Postpartum Psychosis:

Treatment, follow-up and immunological parameters

Karin M. Burgerhout

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Postpartum Psychosis:
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Postpartum psychose:
Behandeling, follow-up en immunologische parameters

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Copromotor:	Dr. V. Bergink
Overige leden:	Prof. dr. W.W. van den Broek Prof. dr. V.J.M. Pop Dr. M.A. Versnel

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Chapter 1

Introduction

History of postpartum psychosis

In 400 BC Hippocrates described a case of postpartum psychosis in his book 'Third Epidemics':

"A woman in Cyzicus gave birth to four twin daughters and soon after birth she began to suffer severe insomnia and restlessness. She was silent, sullen and disobedient. On the sixth day after birth, towards night, she talked much and incoherently and did not sleep anymore. On the eleventh day she became delirious and then comatose. On the seventeenth day she died." [1]

This is the first description of the relationship between birth and psychiatric illnesses. Hippocrates called it phrenitis; this term is from the ancient Greeks and it refers to acute inflammation of the mind and body, not in theoretical sense, but in a descriptive sense. It was a presumed disease that was never anatomically or conceptually well determined. The diagnosis was also used during the Middle Ages; it referred to mental confusion or continuous delirium with fever [2]. This example demonstrates the first sign of the relationship between immunology and postpartum psychiatry, which is an important theme in my thesis.

Another report of postpartum psychosis is from the autobiographical work of Margery Kempe [3]. She delivered the first of her fourteen children in the United Kingdom in 1393. After the birth of her first child, she had a mental breakdown in which, as she describes, she was possessed by the devil. She cursed her husband, family, friends, and herself repeatedly during that period. She also injured herself; she attempted to bite her wrist and throw herself out of the window. To protect her, her husband John chained Margery in a storeroom. After six months she had a vision of Jesus, who spoke and admonished her, and she came to rest. She dressed flashy and successively and began two companies: a brewery and a mill. After this episode, Margery Kempe became the largest brewer in town [3, 4].

Other old case reports from European countries show similar cases of women with severe affective psychosis that began immediately postpartum. Overtime, several names have been given to postpartum psychosis, such as: 'mania lacteal', 'folie circulaire', 'amentia', 'puerperal insanity', 'puerperal mania', 'dreamlike delirium', and finally 'postpartum or puerperal psychosis'. Since the 18th century, postpartum psychosis has been widely appreciated as a severe disease that requires acute intervention [5]. One of the first doctors in the 19th century who started to systematically study postpartum psychosis was the French psychiatrist Esquirol, and later his pupil Louis Marcé. In his classical book: 'Des maliedes mentales', [6] he proposed (according to Boerhaave) that the various psychopathological syndromes that occur in the postpartum period should not be regarded as independent illnesses, but as different manifestations of

one syndrome with a common cause. The suspected relationship between postpartum psychosis and other psychiatric diseases (especially bipolar disorder) still exists and is another important topic in this thesis.
Esquirol also followed the course of postpartum psychosis. He describes how eventually 58% of the women from his research recovered and were fit to return home. Of the total of 92 patients, 19% recovered during the first three months, 23% recovered during the second three months, and 16% recovered between six months and two years after admission. We suppose that this could be the natural course of postpartum psychosis because of the supposed effectiveness of the treatments that were common at that time. The treatments described in the 18th century included cutting of hair, applying ice or even mustard packs to the head, neck or legs, and/or application of leaches, supported by sweat-induction or purgative tea. Treatment in the 19th century was focused on protection against suicide, the control of excitement, and supportive management, while waiting for spontaneous remission [2, 5]. It is remarkable that there is still a lack of evidence for the treatment of postpartum psychosis, which is another important theme in my thesis. I have investigated treatment, risk factors, follow-up, and biological factors of postpartum psychosis.

Epidemiology and clinical characteristics of postpartum psychosis
Mood disorders in the postpartum period are serious mental health conditions that negatively affect many women from different cultures [7]. Postpartum mood disorders are commonly classified into three categories: postpartum blues, postpartum depression (PPD), and postpartum psychosis (PP) [7]. Postpartum psychosis is the most severe and uncommon form of postnatal affective illness, with estimated rates of 0.5-1 episodes per 1000 deliveries [8, 9]. Epidemiologic studies demonstrate that women are more likely to be admitted to a psychiatric unit after giving birth than at any other time in their lives [8, 9]. The risk of being admitted with psychosis within 30 days of childbirth increases 20 fold compared to the period before pregnancy [8].
Postpartum psychosis occasionally presents within 48-72 hours postpartum and has been defined as the rapid onset of manic or psychotic symptoms. We previously found a median onset of eight days after delivery [10]. The first presenting symptoms are insomnia, mood lability, or occasionally obsessive concerns regarding to the newborn. Later complaints include an elevated or depressed mood (which can fluctuate rapidly), disorganized behavior, restlessness, irritability, and delusions and hallucinations. Mood symptoms are a characteristic of postpartum psychosis and are more prevalent in postpartum psychosis than in non-postpartum psychosis [11]. Women with postpartum psychosis also show delirium-like features; women can sometimes show atypical cognitive symptoms, such as disorientation, derealisation,

