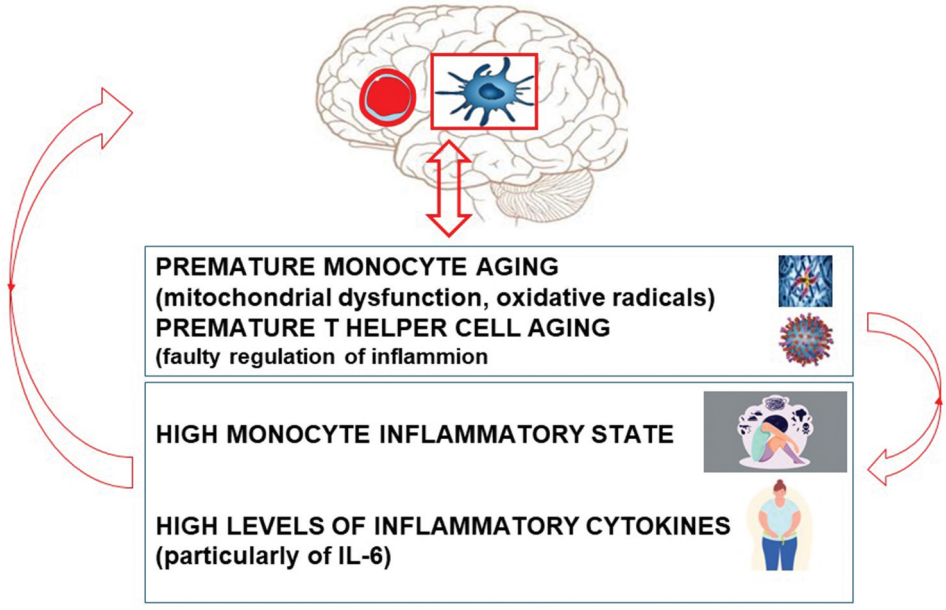

Figure 4. The immune profile of unipolar major depression.

Main characteristics of unipolar major depression are an early premature aging of the T cell and monocyte/macrophage system; characteristics of such early aging are a mitochondrial dysfunction of the cells, a higher production of oxidative radicals, increased memory over naïve T cells and a faulty regulation by the T cell system of the inflammatory response system (IRS). This premature immune aging is the consequence of an inherited predisposition for such premature aging in combination with the effect of chronic infections, extensively studied in this respect are cytomegalovirus, COVID-19 and toxoplasma infections. In cases of obesity and prior childhood trauma an additional activation of the inflammatory response system is found. Figure 1 shows that the monocyte/macrophage and T cell abnormalities impact the function of the microglia, also in the cortico-limbic system, the major regulator of stress responses.

In the various forms of postpartum depression similar abnormalities have been detected as in unipolar depression (see text), supporting a view that these postpartum mood disturbances belong to the same spectrum of neuro-immuno-endocrine disorders.

Thus collectively, there is evidence for a role of T regulatory cells in regulating the putatively enhanced inflammatory state in peripartum depression, yet there is uncertainty on whether this regulatory mechanism is activated or just suppressed (as with the inflammatory compounds in peripartum depression). Again, dynamic fluctuating changes between immune activation and suppression during the perinatal period and antidepressive medication inducing immune suppression (and given to only subgroups of patients), may have played a role.

In addition, T helper populations other than T regulatory cells have been found linked to postpartum depression. Zhihong Min et al [98] found circulating Th17 cells and serum IL-17A in the postpartum period (6 weeks) positively linked to the risk of postpartum depression and postpartum anxiety at 6 weeks postpartum, but not Th1 and Th2 cells (and their related cytokines IFN-γ and IL-4).

5.4. Hormone changes in antenatal and postpartum depression relevant for the immune changes

Research has also begun to unravel the changes in hormones important for the outbreak or aggravation of a postpartum depressive episode [99]. During pregnancy, estradiol and progesterone rise many-fold above levels normally present across the menstrual cycle, then fall rapidly at parturition. Clinical studies have demonstrated that asymptomatic women with a history of postpartum depression experience a recurrence of mood symptoms during supraphysiologic estradiol and progesterone addback and subsequent withdrawal [100,101]. Postpartum depression seems therefore to manifest in women who are especially vulnerable to this rapid drop in estrogen and progesterone derivatives – possibly through the mechanism of immune system dysregulation. In particular, the withdrawal of allopregnanolone (a progesterone metabolite) seems to play a role, since reintroduction of the derivative lowered levels of pro-inflammatory cytokines and is an effective treatment for postpartum depression [102,103]. The literature is mixed on whether levels of allopregnanolone may differ between those who do and do not go on to develop PPD. Osborne et al. [104] showed a relationship between lower antenatal levels of allopregnanolone in the second trimester and subsequent postnatal depression, but other studies have averaged both levels and symptoms across time and have contradictory findings [105].

Clearly further research is warranted in this area of sex hormone-immune system interaction in the peripartum period, because there is also conflicting literature on higher estrogen and progesterone levels in the postpartum period linked to more severe depressive symptoms over the peripartum period and a positive correlation of estrogen levels with the pro-inflammatory cytokine IL-6 and conversely, a negative correlation of progesterone levels with IL-1β [99]. Also, consistent differences between women with and without postpartum depression in circulating levels of estrogen and progesterone during pregnancy and parturition have not been established [84]. Patients with postpartum mood disorder might have increased sensitivity for ovarian steroid changes, rather than altered levels of these hormones [101].

