

## Psychiatric disorders and changes in immune response in labor and postpartum

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### TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Immunological dysregulation in psychiatric disorders
4. Psychiatric disorders in postpartum – epidemiology
5. Psychiatric disorders in postpartum – pathogenesis
6. Evidence of immune system dysregulation in postpartum psychiatric disorders
7. The Immune response dysregulation in pregnancy and labor complications
8. Perspectives
9. Acknowledgments
10. References

### 1. ABSTRACT

Women may present with psychiatric disorders during pregnancy, normal labor, following delivery by caesarean section, or in the postpartum period. The accumulating evidence suggests that these disorders may be due to changes in immune responses. During pregnancy complications such as the prolongation of cervical ripening or descent, placental abruption, premature labor, and preeclampsia increase the risk of postpartum psychiatric disorders. Women may exhibit depression and postpartum psychosis following either normal birth or caesarean section. Since psychiatric disorders like schizophrenia, major depression, and bipolar disorder are associated with both alterations in the immune response and changes in immune cell subpopulations, in this study we have chosen to examine whether the psychiatric disorders in women during labor or postpartum also lead to aberrant immune responses.

### 2. INTRODUCTION

There is a growing interest in the subject of postpartum psychiatric disorders due not only to

their wide social repercussions but also to their potentially detrimental effect on the child's development and the functioning of the family. Up to 85% of women suffer from mood disturbances during the postpartum period; however, these disturbances are usually self-limiting and do not require medication (1). The singularity of this period is acknowledged by the fact that the ICD-10 classification sets apart psychiatric disorders that manifest postpartum. However, in both the ICD-10 and DSM-V classifications, the time period for diagnosis has been narrowed down to several weeks after labor (4 in the DSM-V and 6 in the ICD-10), even though it is known that both postpartum psychosis and postpartum depression may take as long as 6 months to manifest. Despite the increased interest, the etiology of these disorders remains elusive. The prevailing notion that hormonal changes play a major role in the pathophysiology of postpartum psychiatric disorders has not been entirely disproven. Furthermore, evidence suggests that the growing number of elective caesarean sections is related to the increased prevalence of postpartum depression (2-3).

On account of this evidence, a search for additional factors that might be involved in the development of postpartum psychiatric disorders has been initiated. Studies have looked into the potential role of the immune system in the etiology and pathophysiology of such psychiatric disorders as schizophrenia, mood disorders, anxiety, dementia, pervasive developmental disorder, and suicidal ideation. There are also preliminary reports confirming the usefulness of adding non-steroidal anti-inflammatory drugs (NSAIDs) to the therapy for schizophrenia (4), depression (5), bipolar disorder (6), and obsessive-compulsive disorder (7).

Pregnancy and birth are characterized by the exceptional phenomenon of maternal immunological tolerance towards fetal antigens. The precise regulation of the interaction between maternal and fetal immune systems is essential for a pregnancy to develop undisturbed (8). Over time the regulatory process becomes more complex as the growing fetus begins to influence the maternal immune response. Consequently, women are especially vulnerable to complications caused by a dysfunction of this delicate balance when they are close to labor. Shah *et al.* have concluded that during the spontaneous beginning of labor the maternal immune system is transforming into a more reactive phenotype (9). Furthermore, it has been observed that as the fetus develops, fetal macrophages also begin to play a role in the regulation of the maternal immune response (10). This complex process may be disturbed on many levels, especially by the instrumentalization of the labor or as a secondary effect of an abnormal immune response associated with pregnancy complications such as preterm birth, preeclampsia, or premature rupture of membranes (PROM) (11-16).

On the one hand, it has been confirmed that women with psychiatric diseases like schizophrenia and depression have an increased risk of pregnancy-related complications caused by the dysregulation of this delicate immunological balance (schizophrenia: 17-18; depression: 19). On the other hand, patients who develop complications of pregnancy and delivery with a confirmed underlying immunological component (for example, placental abruption,

preeclampsia, premature rupture of membranes (PROM), preterm birth, and elective caesarean section) have an increased risk of postpartum depression, postpartum psychosis, anxiety, and post-traumatic stress disorder (PTSD) (20-23).

There is a growing interest in the role of immune system disturbances in psychiatric disorders. It has been postulated that some, if not all, psychiatric disorders may be triggered by an underlying immune dysregulation. Accordingly, we formulated the hypothesis that maternal postpartum psychiatric disorders are caused in part by disturbances in the maternal immune response during pregnancy that manifest clinically in complications of pregnancy and labor. This study aims to review the current literature on the relationship between the maternal immune response during labor and postpartum psychiatric disorders and to present prospects for future research.

### 3. IMMUNOLOGICAL DYSREGULATION IN PSYCHIATRIC DISORDERS

Immunopsychiatry is developing as a field even as the evidence of immune system dysregulation in such psychiatric disorders as schizophrenia, bipolar disorder, and major depressive disorder accumulates. Studies examining multiple factors, from a genetic predisposition found in the immune response related genes to changes in the levels of immune cells and cytokines as well as in the percentages of immune cell subtypes, may shed more light on the neurobiological basis of these psychiatric disorders.

For example, polymorphisms in the MHC locus on chromosome 6, among which was the gene variant C4 (a coding protein of the complement system) (24), were found in patients suffering from schizophrenia (25). It has also been reported that the complement proteins Cq, C3, and C4 play an important role in brain development during the period of synaptic pruning. These proteins mark abnormal synapses, and this process later leads to synaptic elimination by phagocytic microglia cells (26). A decrease in the number of synapses was observed in patients suffering from schizophrenia (24). Furthermore, there is a report suggesting a link

between T-cell deficits in 22q11.2DS deficiency, and particularly in Th17, and the presence of positive psychotic symptoms. This genetic defect has even been proposed as a model for the development of psychosis (27).