depersonalization, confusion, perplexity, and misrecognition of people [11-14]. Remarkably, the incidence of schizophrenia-like symptoms is low [11, 13-15]. The name postpartum psychosis is confusing because it is usually defined as a mood disorder and not a primary psychotic disorder. Postpartum psychosis is a severe disorder with a high risk of suicide and infanticide, which makes early recognition important [4, 10, 16].

Nosology of postpartum psychosis

Two primary areas of confusion in the nosology of all postpartum psychiatric disorders are (1) whether these are discrete diagnostic entities, and (2) what time frame should be given for the term postpartum [17]. The widely used Diagnostic Statistic Manual of Disease (DSM-IV/V) does not distinguish 'postpartum' or 'puerperal' psychiatric disorders as distinct diagnoses. Thus, postpartum onset may be applied to a major depressive episode with psychotic features, a manic or mixed episode in a bipolar I or bipolar II disorder, and a brief psychotic disorder [17]. The second major area of nosological debate is about the time frame of postpartum. The most restrictive definition is used in the DSM-IV/V, which requires the onset of illness to occur within four weeks after birth. Often, researchers use a less restrictive boundary of three months postpartum [8] and some clinicians and researchers use a liberal boundary of one year postpartum, which contributes to the lack of consensus of diagnosing postpartum psychosis [17].

An important risk factor for developing postpartum psychosis is having bipolar disorder, but a considerable percentage of women with postpartum psychosis have no history of manic or psychotic episodes. Previous studies of our group confirmed that women with postpartum psychosis that is limited to the postpartum period have a unique risk profile and phenomenology. Compared to women with postpartum psychosis and bipolar disorder, the women with psychosis that is limited to the postpartum period show a delayed postpartum onset, the absence of obstetric complications as a risk factor, and a prominence of mood-incongruent psychosis [10]. Previous studies postulated that postpartum psychosis that is limited to the postpartum period should be diagnosed as a separate disease entity in the DSM classification [10]. In our research, we have specifically focused on women with the first-onset of postpartum psychosis. We studied the phenomenological characteristics, treatment response, prevention of further episodes, and risk factors in women with postpartum psychosis [10].

Risk factors for developing postpartum psychosis

Previous studies have found several characteristics that could be related to a higher risk of developing postpartum psychosis. Some of these characteristics are primiparity, higher maternal age (older than 35), previous psychiatric admissions, and complications during delivery [18-20]. Indeed, primiparity has been repeatedly observed as a significant covariate when modeling the risk factors for postpartum psychosis [10, 18]. A large Swedish register study of approximately 750, 000 first-time mothers a limited increase in the risk of postpartum psychosis due to a low level of education, not cohabitating with the infant's father, and maternal smoking [10, 18]. Women without any previous psychiatric hospitalization had an increased risk of psychosis when giving birth to a child with a very low birth weight (≤1500 gram). In contrast, a high birth weight (≥4500 gram) decreased the risk [18]. Miscarriage or termination of pregnancy, perinatal death, congenital malformations, preterm birth (≤32 weeks), cesarean section, and poor sleeping in the postpartum period were not significant statistical risk factors for postpartum psychosis among women with no previous psychiatric hospitalization [10, 18, 21, 22]. A recent study in the Danish population-based cohort found that there was an association between postpartum psychiatric episodes and pre-eclampsia, and that the combination of having preeclampsia and a somatic comorbidity resulted in the highest risk of psychiatric episodes during the first three months after childbirth [23].