Recent research also revealed a role for placental factors in the dysregulation of the HPA axis, which is seen in postpartum

depression as in most major depressive episodes [106]. During pregnancy, the placenta increasingly activates the maternal HPA-axis by secreting the placental CRH (pCRH), driving progressively higher maternal circulating cortisol concentrations, which parallels a blunted response of the maternal own HPA axis to external stressors. Cortisol then dramatically drops soon after delivery and the end of pCRH secretion (see also before). Available studies suggest that a higher instability in these HPA axis mechanisms could partly underpin mood and anxiety symptoms during pregnancy, predisposing the mothers to PPD, and also shaping the HPA reactivity of the newborns [107,108]. Further research is needed to clarify the precise pattern of change of these hormones in postpartum depression, and whether higher changes of HPA axis activity could impact the immune-inflammatory abnormalities observed in postpartum depression.

5.5. The biological clock and the immune abnormalities in peripartum depression

Mood disorders are closely intertwined with abnormalities of the circadian rhythm in a variety of physiological processes, with disruptions of sleep and light/dark changes precipitating depressive episodes, and depressive symptoms in turn exacerbating poor sleep and disrupting clock-controlled processes [109,110]. This vicious circle appears to characterize peripartum depression, too.

The overall prevalence of insomnia during pregnancy, based on meta-analysis, is around 40% [111,112]. Recent meta-analyses and systematic reviews indicated that sleep disorders during pregnancy resulted in a statistically significant increased risk of peripartum depression, with antenatal insomnia both, increasing the overall risk for perinatal depression, and increasing the specific odds of suicidal risk in pregnant women, by more than threefold [113–116].

Animal models show that sleep loss associates with measures of neuroinflammation, such as increased secretion of pro-inflammatory cytokines [117], increased blood–brain barrier permeability [118], and activation of microglia [119]. In humans, sleep affects immune parameters [120], and sleep disturbances associate with increased markers of systemic inflammation [121], an effect worse in females [122].

On the other hand, the immune/inflammatory system is needed to maintain sleep homeostasis. Cytokines interact with serotonin to shape sleep architecture both in normal conditions and during infection [123] and are needed for spine density and synaptic homeostasis during sleep [124], together with microglial activation [119,125].

In medical conditions, sleep disturbances cause alterations of innate and adaptive immune parameters, leading to a chronic inflammatory state and an increased risk for infectious/inflammatory pathologies, which in turn disrupt sleep [126]. The few available data confirm that sleep quality and peripheral cytokines are associated during pregnancy, too [127]. These data are clearly not yet sufficient to draw complete models, but all suggest that the immune system and the circadian timing system could closely interact in peripartum depression, as in the other mood disorders. Future research is needed to clarify this relationship.

5.6. Conclusion on immune abnormalities in antenatal and postpartum depression. Similarities to those of major depressive disorder

In sum, there is thus evidence for low grade inflammation (i.e. an increase of inflammation regulating cytokines and growth factors), an early aging of the T cell system (i.e. short telomere lengths of T cells) and deficits of T regulator cells and increases of IL-17 cells in antenatal and postpartum depression. The inflammatory response system is thought to be activated due to the pregnancy-related hormonal state of women with a peripartum depression, though a study indicates that this is probably in a fluctuating fashion depending on prior stress, such as childhood abuse, and current stress such as relationship dissatisfaction and undesired pregnancy [128].

In studies on unipolar depressed patients outside pregnancy and the postpartum period, similar if not the same immune alterations have been found. The T cell system of unipolar depressed patients also shows signs of early aging, i.e. reduced naïve and increased CD4+ and CD8+ memory cells with reduced telomere length [25] (Figure 4). In severe and suicidal unipolar cases, we found Th17 cells to be increased [129], while we found T regulatory cells decreased in older and melancholic patients [130,131]. Also, an activation of low grade inflammation has been established in numerous reports on unipolar major depression [130,132]. These reports describe increased levels of various pro- and anti-inflammatory cytokines, amongst which IL-6, which shows the most consistent elevation in the serum of unipolar depressed patients. Particularly when MDD patients are obese pro-inflammatory cytokines are raised in the circulation, and the low-grade inflammation of the adipose tissue is thought to be responsible for this excessive increase (See before and also Figures 1 and 4). Monocytes of unipolar patients are inflammatory activated, provided patients are older, melancholic and/or have a history of child abuse [24,131] (Figure 4).

A recent study [133] comprehensively studied a rostrum of inflammatory compound and immune cellular abnormalities in active and remitted unipolar and bipolar depressed patients. This study confirms the above listed abnormalities in monocyte, T cell and cytokine abnormalities in particularly active depression by showing signs of T cell activation and senescence (more CD69+, PD1+ and LAG-1+ T cells), activation of monocytes (more intermediate and non-classical monocytes) and high levels of sTREM-2 (a monocyte/macrophage activation marker). T regulatory cells were increased, most likely to control the low grade inflammatory activation in the patients. In addition the study showed three patterns of immune activation across active and remitted patients, a predominantly lymphocyte activation, a high inflammatory activation (with high levels of pro-inflammatory cytokines including IL-17), and a low inflammatory activation, the latter pattern suggesting an initiation of the immune activation process. Therefore the authors assumed a dynamic process behind the mood dysregulation.

In conclusion, there are many similarities (signs of T cell senescence, monocyte activation, raised inflammatory

compounds and most likely fluctuations in T regulatory and Th17 cells) between the immune activation state of major depressed patients outside pregnancy and depressed patients in the peripartum period. This strengthens the view that depression starting in the peripartum period is an aggravation or a de novo outbreak in an already ongoing depression-inducing-trajectory of neuro-immune abnormalities, elicited by the immune-endocrine changes associated with pregnancy, parturition, or the puerperium.

6. Depression as a symptom of a transient postpartum autoimmune hypothyroidism (AITD), and the consequence of an exacerbation of an already existing and ongoing thyroid autoimmune process prior to pregnancy and childbirth

Depression is the most prominent symptom of the hypothyroid phase of postpartum thyroiditis [134]. Postpartum thyroiditis is a transient destructive autoimmune inflammation of the thyroid within the first year after delivery, and is characterized by an episode of raised titers of Thyroid Peroxidase autoantibodies (TPO-abs) in the circulation [56]. The TPO-abs are a sign of the autoimmune destruction, but not the cause thereof. Thyroid antigen specific Th1, Th17 and T cytotoxic cells, also the consequence of the thyroid autosensitization process, are causal to the destruction of the thyrocytes [56].