Changes in immune system activity have been observed in patients with schizophrenia. Moreover, changes in the peripheral blood and cerebro-spinal fluid (CSF) have been found in patients as early as the time of the first episode of psychosis. Autopsies of the brain and brain imaging with positron emission tomography (PET) with peripheral benzodiazepine receptor ligand have confirmed the role of neuroinflammation and the activation of microglia in patients with schizophrenia (4, 28-30). Schizophrenia also constitutes a risk factor for a number of autoimmune diseases including diabetes mellitus type 1, multiple sclerosis, systemic lupus erythematosus, celiac disease, Sjörger's syndrome, thyrotoxicosis, and acquired autoimmune hemolytic anemia (4, 28, 31-34). A recent analysis has led to the confirmation of shared genetic risk factors, consistent with epidemiological data, between schizophrenia and inflammatory bowel disease, Crohn's disease, ulcerative colitis, primary biliary cirrhosis, psoriasis, and systemic lupus erythematosus (35).

As the MHC complex's role in the proper functioning of T cells CD3+ is so essential, it would seem logical to search for alterations in this cell population (36-40). A meta-analysis of 16 studies on immune system dysregulation in schizophrenia published in 2013 reported a significant increase in the percentages of CD4+ and CD56+ cells, total lymphocyte levels, total CD3+ cells, and CD4+ cells, as well as an increase in the CD4/CD8 ratio. Furthermore, the percentage of CD3+ cells in patients at the first onset of psychosis was significantly decreased. Antipsychotic treatment led to a decrease in the CD4/CD8 ratio along with an increase in the total number of CD56+ cells (38). Two extensive meta-analyses of the extent of cytokine alterations in patients with schizophrenia were also published (41-42).

The role of T regulatory cells (Tregs) in schizophrenia seems particularly important. In

several studies, an increase in the percentage of Treg cells as well as in sIL-2R was reported in patients with schizophrenia. Furthermore, this increase correlated with the percentage of CD3+CD25+ cells and lymphocytes with IL-4. An increased Treg cell level upon admission of the patient correlated with a better Global Assessment of Functioning score upon discharge (GAF). It is thus believed that Treg cells have the ability to suppress excessive activity of the immune system in the central nervous system (CNS) (36, 39).

In cases of depression, single nucleotide polymorphisms (SNP) PSMB4 and TBX21 (related to the functioning of T lymphocytes) and STAT3 (responsible for signal transduction) have been described (43-44). Furthermore, certain SNP (CD3E, PRKCH, PSMD9, and STAT3 related to the function of T lymphocytes) were linked with a better response to treatment. Other polymorphisms in genes linked with IL-6 and genes participating in prostaglandin synthesis were found in certain circumstances to be connected with depression (45-47).

Furthermore, an increase in TNF, IL-1, and IL-6 CRP in the blood serum was reported in cases of major depressive disorder, especially those that were treatment-resistant (48-52). The administration of cytokines, including INF-alfa and their induction with either lipopolysaccharide or the typhoid fever vaccination, led to symptoms similar to those of depression. On the one hand, the administration of drugs that inhibit cytokines may lead to better control of the symptoms and a decrease in the inflammatory response. On the other hand, however, it has been confirmed that antidepressants can decrease the *in vitro* production of pro-inflammatory cytokines. Furthermore, it has been conjectured that these cytokines may influence the metabolism of such neurotransmitters as serotonin, noradrenalin, and dopamine. These cytokines can also influence the daily excretion curve of cortisol and increase its evening level (52).

Patients with major depressive disorders were reported to have decreased total levels of lymphocytes, including T lymphocytes and Tregs. The Treg level correlated with the intensity of the patient's symptoms (53-56). CD4+ cells have an

increased tendency towards spontaneous apoptosis and a higher expression of FAS receptor (CD95). Furthermore, a correlation has been reported between depression in patients with HIV, liver cirrhosis, multiple sclerosis, and an increase in CD8+ cells. Higher levels of CD3+CD8+ at the beginning of treatment are related to a poorer response to treatment (56).

Patients suffering from major depressive disorder were reported to have lower levels of T regulatory lymphocytes and an increased INF-gamma/TGF-beta ratio compared to the control group. Additionally, in such cases there was a negative correlation of serum TGF-beta with depressive symptoms (52). It has been observed that even though Treg levels increase in response to treatment, they are not a predictive factor of treatment effectiveness. In those patients who responded well to treatment, an increase in monocyte percentage and a decrease in total lymphocyte levels were observed (56). Patients who were resistant to treatment prior to its initiation had an increased level of cytotoxic CD8+ cells and decreased levels of NK cells compared to those patients who responded well to treatment. Consequently, it is believed that antidepressants may directly influence Treg cell activity. It has been reported that Tregs have both adrenergic (57) and serotonergic receptors on their surface (58). There are also indications that Tregs may constitute a potential target for stimulation in patients with major depressive disorder (59).

In cases of bipolar disorder, mutations of toll-like receptor (TLR) genes have been described. It is worth mentioning that a genetic overlap has been observed between schizophrenia, bipolar disorder, and major depressive disorder, suggesting that these disorders share at least some pathophysiological mechanisms (35). Moreover, there is an epidemiological correlation between bipolar disorder and many inflammatory diseases, such as atony, cardiovascular diseases, osteoporosis, and diabetes mellitus. Like patients with schizophrenia, those with bipolar disorder are twice as likely as the rest of the population to develop metabolic syndrome. It is speculated that this risk is not a

side effect of the drugs, but a part of the disorder symptomatology (60-61). Comorbidity of bipolar disorder with autoimmune diseases, including pemphigus (62), Crohn's disease (34), and thyroid autoimmunity (63) has been reported. Furthermore, in cases of bipolar disorder, an increase in pro-inflammatory cytokines (IL-4, TNF-alfa, aIL-2R, IL-1b, IL-6, STNFR1, and CRP) in the blood serum as well as an increase in Treg-activated T lymphocytes and pro-inflammatory monocyte cytokine levels were observed (64-68).

The dysregulation of the immune system in patients with other psychiatric disorders, such as post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD), has been reported. Half of patients with PTSD also suffer from other psychiatric disorders, particularly anxiety or affective disorders. Studies conducted on twins, confirmed that there is a genetic component to the development of these disorders. Furthermore, patients with PTSD were found to have a significant drop (48%) in the percentage of Treg cells (69).