Postpartum psychosis and differentiation from other postpartum psychiatric diseases

Postpartum psychosis, postpartum depression, and postpartum blues have similarities in terms of when they occur, the new parent role, and symptoms such as a depressed mood. But, there are also important differences between these three conditions that must be clearly differentiated (Table 1). Postpartum depression affects approximately 10% of mothers after childbirth and has symptoms of anxiety, failure to cope and guilt, misery, apathy, irritability, and social isolation. The disease entity is highly heterogeneous; psychosocial risk factors influence the risk and clinical manifestations. The onset of postpartum depression is highly variable, and almost half of women experience symptoms during pregnancy. Other women experience episodes of depression throughout the entire first year postpartum [5, 24-26]. A recent study stated that there is no difference in the pattern of symptoms of depression during pregnancy or postpartum. Thus, postpartum depression does not seem to be a distinct syndrome [24]. It is sometimes difficult to distinguish the prodromal symptoms of postpartum psychosis from normal, physiological maternity blues. Between day three and day five postpartum, it is estimated that between 40% and 60% of new mothers

experience maternity blues [27]. Maternity blues is described as the brief occurrence of dysphoria, mood swings, and irritability. The duration of maternity blues is short and ranges from hours to days (Table 1) [19]. Postpartum psychosis does not appear to be initiated by psychosocial factors; the role of biological factors is more important. The range of severity in postnatal depression ranges from mild to severe, whereas postpartum psychosis is a more homogenous illness that tends to be severe and

Table 1. Mood symptoms and psychiatric syndromes during the postpartum period [7, 17, 27, 29].

	Postpartum Psychosis (including postpartum mania and depression with psychotic features)	**Postpartum Depression**	**Postpartum Blues**
Estimated incidence	0.1%	10%	40-60%
Risk factors	Personal/family history of PP	Personal history of depression	<35 or >39 years
	Personal/family history of BPD	Depression/anxiety during pregnancy	Delivery with caesarian section
	Genetics	Family psychiatric disorder	
	Primiparity	Life stress	
	Hormonal changes	Hormonal changes	
	Sleep loss	Low social support	
	Higher educated	Poor marital relationship	
Onset	Within 4 weeks postpartum	2 Weeks to 1 year postpartum	3-5 days postpartum -2 weeks postpartum
Symptoms	Manic or affective	Non-psychotic	Non-psychotic
	Mania	Depressed mood	Crying
	Mood lability	Loss of interest	Emotional lability
	Delusions	Weight change	Irritability
	Hallucinations	Insomnia or hypersomnia	Mood swings
	Bizarre behavior	Psychomotor agitation	Anxiety
	Severe depression	Fatigue or loss of energy	Dysphoric mood
	Confusion	Feeling worthlessness or guilt	Insomnia
	Perplexity	Decreased concentration	Loss of appetite
	Thought of death or suicide	Thought of death or suicide	
Management	Hospitalization	Nondirective counseling	Usually self-limited
	Mood stabilizers	Cognitive behavior therapy	Reassurance
	Antipsychotics	Interpersonal psychotherapy	Education
	Hormones	Hormones	Emotional support
	ECT	Psychodynamic therapy	Counseling
	Antidepressants (with caution)	Antidepressants	

usually necessitates hospitalization [28]. More studies are conducted on postpartum blues and depression than on postpartum psychosis; this could be because of the diagnostic difficulties, the low incidence, or the severity of the disease [4].

Postpartum psychosis: Etiology and relationship with bipolar disorder

Overall, rates of psychiatric admission decrease during pregnancy, increase in the early postpartum period (particularly during the first two weeks after birth), and remain elevated above baseline during the first two years postpartum [30]. Most patients with postpartum psychosis have had no previous psychiatric illnesses, which makes it difficult to study the etiology of first-onset postpartum [31]. Most longitudinal studies suggest that postpartum psychosis is not a discrete nosologic entity; they suggest it is a presentation of an underlying mood disorder that is within the bipolar spectrum in most cases [17, 32, 33]. The prevalence of postpartum psychosis is ten-fold lower (0.1-0.2%) than the prevalence of bipolar disorder (1-2%). Women with bipolar disorder have an elevated risk of developing a puerperal illness episode, and they have a 100-fold higher risk of developing postpartum psychosis than women without a history of bipolar disorder [34]; estimated rates of occurrence range from 30% to 50% per delivery [8, 28, 35]. Several studies have described higher relapse rates during the postpartum period of bipolar disorder compared to women with schizophrenia or depression [8]. The risk of developing postpartum psychosis is also elevated in women who have had a previous episode of postpartum psychosis, and a recent study [36] found an overall relapse risk of 31% in patients with postpartum psychosis (95% CI=22.42). Another risk factor for developing postpartum psychosis is a family history of postpartum psychosis or bipolar disorder. Affective disorders and postpartum psychosis seem to cluster in families [37]. In conclusion, the majority of previous studies suggest that many, but not all, episodes of postpartum psychosis may be variants or atypical forms of bipolar disorder. Indicators for a possible bipolar diagnosis include a previous history of 'missed' or misdiagnosed mood episodes, any evidence of previous mania or hypomania, and a strong family history of bipolar disorder or postpartum psychosis [17].