Postpartum thyroiditis is an exacerbation of an already existing, ongoing and fluctuating thyroid autoimmune process starting before delivery and pregnancy (Figure 5). It is often the first clinical outburst of the process elicited by the immune-endocrine changes characteristic of the peripartum period [59]. Postpartum thyroiditis has a prevalence of 5–7% in the general population [56]. It follows after delivery a dynamic and episodic course, with first a phase of hyperthyroidism (not always present and supposedly due to leakage of thyroid hormones from the partially autoimmune destroyed thyroid gland) and thereafter a phase of hypothyroidism, due to hypofunction of the gland, which often vanishes when the autoimmune destructive process vanishes.

During the thyrotoxic phase the physical symptoms are usually mild (fatigue, palpitations, weight loss, heat intolerance, irritability). The hypothyroid phase, developing approximately 4–8 months postpartum and usually lasting 4–6 months, is clinically more important. Depression is the most prominent symptom, often just only ascribed to the emotional changes and psychological stress of motherhood and the lack of night rest.

Considering the somatic mechanism behind the association between postpartum hypothyroidism and depression, it is noteworthy that thyroid hormones are necessary for optimal brain function, including that of the frontal brain-limbic system [135]. Hypothyroidism also influences neurotransmission important in affective disorders such as reduction of central 5-hydroxytryptamine neurotransmission [136], which reverses with thyroxine replacement [137].

Therefore, it has been proposed that screening for TPO-Abs is warranted in patients with a postpartum depression, and that in case of hypothyroidism treatment with thyroxine

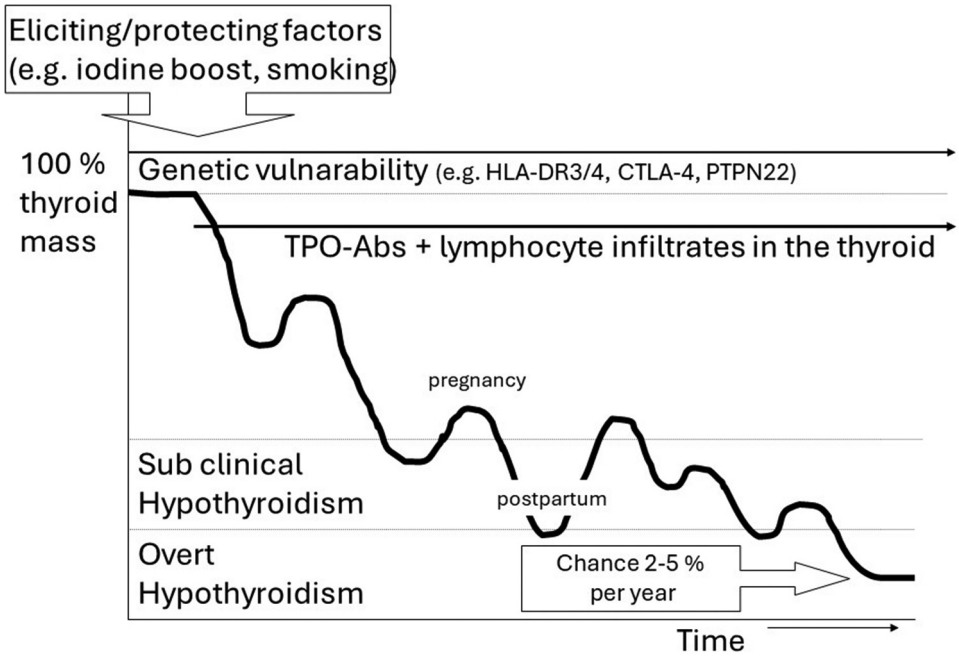

Figure 5. The trajectory of immune abnormalities leading to postpartum thyroiditis.

The main symptom of the (often transient) hypothyroid phase of postpartum thyroiditis is depression. Postpartum thyroiditis is a clinically overt phase in the trajectory to often permanent hypothyroidism due to autoimmune destruction of the thyroid gland. When more than 90% of the gland is destroyed thyroid failure occurs, which is counteracted in first instance by regrowth due to raised TSH (subclinical hypothyroidism).

The process starts on the basis of a genetic vulnerability (certain polymorphisms of HLA-DR, CTLA-4, and PTPN22, molecules regulating the interaction between antigen presenting macrophages and T cells) and the influence of several eliciting and modulating factors, which are at present not fully known (though high iodine intake is a known eliciting factor, as well as the usage of oral contraceptives). Thereafter and as a sign of the initiated active autoimmune process, TPO-abs appear in the serum and small lymphocytic infiltrates in the thyroid. Then, the process takes a fluctuating course. The pregnant state has an attenuating tolerogenic effect on the autoimmune thyroid destruction (see also Figure 2), while the postpartum state has an aggravating effect due to the 'rebound activation' of the T cell system in that period (see Figure 2).

should be initiated. However, in a randomized double-blind placebo-controlled trial, thyroxine given to a large group of TPO-Ab-positive women from 6 weeks to 6 months postpartum did not have any effect on the occurrence of postpartum depression [138]. This brings forward the question of whether there are other causes for the association between postpartum thyroiditis and depression than reduced thyroxine levels affecting cortico-limbic function.