In patients suffering from OCD, comorbidity with some autoimmune diseases, including systemic lupus erythematosus and thyroid diseases, has been reported. This disorder may develop in children following infection with group A Streptococci (Pediatric Acute-onset Neuropsychiatric Syndrome -PANS). In patients with OCD, the presence of anti-basal ganglia antibodies (ABGA), a decrease in both NK cell and lymphocyte CD4+ activity, an increase in the number of CD8+ cells, a decrease in levels of IL-1  $\beta$ , and an increase in TNF-alfa and IL-6 were all reported (70). However, these observed changes normalized in the wake of successful therapy with selective serotonin-reuptake inhibitors (SSRIs). In patients with Tourette syndrome, a decrease in Tregs was observed compared to the control group and symptom intensity was positively correlated with the levels of these cells (71). However, as studies on this subject have been rare, it is too early to make any definitive conclusions.

Most current studies have been conducted on small groups of patients and have

neglected to analyze all of the immune system components, focusing instead mainly on cytokines. Only a few studies on T lymphocyte subpopulations, particularly Tregs, have been conducted. Tregs are important because of their regulatory function and have proved useful in other fields of medicine, especially oncology, as a target for immunotherapy (72). Moreover, few studies specifically analyze the correlation between immune cell subsets and cytokines in the blood and the CSF of patients with psychiatric disorders.

The present study does not aspire to be a comprehensive review of the subject of immunopsychiatry, especially since a number of fine works have now been published in that field (for example, 28, 38, 45, 52, 59, 61, 73, 74). The study aims instead to present immunopsychiatry as a dynamically expanding field worthy of further investigation.

#### 4. PSYCHIATRIC DISORDERS IN POSTPARTUM – EPIDEMIOLOGY

The most commonly reported psychiatric disorders to occur during the postpartum period are postpartum depression, depressive or manic episode as a manifestation of bipolar disorder, and postpartum psychosis. There is also an increasing amount of evidence of other disorders that present in the postpartum period, for instance, obsessive-compulsive disorder (OCD), social anxiety, and postpartum childbirth-related post-traumatic stress disorder (CB-PTSD). However, these disorders in the postpartum period have not yet been studied in depth and are frequently misdiagnosed (75).

The risk factors for psychiatric disorders during the postpartum period are unclear. One of the first studies on this topic was conducted by Kendell *et al.* The authors reported that the risk of hospitalization due to psychiatric disorders was considerably higher in primiparous women (76), and this observation was confirmed by subsequent studies. Additionally, risk factors such as *in vitro* fertilization and twin pregnancy were reported (77-79). Finally, there seems to be a familial predisposition towards postpartum psychiatric disorders, though the genes responsible for the

increased risk have yet to be identified (19, 23).

One of the most predictive factors of postpartum psychiatric disorders is previous psychiatric morbidity. Many of those patients suffering from schizophrenia, bipolar disorder, and major depression experience a relapse or an exacerbation of symptoms after giving birth. It is believed that postpartum psychosis and depression are to some extent manifestations of a bipolar disorder. It has been reported that 74% of patients with bipolar disorder and a family history of postpartum psychosis develop postpartum psychosis; however, for those patients with bipolar disorder but no family history of postpartum psychosis, the risk was considerably lower (80). Women with psychotic disorders were found to be at a higher risk for complications including induced labor, hemorrhage, and premature rupture of membranes. They were also at a greater risk for fetal complications like stillbirth, fetal abnormalities, poor fetal growth, and fetal distress (81-82). Moreover, it has been reported that women with schizophrenia and an immunological background that includes preeclampsia, uterine atony, Rh disease, bleeding, hypertension, or diabetes are at a greater risk of developing complications during pregnancy and birth. Such patients often have an increased prevalence of thromboembolic disease (17). Furthermore, in women with schizophrenia, complications such as asphyxia, low birth weight, and higher new born mortality have been reported (18).

On the other hand, some studies have suggested a correlation between the complications of pregnancy and birth and the risk of postpartum psychiatric disorders. One such complication that has received special attention due to its immunological background is preeclampsia. A comparison between preeclampsia and postpartum psychosis reveals many clinical similarities: both conditions have primiparity as a risk factor, and their development after the first pregnancy increases the risk in subsequent pregnancies (23). The first study reporting an increased prevalence of postpartum depression in patients who suffered from preeclampsia was published by Kurki *et al.* in 2000 (83). Subsequent studies confirmed an increased prevalence of postpartum depression following a



hypertensive disorder of pregnancy (HDP) (84-89) and first-onset postpartum episodes, including both postpartum depression and postpartum psychosis (23, 90).

A systematic review of this topic begun in 2013 found an association between preeclampsia, HELLP syndrome (consisting of hemolysis, elevated liver enzymes, and a low platelet count), and postpartum depression. However, in patients with anxiety and PTSD, the results of the review were either conflicting or insignificant (21). A more recent review of literature concluded that hypertensive disorder of pregnancy (HDP) is correlated with an increased prevalence of depression (7-44% of patients with HDP) and PTSD (5-43%). The correlation was proportional to the severity of the HDP. Although higher anxiety scores were reported in those patients with preeclampsia, the associations were not significant (22). Furthermore, comorbidity between postpartum depression and CB-PTS was observed (91).

Preterm birth and placental abruption have also been strongly linked to the increased risk of postpartum depression, postpartum psychosis, anxiety, and PTSD (20, 22, 81, 87). Not only is preterm birth a risk factor for postpartum depression, but patients with depression are also at increased risk of preterm birth (19). Moreover, an increased prevalence of postpartum depression was observed following uterine atony, induced labor, prolongation of cervical ripening, protracted descent, intrauterine growth restriction, low birthweight, amniotic fluid anomaly, and suspicion of fetal distress (85-88). The evidence linking postpartum depression with placenta previa (86-87) was conflicting. It was also observed that a statistically significantly higher number of postpartum psychosis patients had experienced a protracted descent (82).

It might be conjectured that maternal depressive symptoms represent a psychological inadaptation to the impact of pregnancy complications on the child's health. Interestingly, Blom *et al.* failed to find any association between the newborn's Apgar score and the mother's postpartum

depression, suggesting that maternal psychiatric disorders are not necessarily triggered by the child's medical complications. They further reported that the risk of postpartum depression increased with the number of complications (85). Dekel *et al.* also observed that many women experienced postpartum depression and CB-PTSD regardless of the status of their child's health. However, there are still only a limited number of studies on this subject (21-22).