Treatment of postpartum psychosis

In recent literature (since 1970), 19 treatment studies of first-onset postpartum psychosis can be found. These treatment studies are summarised in Table 2. The effects of sex steroid hormones, electro convulsion therapy (ECT), propranolol, lithium, and antipsychotics were examined. These studies have small sample sizes: ten studies are case reports that describe a single patient, and only three studies included more than ten patients. These studies all used different diagnostic criteria and measurements of treatment efficiency [38, 39].

Five studies explored the influence of electro convulsion therapy (ECT) in the treatment of postpartum psychosis [40-44]. Two studies are case-studies and two studies included a higher number of patients, 58 and 34 women [44, 45]. In one case study, treatment with chlorpromazine was ineffective, while ECT treatment led to remission [41]. Similarly, a case series of five women described positive treatment outcomes with ECT [40]. A retrospective study compared the clinical responses to ECT of women with postpartum psychosis to outcomes of women following ECT with non-postpartum psychosis, and greater clinical improvement was found in the postpartum group compared to the non-postpartum group with ECT treatment [42]. Another study described a woman with postpartum psychosis and catatonia and who did not respond to medication, but who did respond to electro convulsion therapy [43]. The most recent study compared women with postpartum psychosis who were admitted and treated with and without ECT. They found no differences in duration of hospitalization or psychopathology in the group of women who were treated with ECT compared to the women who were not treated with ECT [44].

The use of progesterone and hormonal replacement therapy has been described in five studies, mainly in case reports. One research group published three studies about this topic and found positive effects of estradiol [46-48]. The fourth study is a case report of a patient with postpartum mania and no remission with lithium, antipsychotics, and a moodstabiliser, who achieved remission with hormonal treatment within two weeks [49]. The last study that describes hormonal treatment is a case report written by an affected mother and her partner about the decrease in psychotic complaints within one month with progesterone treatment [50].

As described above, postpartum psychosis is considered a bipolar spectrum disorder and therefore, antipsychotics and lithium are used as treatment [17]. The effects of antipsychotics in the treatment of postpartum psychosis are described in four case reports [51-53] in addition to reporting successful treatment with chlorpromazine, clozapine, and pimozide. Lithium as a treatment for postpartum psychosis [54-56] was investigated in three studies: in one case study, where it was used as a beneficial monotherapy [54] and in two studies that used it as an addition to an antipsychotic [55, 56]. Two other studies have provided support for propranolol (a beta-adrenergic blocker used to treat hypertension) as a treatment option for postpartum psychosis [57, 58]. In Table 2, the treatment options that were previously studied are summarised.

Table 2. Summary of treatment of postpartum psychosis studies.

Author + year	Treatment	Inclusion	Study design	Patients with treatment	Most important findings
Stanworth, 1982 [59]	ECT: 2 sessions	Carbamazepine and ECT	Case study	1	Little improvement with carbamazepine alone. Good improvement with carbamazepine + ECT.
Reed, 1999 [45]	ECT: 3-6 sessions	Onset <3 months postpartum	Case-note study	58 PP, 56 non-postpartum patients	Women with PP had significantly greater clinical improvement following ECT compared to the non-postpartum group.
Forray, 2007 [60]	ECT: 3 times a week	Onset 3 weeks – 11 months postpartum.	Case series	5	All 5 women improved < 3-6 sessions when pharmacotherapy was unsuccessful.
Strain, 2012 [61]	ECT: Olanzapine, lorazepam, citalopram.	Onset <5 months postpartum	Case report	1	No effect with previous medication. ECT directly effective, 6 sessions needed. Olanzapine and citalopram as maintenance treatment, stable over 18 months.
Babu, 2013 [44]	ECT: median 6 session	Onset<6 months postpartum	Naturalistic prospective	34	No differences in duration of hospitalization or psychopathology in women with and without ECT treatment.
Atkinson, 1983 [62]	Hormonal-progesterone	Onset <7 weeks postpartum	Case study	1	Hallucinations + delusions decreased within 1 month.
Ahokas, 1999 [63]	Hormonal-17estradiol. One women first chlorpromazine.	Onset <4 weeks postpartum	Case series	2	Little effect of chlorpromazine alone. Psychotic symptoms decreased with hormones, complete remission with chlorpromazine and hormones. Both stopped treatment and relapsed <2 weeks.
Ahokas, 2000 [64]	Hormonal-17estradiol	Mean onset 12.3 days postpartum	Open label, 6 weeks	10	Psychotic symptoms decreased within 1 week. One women stopped treatment and relapsed <1 week.
Ahokas, 2000 [65]	Hormonal-17estradiol	Onset <2 weeks postpartum	Case series	2	Psychotic symptoms decreased within 10 days. One women stopped treatment and relapsed <1 week.
Huang, 2000 [66]	Hormonal: Lithium, carbamazepine, valproic acid, haloperidol.	Onset <1 month postpartum, history with mania	Case study	1	Poor treatment response with previous treatments, hormone therapy effective < 2 weeks.
Marshall, 1981 [67]	Antipsychotics: Chlorpromazine + Lorazepam → Chlorpromazine + Imipramine	Onset <8 days postpartum:	Case report	1	Effect on combination chlorpromanzine + imipramine < 1week, remained 12 weeks symptom free.