6.1. Postpartum depression/psychosis and postpartum thyroiditis viewed as separate but co-occurring disorders rooted in the same immune pathologic changes after childbirth

Another possibility for the co-occurrence of postpartum thyroiditis and depression is that both are the consequence of the same or a similar underlying immune dysregulation, which is activated in the postpartum period (Figure 6). Of note in this consideration is that patients with a severe mood disorder anyway have a higher chance to suffer from autoimmune thyroiditis, also outside the peripartum period [139]. To explain the association, it can be hypothesized that a dysregulated immune state leading to autoimmune thyroiditis also predisposes to an abnormal structure and function of the frontal brain-limbic system with consequent mood dysregulations, or with other words the aberrant immune state leading to thyroid autoimmunity is similar to the above-described immune states leading to BD and MDD (Figure 6).

6.2. The trajectory of immune abnormalities in individuals at risk to develop autoimmune thyroiditis: Thyroid Peroxidase (TPO)-autoantibodies (ab)

Regarding the dynamics of immune abnormalities in pre-stages of overt thyroid autoimmune disease the team of one of us (HAD) was involved in studies on the Amsterdam autoimmune thyroid disease cohort, which studied around 800 euthyroid females with at least one first or second degree relative with a documented autoimmune hyper- or hypothyroidism in a follow up of 5 years [140]. TPO-ab positivity at the start of the study in the euthyroid women was more frequent than in the general population as a sign of an already existing mild autoimmune thyroiditis without clinical consequences. Such TPO-ab positivity represented a higher risk to develop overt hypothyroidism in a follow-up of 5 years, particularly in those women with

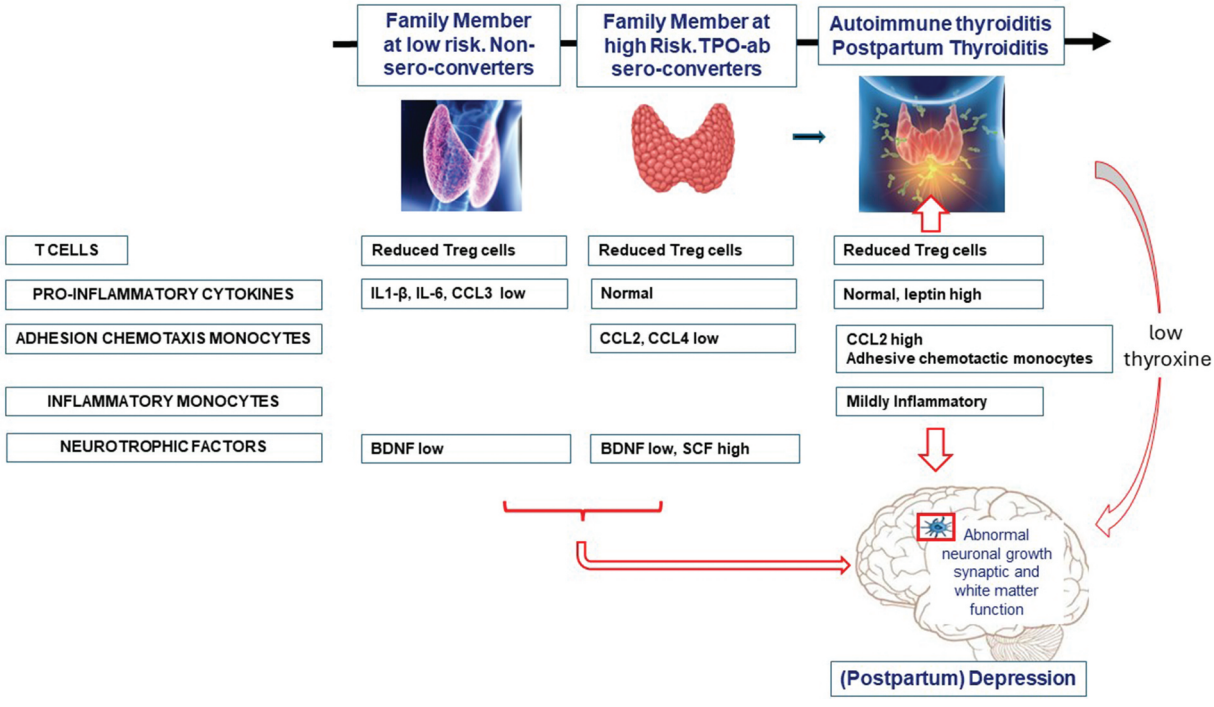

Figure 6. The different immune states of female first degree family members of female autoimmune thyroiditis patients.

Female first degree family members of female autoimmune thyroiditis patients are at risk to develop autoimmune thyroiditis, there are those with low risk and high risk (see text).

Family members at low risk (defined as family members not converting to TPO-ab positivity in the 5 years of the follow-up period in the study, see text) are characterized by reduced T regulatory cells, but a suppressed inflammatory response system (reduced pro-inflammatory cytokines). They also have reduced serum BDNF.

Family members at higher risk (those converting to TPO-ab positivity in the follow up period of 5 years) are characterized by reduced T regulator cells, normal levels of pro-inflammatory cytokines, but signs of a reduced chemotactic ability and diapedesis of monocytes (low CCL2 and CCL4). Serum BDNF is reduced.

Patients with overt destructive autoimmune thyroiditis (defined as positive for TPO-abs and hypothyroidism) are characterized by reduced T regulatory cells and circulating monocytes with a high chemotactic and adhesion capability. There is a limited activation of the inflammatory response system (limited pro-inflammatory gene expression in circulating monocytes and a rise in the pro-inflammatory serum cytokine leptin).