In 1987, Kendell *et al.* had already observed an increased prevalence of psychiatric disorders in those patients who underwent caesarean section compared to those who experienced vaginal delivery (76). Since then the subject has received considerable attention (for example, see 81, 85, 87-88), but the results of the studies were often inconsistent; in some cases, undergoing a caesarean section was even found to have a protective effect (92). In 2017, a meta-analysis including 532,630 women was published that reported an increased prevalence of postpartum depression following caesarean section; however, there were considerable differences between the studies included in the meta-analysis. Xu *et al.* reported an increased risk of postpartum depression in patients with unplanned and emergency caesarean section, but not in patients with elective caesarean section (93). However, a study by Dekel *et al.* found that women who underwent either a caesarean section (whether planned or unplanned) or instrumental vaginal delivery had a greater prevalence of somatization, obsessive-compulsive disorder, depression, anxiety, and hostility postpartum compared to those women who had experienced a vaginal or natural delivery. Unplanned caesarean section was also correlated with a greater risk of PTSD (1).

This subject is worth investigating in the context of immunopsychiatry as, to our knowledge, none of the studies so far conducted in this field have considered the progression of the birth process and cervix dilation. Most elective caesarean sections are performed prior to the beginning of spontaneous birth; this is not a rule, however, as emergency indications that warrant performing a caesarean section may arise either

**Table 1.** The association of pregnancy and labor complications with psychiatric disorders

Postpartum depression	Postpartum psychosis	Anxiety	Post-traumatic stress disorder PTSD	References
<ul style="list-style-type: none"> <li>• Caesarean section,</li> <li>• HDP,</li> <li>• HELLP syndrome,</li> <li>• Preterm birth,</li> <li>• Placental abruption,</li> <li>• Uterine atony,</li> <li>• Induction labor,</li> <li>• Prolongation of cervical ripening,</li> <li>• Protraction of descent,</li> <li>• Intrauterine growth restriction,</li> <li>• Low birthweight,</li> <li>• Amniotic fluid anomaly,</li> <li>• Suspicion of fetal distress</li> </ul>	<ul style="list-style-type: none"> <li>• HDP,</li> <li>• Preterm birth</li> <li>• Placental abruption</li> </ul>	<ul style="list-style-type: none"> <li>• Preterm birth</li> <li>• Placenta abruption</li> </ul>	<ul style="list-style-type: none"> <li>• HDP,</li> <li>• Preterm birth</li> <li>• Placenta abruption</li> </ul>	20-23, 81, 83-90
HDP - hypertensive disorder of pregnancy; HELLP - hemolysis, elevated liver enzymes, and low platelet count				

before or after the spontaneous beginning of birth, which is defined as the beginning of cervix ripening and contractions.

The inclusion of cervix ripening in such an analysis is crucial to understanding the immunology of pregnancy. Cervix ripening is associated with the alteration of the maternal immune system tolerance towards fetal antigens. Winkler *et al.* have reported that maternal immune system activation is essential for the initiation of cervix ripening. Maternal immune response increases until dilation reaches 2 cm. The main factor responsible for this process is the concentration of IL-8 in the cervix, which derives mostly from maternal immune cells. This is followed by several mechanisms suppressing the maternal immune response until full dilation of the cervix is achieved. Prior to that matrix, metalloproteinases were secreted from immune cells, mediating further ripening of the cervix (94-96).

Although the correlation between psychiatric disorders and complications of pregnancy and birth has not been thoroughly studied, the research in this area is promising and suggests a causal relation between immune dysregulation and postpartum psychiatric disorders as well as birth and pregnancy complications. Considering cervix dilation when analyzing the prevalence of psychiatric disorders in women according to the type of delivery they experienced may shed more light on this subject and explain the discrepancies found in the previous studies. Table 1 summarizes the

association between psychiatric disorders and pregnancy complications.

## 5. PSYCHIATRIC DISORDERS IN POSTPARTUM – PATHOGENESIS

Psychiatric disorders that arise during pregnancy and the postpartum period are especially interesting due to the phenomenon of fetal evasion of maternal immune system detection and to the interaction between the immune system and the hormonal changes associated with pregnancy. However, the mechanisms leading to an increased risk of psychiatric disorders following labor are still elusive.

Even though the link between psychiatric disorders and hormonal changes appears clear, the exact mechanisms involved remain far from evident (23). This is partly because of the increase in the prevalence of psychiatric disorders at certain periods of life, such as postpartum or menopause, that are associated with major hormonal changes. Sex steroid hormones have a multidimensional effect on dopamine, serotonin, and noradrenalin (97). In particular, estrogen was found to have antipsychotic properties as well as a neuroprotective effect in patients suffering from such diseases as multiple sclerosis, Parkinson's disease, and Alzheimer's. Additionally, estrogen suppresses neuroinflammation (4, 98-99). On the other hand, however, no

correlation between hormone concentration and postpartum depression symptoms has been found (100). Studies on mice reported no changes in serotonin levels in the hippocampus correlating with any particular phase of the estrous cycle in the females. This lack of change is explained by a tighter autoreceptor control (101).

It seems that sudden changes in hormone levels, in particular, a drop in estrogen after the expulsion of the placenta, may be related to the risk of postpartum psychiatric disorders, especially in susceptible women, yet the precise neurobiological mechanisms involved are elusive (100, 102). Moreover, there is evidence linking major depression to glucocorticoid resistance (45). Reports on cortisol levels and the risk of postpartum depression are inconsistent; however, an association with glucocorticoid resistance has been reported in cases of postpartum psychosis (100, 103). It is also important to note that cytokines have a direct influence on the expression of glucocorticoid receptors (52).

The current predominant theory posits that sudden changes in hormone levels connected with pregnancy, labor, and postpartum may lead to the development of psychiatric disorders in predisposed woman, though the evidence for this is still insufficient (23, 100, 102). A familial prevalence of postpartum psychiatric disorders has been reported, though the exact genes responsible for the increased risk have not been identified (104, 105). It is also possible that postpartum psychiatric disorders constitute a more heterogeneous group than the classifications would seem to indicate, and consequently, only a portion of patients actually have hormone-dependent psychiatric disorders (102, 106). Finally, the missing link in our understanding could have to do with the interaction of the immune system with the endocrine and nervous systems.