In the depression of TPO-Ab positive postpartum thyroiditis females various factors might play a role in the mental destabilization. First of all the clinical or subclinical hypothyroidism may hamper brain activity, but the low serum levels of BDNF and high serum levels of SCF in at risk persons may also have impacted the function of the fronto-limbic system. Furthermore the low Treg cells, the mild inflammatory state of the monocyte/macrophage system and the adhesion, chemotaxis and motility disturbances of the monocytes found in the females with (postpartum) autoimmune thyroiditis are similar to the abnormalities found in the developmental trajectories to BD (Figure 3) and to MDD (Figure 4). As discussed in the text these immune abnormalities may also have had an impact on the development and function of the fronto-limbic system (See also Figure 1).

already high serum levels of Thyroid Stimulating Hormone (TSH), that is, with subclinical hypothyroidism [141]. In women of the cohort without TPO-Ab and without subclinical hypothyroidism there was a higher conversion rate from TPO-Ab negativity to positivity, showing an inborn proneness for thyroid autoimmune reactivity and finally autoimmune thyroiditis in the selected families [142].

6.3. The trajectory of immune abnormalities in euthyroid women at risk to develop autoimmune thyroiditis: T regulatory cells

The future transition to TPO-Abs positivity in the families was accompanied by signs of reduced levels of T regulatory cells [143], suggesting an early T regulatory cell defect in those family members converting to overt thyroid autoimmunity. With regard to the literature on T regulatory cells in patients with clinical thyroid autoimmune disease, a variety of T regulatory cell deficits have been described [144]. Already since the 1980s functional suppressor cell defects of T cells have been reported in autoimmune thyroiditis patients [145,146], but with the recent advances in identifying regulatory T cell subsets via Fluorescent Cell Sorting (FACS) markers it has been established that the FOXP3+ T regulatory cell population tends to be lower in untreated and treated patients with autoimmune thyroid disease, strengthening the view that T regulatory cells contribute to the pathogenesis of autoimmune thyroid disease (Figure 6) [147].

6.3.1. Adhesion, chemotactic and differentiation abnormalities of monocytes and macrophages

The liability to TPO-ab serum conversion in relatives was also indicated by aberrant serum levels of hematopoietic growth and differentiation factors and chemokines [148,149]. Stem Cell Factor (SCF) was particularly high in the relatives, who converted in the following 5 years to TPO-Ab positivity, while the chemokines CCL2, CCL4, and the adhesion molecule sVCAM-1 were reduced. Taken this pattern of serum factors together, the aberrancies suggest another state of growth regulation of hematopoietic cells and another state of leukocyte migration in relatives of AITD patients with a high chance of initiating the thyroid autoimmune process.

Similar immune abnormalities exist in clinically overt AITD patients [150,151]. Integrin adhesion and chemokine-mediated functions of monocytes are hampered and such functions are pivotal for processes such as monocyte interactions with endothelial cells, uropod formation, migration into tissues and differentiation of monocytes into antigen presenting dendritic cells and macrophages. Moreover, in clinically overt TPO-Ab-positive AITD patients and in TPO-Ab-positive postpartum women with a high risk for postpartum hypothyroidism monocytes show an activation of the transcription of genes involved in adhesion and chemotaxis, amongst which the chemokine CCL2 (151, Supplementary Material). CCL2 is also raised in the serum of patients [151].

6.4. The absence of suppression of low grade inflammation

Low levels of the pro-inflammatory factors IL1-β, IL-6, and CCL3 are typical for relatives that do not progress to TPO-ab positivity (thus relatively resistant to starting the autoimmune process) (Figure 6) [148,149]. We assume that the generally low expression in the non-progressors reflects an immune suppressive state preventing autoimmunity. Indeed, a normalization of this reduced expression of the pro-inflammatory compounds preceded a conversion to TPO-Ab positivity, thus representing a very early stage of thyroid autoimmune reactivity [148,149].

6.4.1. BDNF and other growth factors

Of interest for the liability to thyroid autoimmunity in association to a vulnerability for mood disorders is that the neurotrophic factor BDNF was reduced in euthyroid women in the AITD-prone families, irrespective of later TPO-ab seroconversion [148]. BDNF plays an important role in neuronal plasticity, modulating axonal and neuron dendritic growth and remodeling, and also in neurotransmitter release and synapse formation [152]. It is also of note that SCF (which was found increased in seroconverting AITD family members) has been highlighted as a serum biomarker for major depression and is also involved in neurogenesis [153]. In other studies of our team, we found SCF levels to correlate to the responsiveness to antidepressants and with functional and structural MRI measures in cortical areas that are involved in the cognitive generation and control of affect [154].

6.5. Conclusion: there might be a common blueprint of immune dysregulations leading to autoimmune thyroid dysfunction and to mood dysregulation

Reduced numbers of T regulatory cells, an abnormal adhesion and chemotaxis of monocytes/macrophages, with a later conversion to a mild activation of low grade inflammation are abnormalities in the pre-phase to active phase of thyroid autoimmune disease in females inherently prone to thyroid autoimmune disease (Figure 6). Animal models of spontaneous autoimmune thyroiditis indicate that such monocyte/macrophage and T cell aberrancies are cornerstones in the development of the destructive thyroid autoimmune reaction, since the correction of these monocyte/macrophage and/or T regulatory cell aberrancies via transfers of normal cells led to the prevention of thyroid autoimmune disease [155–157].

Interestingly, the immune abnormalities leading up to thyroid autoimmunity are reminiscent of the abnormalities that can be found in a fluctuating mode in the trajectory leading up to and in the active and inactive stages of BD, such as the T regulatory cell decreases (in pre-stages of BD), the high adhesion and chemotactic capability of monocytes (throughout the bipolar process), and the decreases in BDNF and increases in SCF. Interestingly, T regulatory cells are increased in the euthyroid quiescent phases after lithium treatment of BD (see Figure 3), and T regulatory insufficiencies play a role in BD and MDD development, since an intervention targeting

this abnormality by low-dose IL-2 treatment diminishes the signs and symptoms of the disorders [158,159]. Apparently, the postpartum period is a period in which these preexisting thyroid autoimmune abnormalities become aggravated due to the immune-endocrine changes linked to this period, with consequences for thyroid autosensitization, brain, behavior and emotion regulation.