### 6. EVIDENCE OF IMMUNE SYSTEM DYSREGULATION IN POSTPARTUM PSYCHIATRIC DISORDERS

There is an increasing quantity of literature on the possible associations between postpartum psychiatric disorders and autoimmune diseases. The postpartum period is characterized by a „rebound

phenomenon” where an increase in both autoimmune diseases (such as multiple sclerosis) and psychiatric disorders has been observed. Moreover, comorbidity has been confirmed between postpartum psychosis and autoimmune thyroid disorders (107), the latter of which have already been established as a risk factor for postpartum depression and other psychiatric disorders (108, 109).

Women are especially vulnerable to developing depressive symptoms during the postpartum period. It has been estimated that in 40% of cases, the first episode of depression manifests within 6 weeks postpartum, and in 33% of cases, during pregnancy. Additionally, up to 20% of deaths in women postpartum are due to suicide (110, 111). Several risk factors for suicide have been reported, such as poor social support, positive history of depression or anxiety, positive family history of psychiatric disorders, abortion, and substance abuse, among others, including the obstetric complications discussed above. Although the link is still controversial, primiparity also seems to be a risk factor for postpartum (87).

Krause *et al.* have observed that decreased antenatal and postnatal levels of Tregs correlate with the symptoms of postpartum depression. In patients with postpartum depression the authors have also reported an increase in prenatal and a decrease in postnatal CXCR1 expression on monocytes along with a statistically nonsignificant increase in postnatal CCR2-positive monocytes (112). Bränn *et al.* analyzed 92 inflammation-associated markers and found that STAM-BP (or otherwise AMSh), AXIN-1, ADA, ST1A1, and IL-10 were all statistically significantly lower in women with postpartum depressive symptoms compared to controls (113). Previous studies also reported lower INF- $\gamma$  along with a lower ratio of INF- $\gamma$  to IL-10. Additionally, a positive correlation of TNF- $\alpha$  (in CSF and plasma) and cytokines IL-1 $\beta$ , IL-8, and IL-18 (both maternal and in the cord blood) with depressive symptoms was observed. The results concerning IL-6 were contradictory. Lastly, an association between total lymphocyte count and postpartum depression was reported (114).



Postpartum psychosis is a rare disorder, estimated to occur in only 1-2/1000 births. Although there is a strong correlation with bipolar disorder, the main risk factor for postpartum psychosis is primiparity (80, 115). Moreover, a greater prevalence of autoimmune thyroid disorders has been confirmed in patients suffering from postpartum psychosis (107). In one study, it was observed that 4% of such patients had autoimmune encephalitis; 2% were NMDA positive, and in 2% the condition was caused by antibodies against an unknown target (116). A study by de Witte *et al.* has found no correlation between postpartum psychosis and the seroprevalence of antibodies against herpes simplex 1, herpes simplex 2, the Epstein-Barr virus, cytomegalovirus, or Toxoplasmosis gondii (82).

In cases of physiological postpartum, a decrease in peripheral NK cells and B lymphocytes, along with an increase in T lymphocytes, especially Th and Treg, was reported, suggesting a balance between the effector and regulatory arms of the immune response. In patients with postpartum psychosis (PP), such a physiological drop in NK and B cells with a corresponding rise in T cells was not observed. Moreover, these patients were found to have a greater number of monocytes compared to both healthy postpartum controls (HP) and healthy controls who were not postpartum (HC). Additionally, a greater expression of immune-related genes was reported within the monocytes of women with PP (103).

These observations were largely confirmed in a subsequent study by Kumar *et al.* Although that study also found that the number of monocytes was increased, the level was not considered statistically significant. Additionally, the number of non-classical monocytes (CD14-CD16+) was decreased in the patients with PP compared to those who were HP. Furthermore, Kumar *et al.* reported a decrease in the number of naïve CD4+ and CD8+ T cells in patients suffering from PP compared to those who were HP along with an increase in the number of activated CD8+ T cells. While the numbers of total Tregs (CD4+ CD25+ CD127dim) were similar, the number of memory Tregs was increased in patients with PP compared to those who were HP. As for dendritic cells, the number of mDCs (CD11c+ HLADR+) was

decreased in patients with PP compared to those who were HP; however, no difference was reported in the number of pDCs. Furthermore, the number of CD56dimCD16+ NK cells was decreased in patients suffering from PP compared to those who were HP, while CD56brtCD16+/- NK cells were increased in patients with PP compared to those who were HP (117). As for cytokines, it was observed that the levels of IL-8 and IL-6 were increased compared to those of the healthy non-postpartum control, but not to those of the healthy postpartum control. Sathyanarayanan *et al.* also failed to confirm an association between IL-1 $\beta$  and MCP1 noted in the 2013 study by Bergink *et al.* (103, 118).

Overall, an increased maternal cytotoxic response to fetal antigens was observed in patients with postpartum psychosis; this finding is similar to what was observed in patients with preeclampsia and placental abruption (13, 14, 148). The abrupt increase in maternal immune activation that mediates physiological labor, in the case of inadequate response, may be a factor contributing to the manifestation of psychiatric symptoms after giving birth (10). This finding would confirm the hypothesis that immune system dysregulation is a cause of postpartum psychosis (117).

The manifestation of obsessive compulsive disorder (OCD) is strongly linked with a woman's first menstrual period, first pregnancy, or to the postpartum time period. A link with pregnancy and birth complications has also been reported. Additionally, most OCD patients have other coexisting psychiatric disorders such as depression (119). Postpartum OCD has been set apart due to characteristic symptoms, including obsessive thoughts and compulsions that are focused on the child and a different kind of disorder progression. Recently, it has been reported that 11% of women had symptoms of OCD 2 weeks after giving birth and in almost half of these women the symptoms persisted for 6 months. The majority of patients with OCD also had other psychiatric diagnoses, such as anxiety disorders (27.5%) and depression (70.6%). Furthermore, 25-75% of patients with a history of OCD suffered a relapse after giving birth. As obsessive-compulsive symptoms may be an early manifestation of bipolar disorder or schizophrenia,

any coexisting diseases and family history should be thoroughly studied (75). To the best of our knowledge, no studies on immune cell levels, subpopulation percentages, or cytokine levels in postpartum OCD have been conducted.

Additionally, the postpartum period is characterized by an increased prevalence of anxiety and panic attacks. It has been observed that 11% of women develop symptoms in the 12 weeks after giving birth (120). The first study on CRP, IL-6, and TNF- $\alpha$  in patients with anxiety postpartum found no changes in the levels of these cytokines; however, the authors did not include immune cell levels in their analysis (121).

During pregnancy and the postpartum period, patients with schizophrenia and bipolar disorder are especially vulnerable to relapses and exacerbation of symptoms. Bipolar disorder in particular is associated with the postpartum period. In many cases, symptoms that develop during the postpartum period are considered to constitute the first onset of bipolar disorder. Furthermore, in the first 6 months after giving birth, women are at a greater risk of conversion from major depression to bipolar disorder than at any other time in their lives (122-123). Diagnosis of postpartum depression triples the risk of a subsequent diagnosis of bipolar disorder. This subject is especially important because there is a risk that treatment with antidepressants will induce a manic episode in a patient. The link between other disorders in the postpartum period, such as OCD or anxiety, has not been closely studied; however, it is possible that these conditions are, in part, also an early manifestation of bipolar disorder (122). (The familial risk factor for these diseases has been discussed elsewhere.) (80). The subject of schizophrenia in pregnancy has not been studied in-depth, and the results of the research performed are conflicting (115). There are presently no studies that focus specifically on maternal immune system dysregulation in patients with bipolar disorder and schizophrenia in the context of pregnancy and the postpartum period.

Many of the reported complications of pregnancy and delivery are due to immune system

dysfunction. The increased prevalence of psychiatric disorders in the postpartum period is related to immune system changes following pregnancy and birth. The maternal immune tolerance towards fetal antigens is regulated on many different levels by both the mother and the growing fetus. Thus, even a relatively small disruption of the regulating mechanisms may manifest as an increase in postpartum psychiatric disorders. Table 2 summarizes the association between changes in the immune system and psychiatric disorders during pregnancy and the postpartum period.

## 7. THE IMMUNE RESPONSE DYSREGULATION IN PREGNANCY AND LABOR COMPLICATIONS

From the perspective of immune system functioning, pregnancy represents a unique period during which the fetus manages to escape maternal immune system surveillance without hindering the physiological maternal immune response against pathogens. Various molecular mechanisms are involved in the development of maternal immune tolerance. Complete cytotoxic activation of maternal immune cells is essential for the successful implantation and development of pregnancy (124-127). It has been reported that the total lack of NK cells prevents the possibility of pregnancy. This correlation was proven through a genetically modified mouse model in which NK cells were depleted (125, 128).

First, trophoblast cells mask their presence; this occurs because of the lack of HLA-A and HLA-B antigens on their cell membranes. Next, increased expression of the non-classic antigens HLA-C, HLA-G, and HLA-E is observed. These antigens suppress NK cells and cytotoxic T lymphocytes through killer Ig-like receptors (KIR). An increased expression of proteins from the B7 and FAS families is then observed on the cell membranes. In the physiological situation, those proteins are found in the immune cells and their interaction with a corresponding ligand is responsible for the suppression of activated lymphocytes (127, 129, 130). The microenvironment of the implanted ovum and, later on, of the placenta is rebuilt, and the Th2 phenotype of immune response is predominant (131). The maintenance of

**Table 2.** The relationship between alterations in immune system with pregnancy related psychiatric disorders

Psychiatric Manifestation	Immunological Manifestations	References
Antenatal depression	Positive association of symptoms with IL-6 and IL-1 $\beta$ concentration	114
Postpartum Depression	Association with autoimmune diseases Mother's serum <ul style="list-style-type: none"> <li>• Decreased antenatal and postnatal levels of Tregs</li> <li>• Increased prenatal and decreased postnatal CXCR1 expression on monocytes</li> <li>• Lowered STAM-BP (AMSH), AXIN-1, ADA, ST1A1, and IL-10</li> <li>• Lowered INF-<math>\gamma</math></li> <li>• Lowered INF-<math>\gamma</math> / IL-10 ratio</li> <li>• Increased TNF-<math>\alpha</math> (both in CSF and plasma)</li> <li>• Increased IL-1<math>\beta</math>, IL-8 and IL-18 (both maternal and cord blood)</li> <li>• Positive association with IL-6 and TNF-<math>\alpha</math></li> </ul>	108, 109, 112-114
Postpartum Psychosis	<ul style="list-style-type: none"> <li>• Increased maternal cytotoxic response to the fetal antigens</li> <li>• Association with autoimmune diseases</li> <li>• Association with autoimmune encephalitis</li> <li>• Lack of physiological decrease of NK and B cells and increase of T cells in peripheral blood</li> <li>• Increased number of monocytes</li> <li>• Greater expression of immune-related genes in the monocytes</li> <li>• Decreased number of non-classical monocytes (CD14-CD16<math>^{+}</math>)</li> <li>• Decrease in naïve CD4<math>^{+}</math> and CD8<math>^{+}</math> T cells</li> <li>• Increase in activated CD8<math>^{+}</math> T cells</li> <li>• Increased number of memory Tregs</li> <li>• Decreased number of mDCs (CD11c<math>^{+}</math> HLADR<math>^{+}</math>)</li> <li>• Decreased number of CD56dimCD16<math>^{+}</math> NK cells</li> <li>• Increased number of CD56brcd16<math>^{+/-}</math> NK cells</li> </ul>	13, 14, 103, 107, 116-118, 148
Tregs - regulatory T cells; CXCR1 - C-X-C motif chemokine receptor 1; STAM-BP - STAM-binding protein (AMSH); ST1A1 - Sulfotransferase 1A1; IL - interleukin; INF - interferon; TNF - tumor necrosis factor; CD - cluster of differentiation;		

pregnancy is related to indoleamine dioxygenase (IDO) pathway activation, mainly in macrophages infiltrating the decidua (132). The subsequent steps of maternal immune tolerance are linked with the increased activity of Treg cells infiltrating the maternal-fetal interface (133-135). The accumulation of the T regulatory cells on the maternal-fetal interface is essential to determining the level of T lymphocytes and NK cell suppression. The size of this cell's population within the reproductive organs and peripheral blood vessels determines the cytotoxic reaction (134, 136-137).