7. Novel immune treatment and immune prevention possibilities

7.1. Current treatments and prevention schemes

Current treatments of postpartum psychosis and depression [160] are based on the knowledge of effective treatments for BD and MDD. Lithium is the preferred treatment for postpartum psychosis, but adjunctive treatments with benzodiazepines or antipsychotics are useful for the acute treatment of agitation, mania, and psychotic symptoms, given the well-documented effectiveness in non-perinatal populations. Also, electroconvulsive therapy (ECT) has been used in cases with catatonia or severe depressive symptoms.

It is important to note that lithium used in the treatment of postpartum mood disorders can be toxic for thyrocytes, and the combination of lithium treatment and TPO-ab positivity of the young mother (as a sign of mild thyroid destruction in the process of autoimmune thyroiditis) is particularly harmful which can lead to permanent hypothyroidism [139]. Therefore extra care and follow-up are needed.

Women with a history of BD and/or postpartum psychosis are at high risk for postpartum psychosis and should receive care during pregnancy so that a postpartum psychosis prevention plan can be made [2]. This plan should include pharmacologic prophylaxis immediately after delivery and strategies to ensure rest and sleep in the postpartum period. Pharmacologic prophylaxis immediately after delivery is highly effective to prevent postpartum psychosis, with the strongest evidence for lithium in high dosages.

Treatments for postpartum depression [161] have mostly focused on interventions with antidepressants, such as Serotonin Re-uptake Inhibitors (SSRIs) and Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs), followed by step-up treatments, such as lithium, Mono Amino Oxidase (MAO)-inhibitors and ECT, if not successful.

Postpartum thyroiditis and the hypothyroid phase of postpartum thyroiditis are generally self-limiting (and therefore go often unnoticed), but they can also progress to overt permanent clinical hypothyroidism in around 25–30% of cases [59]. Thyroxine treatment for the hypothyroid phase has been tried out to combat depression in that phase, but the treatment had only limited effects [138].

Thus, there is room for novel treatments targeting the abnormal immune response underlying postpartum depression and psychosis, particularly in cases of TPO-ab positivity, where lithium can be harmful for the thyroid.

7.2. Novel approaches targeting the abnormal immuno-endocrine response

Brexanolone became the first FDA-approved treatment for postpartum depression in 2019. Brexanolone is a proprietary, synthetic, intravenous formulation of allopregnanolone, a derivative of progesterone that is a highly active neuroactive steroid and a positive allosteric modulator of both synaptic and extrasynaptic GABA-A receptors. GABA-A receptors are pentameric ligand-gated ion channels that are the target of the chief inhibitory neurotransmitter Gamma AminoButyric Acid, as well as the target of numerous other compounds that can thus exert an inhibitory effect, including alcohol, benzodiazepines, barbiturates, and neuroactive steroids. Neuroactive steroids can have both immediate and longer-term effects, as they can bind both these membrane GABA receptors and nuclear steroid hormone receptors. Considerable evidence points to GABAergic dysfunction in postpartum depression, but the exact nature of that dysfunction (and thus most powerful mechanisms through which neuroactive steroid treatments work) is not certain. Direct inhibitory effect by binding the GABA receptor (and thus returning individuals to a third-trimester level of allopregnanolone) is the most obvious mechanism, but it is clear that interactions with other systems (HPA axis, other neurotransmitters) may also play a mechanistic role in the drug's efficacy [161]. There is also evidence that brexanolone infusion reduces serum levels of the inflammatory compounds TNF-α and IL-6, and inhibits immune cells from responding to inflammatory compounds activating TLR4 and TLR-7 receptors [102–104]. These immune effects are correlated to improvement of the Hamilton Depression (HAM-D) rating score. Especially important to the drug's mechanism may be the impact on plasticity of the receptor. The receptor undergoes a conformational change as well as down-regulation during pregnancy, and failure of the receptor to return to its pre-pregnancy state and levels may be a crucial factor in the development of symptoms [162], which may be overcome temporarily by the introduction of the synthetic allopregnanolone. Recently, an oral formulation of allopregnanolone (zuranolone) was also approved for postpartum depression; there are as yet no studies examining its effect on immune regulation and there is an urgent need to compare effectiveness of zuranolone to conventional antidepressant treatment with an SSRI.

There is extensive literature on add-on COX-2 inhibitor therapy in major depression having positive though limited success as an antidepressant regimen in MDD, particularly in those patients with signs of low-grade inflammation [132]. Very recently a study was published on a placebo-controlled trial using the anti-inflammatory COX-2 inhibitor celecoxib in addition to cognitive behavioral therapy in mild postpartum depression (HAM-D scores between 10 and 18 on the rating list with 17 score items) at 4 weeks after delivery [163]. Patients in the celecoxib group showed a greater decline in HAM-D scores compared to the placebo group, and rates of response to treatment and remissions were significantly higher after 4 and 6 weeks treatment. Levels of the inflammatory factors CRP, IL-6 and TNF-α were significantly lower, and of the neurotrophic factor BDNF higher, as compared to the CBT-only controls at 6 weeks of treatment.

The team of HD, FB, and SP was involved in a recent study targeting the premature senescence of the T cell system and the accompanying defects in the T regulatory cell system in unipolar and bipolar depression using low-dose IL-2 therapy and thymus hormones [158]. Treatment with low-dose IL-2 significantly potentiated the antidepressant response to ongoing SSRI/SNRI treatment in both diagnostic groups, and expanded the population of T regulatory and T helper 2 cells and the percentage of naive CD4+/CD8 + immune cells. Changes in cell frequencies were rapidly induced in the first five days of treatment, and predicted the later improvement of depression severity. No serious adverse effect was observed. This first randomized control trial (RCT) on IL-2 in depression showed evidence that strengthening the T cell system is a successful way to correct the immuno-inflammatory abnormalities associated with mood disorders, and potentiate the antidepressant response. Moreover, low-dose IL-2 is a treatment for autoimmune diseases and might thus have beneficial effects for the mood disorder associated AITD.