T regulatory lymphocytes have CD25 receptors via which they are activated in an environment rich in IL-2, a cytokine essential to the development of the cytotoxic response. Furthermore, these lymphocytes have an ability to suppress this response thanks to molecular mechanisms mediated by TGF- $\beta$  and CTLA-4, as well as other pathways. Their activation is gradual

and indirectly dependent on the level of the initiated immune system response. With the proper level of activation, these cells are able to completely suppress the immune system response. Moreover, all the evidence suggests that the immune system has an ability to match the immune response to the particular pathogen. The antigens used for monitoring the Treg activity are FoxP3 transcription factor, CD127 antigen, and chemokines CCL4 and CCL5 (72, 138-142).

The phenomenon of immune system tolerance during pregnancy, understood as a balance between the activation and suppression of the maternal and fetal immune responses, is intriguing because it both protects the fetus and directs the proper development of the pregnancy. It regulates the implantation process, proper trophoblast invasion (135), and the remodeling of the spiral artery (143). It also regulates fetal immune system development (8, 127, 129) and the

initiation of term delivery (9).

Disturbance of the regulation of immune tolerance has been found to contribute to preterm premature rupture of membranes (144) as well as to preterm labor (145). It has also been found to be responsible for spontaneous abortion (146), unexplained infertility (135), the development of preeclampsia, and placental abruption (146). Nguyen *et al.* have demonstrated that Treg cell suppressing activity differs depending on the localization of the placenta during pregnancy following a caesarean section. For example, those patients whose placentas were located far from the uterine scar (on the posterior wall of the uterus) had a different Treg cell phenotype in the cord blood compared to those patients with localization close to the scar (the anterior wall of the uterus). If the placenta was localized in contact with the scar from a previous caesarean section, the Tregs were of a more activated phenotype (147). Thus, while the level of maternal immune tolerance is related to maternal-fetal interaction, it is also affected by medical intervention and behavioral events. In particular, surgical intervention within the uterus may have a negative influence on immune tolerance in a subsequent pregnancy (148).

Advancing gestation and the beginning of spontaneous labor are associated with an increasing number of monocytes and neutrophils in the peripheral blood of the mother (9). Macrophages seem not only to be involved in the onset of labor but to be responsible for other aspects of parturition, such as cervix ripening and the postpartum repair of the uterine cervix (143). Macrophages infiltrating the lower segment of the uterus in the peripartum period alter the polarized phenotype from M2 to M1. The M1 phenotype is an inflammatory phenotype related to the secretion of tumor necrosis factor (TNF) and interleukin-12 (IL-12) by macrophages. It contrasts with the more suppressive M2 phenotype (connected with tissue repair and inflammation inhibition) (149). Kopřivová *et al.* have found a slight decrease in peripheral Treg cells on the day of delivery along with a prevalence of the Helios (+) phenotype in the Treg subpopulation, suggesting that the predominate portion of Treg cells present during pregnancy may be of thymic origin (150). During the spontaneous

beginning of labor, a reduction in active Treg cells (CD4+CD25+CD127+FOXP3+HLA-DR-CD45A+) was observed. Furthermore, TLR-induced monocyte interaction with T cells is suppressed during cervix ripening (9). Shah *et al.* demonstrated that Th1/Th17 suppression related to Treg cell activity was diminished at the onset of labor. These changes were observed at the beginning of cervix ripening when dilation was less than 4 cm. Similarly, Galazka *et al.* demonstrated that the percentage of Treg cells CD4+CD25+FOXP3+ within the population of CD4+ lymphocytes was decreased in the maternal decidua deriving from term labor when the dilation of the ripening uterine cervix was less than 2 cm (151).

This data, along with the studies of Winkler on the ripening of the cervix mentioned above, suggest that the advancement of labor may influence or, conversely, depend on the immune tolerance level. An interpretation of a potential relationship between pregnancy complication and the mode of delivery and predisposition to psychiatric disorder appearance in the peripartum period should be supported by an analysis of the degree of cervix ripening at the time of placental detachment. Shah *et al.* have concluded that the maternal immune system is transformed during the spontaneous beginning of labor into a more reactive phenotype (9). The immune reaction during labor is not limited to the decidua and cervix. Singh *et al.* have assessed the mRNA levels of interleukins and chemokines (IL-1 $\beta$ , TNF $\alpha$ , IL-6, IL-4, IL-10, CCL2, CXCL8, CXCL1, and CXCL2) in the myometrium derived from both women who delivered prematurely and those who delivered at term. They found that myometrial inflammation is secondary to an established labor and unrelated to its onset (152).

Even today preterm delivery is associated with newborn mortality and morbidity. One of the main causes of the spontaneous beginning of preterm labor is intra-amniotic inflammation (153). Not all cases of intra-amniotic inflammation are related to microorganism detection using both cultivation and molecular microbiology techniques. When the intra-amniotic fluid is sterile, intra-amniotic inflammation is diagnosed (11, 144). In cases of preterm delivery increasing concentrations of cytokines IL-6, IL-1 $\beta$

(154), and IL-18 (155) were observed in the amniotic fluid and correlated with increasing symptoms of infection. Additionally, the concentration of IL-6 was higher for those women with preterm delivery compared to those who experienced term delivery (11). Elevated levels of CD14<sup>+</sup> monocytes and neutrophils were detected in maternal blood during preterm delivery. The monocytes were typified by bearing enhanced expression of toll-like receptors (TLR4) (156). TLR4 are essential for the induction of innate immune responses and its activation influences the expression of a set of genes for the cytokines IL-1, IL-6, and IL-8 (157). Kumazaki *et al.* have found increased expression of TLR4 on the villous Hofbauer cells of preterm placentas (157). Aberrant inflammatory reactions may be related to the appearance of such complications as preterm labor, intrauterine growth restriction, and spontaneous abortion (158). Singh *et al.* have examined the distribution of inflammation and its relationship with pro-labor gene expression during preterm labor associated with chorioamnionitis and idiopathic inflammation and found that in idiopathic preterm labor inflammation was limited to the choriodecidua (159).

The pathogenesis of preeclampsia is complex. Generally, two different placental pathways may be distinguished: trophoblast and endothelial cell dysfunction (160). These two pathways are connected by immune cells. On the one hand, these cells are responsible for enabling trophoblast cell invasion, but on the other hand, they support endothelial cell differentiation. Immune cell activation in women with preeclampsia may be assessed in a number of ways. Moreover, the abnormal immune response to the allogeneic fetus in preeclampsia is similar to the immunological background of graft versus host disease (12). In women experiencing normal pregnancy, Tregs are present both at the maternal-fetal interface and in the peripheral blood (161). However, in patients with preeclampsia, Tregs are decreased in both the peripheral blood and at the maternal-fetal interface (146). The percentage of the subpopulation of activated CD4<sup>+</sup> CD25<sup>high</sup> FoxP3<sup>high</sup> Tregs among CD4<sup>+</sup> CD25<sup>high</sup> cells was greater in patients with normal pregnancies compared to those with preeclampsia (162).

Increasing apoptotic and stress signaling protein levels in the placenta and umbilical cord, such as p38 phosphorylation, ratio of Bax/Bcl-2, and caspase-9 placental expression, were significantly higher in patients with preeclampsia compared to those with normal pregnancies (160). Increasing apoptosis on the maternal-fetal interface influences the macrophage cell population that is responsible for the removal of apoptotic cells (12). During pregnancy, macrophages predominantly differentiate into the M2 phenotype (143) that produces abundant IL-10. Those cells also participate in the remodeling of uterine vasculature. The uterine vessels lose smooth muscle and endothelial content, and the uterine spiral artery is replaced by extravillous trophoblast cells. Macrophages participate in these processes through the secretion of vascular endothelial growth factor VEGF and fms-like tyrosine kinase-1 (Flt-1) as well as other mechanisms (163). The biological function of VEGF depends on the interaction with Flt-1 (143). Extravillous trophoblast cells infiltrate both the decidua and the myometrium of the uterus and are surrounded by maternal dNK cells. Abnormal placental implantation observed in patients with preeclampsia is related to increased NK cell activity (12; 164-165). Human dNK (CD56<sup>Bright</sup> CD16<sup>-</sup>) cells are a subpopulation of peripheral NK cells. They express KIRs, present reduced cytotoxicity, and are granular (containing perforin and Granzyme B) (166). These cells are responsible for the secretion of the vascular endothelial growth factor VEGF and placental growth factor PLGF (167). They also secrete metalloproteinase MMP7 and MMP9. Abnormal activity of these cells is related to the development of preeclampsia.

Control over the phenomenon of maternal immune tolerance is essential for both maternal and fetal health, including but not limited to the development of the placenta (168).

## 8. PERSPECTIVES

Over the last few years, T regulatory lymphocytes have become a frequent topic of research. The development of immunotherapy has stimulated breakthrough studies on this subject



and led to a better understanding of the mechanisms underlying the functioning of these cells. Treg cells have the ability to suppress most types of immune cells, including CD4+ and CD8+ cells, B lymphocytes, NK and NKT cells, APC cells, monocytes, macrophages, and dendritic cells (139). Furthermore, it is believed that Treg cells can use multiple suppressive pathways, depending on the strength of the antigen stimulation, the anatomic localization, and the type of immune response (138).

It has been suggested that insufficient nonpathological antigen stimulation may lead to the inappropriate development of the Treg cell population, causing an impairment of immunosuppressive abilities (52). This conjecture is similar to the finding that the localization of the placenta after caesarean section leads to a different immunosuppressive phenotype in subsequent pregnancies (147). Because of their special role in immune system regulation, T regulatory cells may also be essential for studying the possible influence of immune system dysregulation during pregnancy on the risk for psychiatric disorders (75).

On the one hand, the increasing prevalence of the instrumentalization of birth and of elective caesarean sections seems to be responsible for the increased prevalence of postpartum psychiatric disorders. On the other hand, learning the details of the immunological mechanisms involved in the beginning of labor, the advancement of labor, placental detachment, and the puerperal period, and, more specifically, discovering the precise role of Treg cells in these processes may lead to a decreased risk of postpartum psychiatric disorders. Such a decrease would not be brought about through the prevention of immune dysfunction and complications but through new treatments that would manipulate the level of maternal immune response and tolerance, thereby nullifying the negative consequences of the inevitable instrumentalization of delivery.

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**Abbreviations:** DSM-V: Diagnostic and Statistical Manual of Mental Disorders, ICD-10: international statistical classification of diseases and related health problems, PROM - premature rupture of membranes , PTSD: post-traumatic stress disorder, CSF: cerebro-spinal fluid, PET: positron emission tomography , MHC: Major histocompatibility complex, Tregs: regulatory T cells , SNP: single nucleotide polymorphisms , PSMB4: Proteasome subunit beta type-4, TBX21: T-box transcription factor TBX21, STAT3 -signal transducer and activator of transcription 3 , CD3E: CD3e Antigen, Epsilon Polypeptide, CXCR1: C-X-C motif chemokine receptor 1, PRKCH: Protein kinase C eta type, PSMD9: 26S proteasome non-ATPase regulatory subunit 9, Il: interleukin, INF:

interferon, FAS: FasR, apoptosis antigen 1 (APO-1 or APT), HIV: human immunodeficiency virus, TGF: Transforming growth factor, TLR: toll-like receptor , CRP - C-reactive protein, OCD: obsessive-compulsive disorder , SSRI: selective serotonin-reuptake inhibitors , ABGA: anti-basal ganglia antibodies , CB-PTSD: postpartum childbirth-related post-traumatic stress disorder , HDP: hypertensive disorder of pregnancy , HELLP: hemolysis, elevated liver enzymes, and low platelet count, STAM-BP: STAM-binding protein (AMSH), ST1A1: Sulfotransferase 1A1, NMDA: N-methyl D-aspartate , PP: postpartum psychosis , HLA: Human Leukocyte Antigen,IDO: indoleamine dioxygenase , CTLA-4: cytotoxic T cell antigen 4, CD: cluster of differentiation, KIR: Killer-cell immunoglobulin-like receptor, VEGF - vascular-endothelial growth factor, MMP: metallo-proteinase, APC: Antigen-presenting cells

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