The beneficial data of this trial have recently been confirmed in a similar study with low-dose IL-2 in 14 patients with bipolar depression: low-dose IL-2 treatment expanded and activated T regulator cells and significant improvements of depressive symptoms and global functioning from day-15 onwards were recorded in the low-dose IL-2-treated patients [159]. Suffice it to say that more trials should be started now.

Preliminary evidence also shows that the thymus hormone thymosin-α1 can be successful in combatting depression. In a non-placebo controlled study on five depressed patients with common variable immune deficiency and a partial T cell defect, the hormone treatment induced higher levels of CD4+ and CD8+ naïve T cells and improved depression scores [164].

The immune system could also be a target for non-pharmacological stimulation. It is known that activation and synchronization of the circadian timing system with bright light therapy has antidepressant effects both in seasonal and non-seasonal depression, with effect sizes comparable to those observed in an RCT of monoaminergic drugs [165]. The antidepressant efficacy of light therapy in winter depression parallels its ability to normalize abnormally higher macrophage-produced IL-1β and TNF-α and Th-1 produced IFN-γ, higher macrophage phagocytosis, and lower mitogen-stimulated lymphocyte proliferation in patients [166]. In women with pre-partum depression, an RCT showed that bright light prompted remission in more than two-third of participants [167], and future studies could address its effect on the immune system. Some small and heterogeneous open trials also reported benefits after antidepressant sleep deprivation [168], a treatment mostly studied in unipolar and bipolar depression, and able to normalize abnormally higher IL-1β blood levels in responders [169].

Finally, a meta-analysis also confirmed benefits in reducing postpartum depressive symptoms with physical exercise [170], an intervention that could target the immune abnormalities associated with depression [171].

In sum, it is time to start–apart from zuranolone–immunomodulatory treatment such as T cell targeting therapies in postpartum depression.

8. Limitations

Reviewing the literature and also our own findings over time a picture is emerging of dynamic fluctuations of various compounds of the complex neuro-immuno-endocrine system in different (pre-)stages of mood disorders and thyroid autoimmune disease. Moreover many of the patient studies are performed in patients treated with a variety of mood stabilizers, which have immune effects on their own. It is thus not surprising that there are many contradictory or not confirmed findings in the literature, because in most studies the stage dependency and therapy status has not fully been taken into account.

Also the mood disorders under study are not well defined (only by descriptive DSM classification). The disorders are most likely heterogeneous with respect to their pathogenesis. Not all might have an immune background, and in a proportion of the patients psychological, neurological and/or endocrine abnormalities might be the predominant pathogenic factors. This also underscores the notion that we should stratify mood disorder patients on the basis of immune abnormalities to identify patients who are amenable to immune treatments.

Last but not the least, most of the studies on mood disorders in patients focus on systemic immune abnormalities, because immune brain investigations are difficult or even impossible to perform. We are therefore too less informed on the actual aberrant neuron-glial interactions in the fronto-limbic system of patients.

$N = 10.186$

9. Expert opinion

Postpartum mood disorders are complex and heterogenous disorders. On the basis of the clinical and immune-endocrine picture and the genetic background, the following entities are presently identified:

a. Postpartum psychosis and severe acute postpartum depression. These start shortly after childbirth and are related to bipolar disorder.
b. Postpartum depression with an antenatal onset, patients might have their onset during pregnancy or even before pregnancy and have thus a more chronic form of depression.
c. Postpartum depression with postpartum onset up to several months after childbirth.
d. Postpartum depression in the presence of autoimmune thyroiditis.

Further epidemiological and neuro-immuno-endocrine studies should be undertaken to clarify, confirm, refute or better characterize these postpartum conditions. Characterization should not only be clinically and descriptive, but also based on outcomes of laboratory examinations in the area of immuno-neuro-endocrinology.

Indeed, a better approach is in our opinion a classification of above described postpartum conditions not based on the meticulous description of their clinical picture, but based on the actual immuno-neuro-endocrine abnormalities leading to

the disorders (the pathogenetic approach). This will enable novel immuno-neuro-endocrine diagnoses, which are targetable by immune and/or endocrine modulating drugs. This will open new avenues for the improvement of the treatment of these disabling postpartum conditions.

Since the immune dysregulations in postpartum psychosis and severe acute postpartum depression (shortly starting after childbirth) are formed by partial T cell defects, that is, an absence of the physiological postpartum T cell surge (including that of T regulatory cells) and an enhanced state of low grade inflammation, i.e. a high inflammatory state of monocytes/macrophages and increases in serum pro-inflammatory cytokines, drug trials should be started using novel approaches to target these immune dysregulations. To be mentioned are anti-inflammatory agents (e.g. COX-2 inhibitors) and T cell targeting agents (e.g. low-dose IL-2 therapy to correct T cell defects in particular of T regulatory cells). Both immune interventions have been shown to have anti-depressant effects in mood disorders in general (see main text). To mention is also allopregnanolone, recently approved by the FDA, which should be further investigated for its potency to correct not only the emotion regulation postpartum, but also the above described postpartum immune dysregulations.

With regard to other forms of postpartum depression, follow-up studies of depressed women starting before pregnancy, during pregnancy and up till one year after pregnancy are needed to be able to precisely identify the various clinical forms and natural histories of these heterogeneous afflictions. Again outcomes of laboratory examinations in the area of immuno-neuro-endocrinology in the follow up of these women are essential to classify the peri- and postpartum conditions based on the actual immuno-neuro-endocrine abnormalities present at that time. The literature indicates that the immune dysregulations characteristic for antenatal and other forms of postpartum depression are most likely premature T cell aging with fluctuating levels of low grade inflammation (changes in inflammation regulating cytokines, growth factors, Th17 and T regulatory cells), partly depending on prior stress (for instance childhood abuse) and/or current stress (for instance relationship dissatisfaction and undesired pregnancy).

Comparisons of the immune profiles of the various forms of postpartum psychosis and depression to those of bipolar disorder and severe forms of depression outside pregnancy and to the immune profiles of healthy pregnant and postpartum women are essential to categorize these complex peripartum conditions and to come to proper immune diagnoses.

Studies on cohorts of individuals at risk for bipolar disorder and major depression (first degree relatives of index cases) and a follow up of these individuals in the cohorts both clinically and immuno-neuro-endocrinologically in and outside pregnancy-postpartum is essential to identify the natural history of the development of (postpartum) mood disorders.

Immune assays suitable for routine clinical use (simple collection, relatively cheap, easy preparation for long lasting storage before testing) would be of great advantage in these endeavors to immunologically and endocrinologically follow all these individuals and to clinically diagnose mood disorder patients immuno-neuro-endocrinologically. Serum is suitable for endocrine factor and cytokine/growth factor determinations. But recent insights show that serum cytokines do not reflect the immune state of circulating monocytes, macrophages and T cells. We have developed a series of gene expression determinations by total leukocyte preparations collected in PAXGENE tubes reflecting the various inflammatory states of monocytes and the apportioning of the various T cell subpopulations (CD4, CD8, Th1, Th17, and T regulator cells) (to be published). PAXGENE tubes can be stored for relatively long times. Apart from this approach, other approaches to simplify immune tests are needed.

In each postpartum depression case, TPO-abs and TSH should be determined to diagnose postpartum autoimmune thyroiditis with and without signs of (subclinical) hypothyroidism. Postpartum autoimmune thyroiditis is an (often transient) outburst of destructive thyroiditis in women with already pre-pregnancy/antenatal ongoing subclinical forms of autoimmune thyroiditis. This outburst leads in severe cases to thyroid hormone deficiency and hypothyroidism. The trajectory of immuno-neuro-endocrine abnormalities in the process leading up to autoimmune thyroiditis are similar to the ones described in individuals at risk for severe mood disorders, i.e. T regulator cell defects and loss of an anti-inflammatory state of immune cells.

Depression is thought to be the main symptom of this postpartum thyroiditis, and one third of women is thought to later progress to permanent autoimmune hypothyroidism. Again more follow up studies are needed not only to precisely identify the depression severity of postpartum thyroiditis, but also characterize the natural history of the disorder after childbirth and in particular the trajectories of immuno-neuro-endocrine abnormalities. Although adequate levels of thyroid hormones are essential for emotion regulation, it has been described that thyroxine treatment has little effect to combat depression in these postpartum women. Targeting the immune dysregulation leading to the exacerbated thyroid autoimmune reaction, that is, the T regulatory cell deficiency with its consequent induction of low grade inflammation, might be a better option. Again the earlier mentioned immune intervention with low-dose IL-2 might be such option, also because the actual immune abnormality might be debit to the mood dysregulation, earlier than the thyroid hormone deficiency.

Glossary

This is a short explanation of the terminology used in the review for T cell subset populations. The reader is referred to textbooks on Immunology for further clarification.

CD3+ T cells	T cells are characterized by the presence of the T cell receptor (CD3) which is the antigen receptor
CD3+CD25+ T cells	Activated T cells are characterized by high expression of the IL-2 receptor CD25
CD3+ CD69+ T cells	Activated T cells are characterized by high expression of the CD69
CD4+ T-helper (Th) cells	T helper cells are cells supporting other cells to execute immune

	functions and are characterized by the expression of CD4, a molecule capable of reacting to antigen in the context of MHC class II molecules on antigen-presenting cells.
CD4+Th1 cells	T helper cells producing IFN-gamma, a pro-inflammatory compound stimulating immune cells.
CD4+Th2 cells	T helper cells producing IL-4, stimulating B cells to produce antibodies and dampening the inflammatory state of Th1 cells and other immune cells.
CD4+Th17cells	T helper cells producing IL-17, pro-inflammatory stimulating other immune cells.
CD4+T regulatory cells	CD4+ T cells also characterized by the transcription factor FOXP3 and a high expression of CD25. The cells produce IL-10 and TGF-beta dampening inflammatory responses
CCR6+ cells	Th17 and T regulatory cells are CCR6 + and are attracted to the chemokine CCL20, which is also expressed in the choroid plexus.
CD8+ T-cytotoxic cells	T cytotoxic cells are cells capable of killing other cells in an antigen specific way and are characterized by the expression of CD8, a molecule capable of reacting to antigen in the context of MHC class I molecules on the target cells.
Naïve T cells	T cells (CD4+ and CD8+) which have not yet encountered their cognate antigen. Decreases of naïve T cells are a sign of an aging immune system.
Effector memory T cells	T cells (CD4+ and CD8+) which have been stimulated by their cognate antigen and are expanded as a population, they can be immediately used in the inflammatory reaction due to their chemokine receptor make up. Increase of this population is a sign of an aging immune system.
Central memory T cells	T cells (CD4+ and CD8+) which have been stimulated by antigen and are expanded as a population, they recirculate in the lymphoid system due to their chemokine receptor make up and can be restimulated by the second encounter with the antigen. Increase of this population is a sign of an aging immune system.
PD1+ and LAG-1+ T memory cells	Aging effector memory cells can become effete and exhausted (non-proliferating and pro-inflammatory, resistant to apoptosis and stimulation). CD57, PD1, LAG-1 and an absence of CD27 and CD28 are characteristics of such cells

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Declaration of interest

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