Table 2. Continued.

Author + year	Treatment	Inclusion	Study design	Patients with treatment	Most important findings
Murray, 1990 [68]	Antipsychotics: Chlorpromazine	Onset 5 days postpartum 1st, 9 days postpartum 2nd delivery	Case report	1 (2x)	Symptoms improved rapidly after both deliveries.
Kornhuber, 1991 [52]	Antipsychotics: Zuclopenthixol → Clozapine	Onset <1 week postpartum	Case report	1	Zuclopenthixol alone → EPS → Clozapine added: Effective <1 week.
Iruela, 1992 [69]	Anxiolytics, antidepressant and antipsychotics: Haloperidol, Levomepromazine, Pimozide	Onset <3 days postpartum	Case study	1	Pimozide was effective < 4 days and remained effective 3 years. All other treatments were ineffective.
Silberman, 1975 [70]	Lithium + antipsychotics: Perfenazine	Lithium and perfenazine group versus comparison group with only AP	Prospective	13 with, 6 without	Lithium and perfenazine were effective within 7-15 days, less relapses and faster recovery in combination group.
Targum, 1979 [71]	Lithium + antipsychotics: Chlorpromazine or Thioridazine.	Onset <2 weeks postpartum, history bipolar disorder, lithium withdrawal during pregnancy	Case series	2	Both responded <17 days.
Lichtenberg, 1988 [72]	Lithium monotherapy	Onset <3 days postpartum	Case study	1	Response <10 days, recovery <1 month. Women had a history of GM2 ganglio-sidosis.
O'Reagan, 1973 [58]	Beta-blocker propranolol and antipsychotics, antidepressant, lithium and ECT	Onset <11 days postpartum; AP, ECT, AD, LI+ propranolol	Case report	1	Antipsychotics, antidepressant and lithium no effect. ECT temporarily effective. Propranolol cured symptoms.
Steiner, 2008 [73]	Beta-blocker propranolol versus antipsychotic chlorpromazine	Onset propranolol group <14 days postpartum, chlorpromazine < 35 days postpartum	Clinical trial	10	Both effective: Propanolol sooner discharge and greater symptom improvement.

Psychosocial effects of postpartum psychosis

Suffering from PP is a stressful life-event with symptoms remaining long after the initial illness episode and discharge. Two qualitative studies on psychosocial functioning are available, which explain that women experience psychosocial problems after the initial illness episode. After discharge, women frequently experienced a depressive episode and milder periods of mood swings, anxiety, and low mood [74]. Women mentioned feelings of guilt (about the suffering of others during their illness, including their baby or other children and major relationships), anxiety, relationship difficulties, fears concerning subsequent pregnancies, the possible effects of their illness on the child's emotional and intellectual development, and potential stressors for further episodes of illness [28, 74]. In the follow-up, women felt socially vulnerable and isolated with a lack of empathy from others [74]. Furthermore, women reported that the illness hampered their ability to experience normal emotions in the long run, as affective responses were viewed as potentially pathogenic [28]. The first study that was mentioned is by Robertson and Lyons, and it was performed with ten women who had been diagnosed and treated for postpartum psychosis during the last ten years [28]. The second study by Heron and Gilbert [74] focused on psychosocial functioning nine years after postpartum psychosis in five women.

Follow-up of postpartum psychosis

Women with first-onset postpartum psychosis are at a high risk of developing subsequent mood episodes, but studies do not provide evidence-based risk estimates. In Table 3, a summary of the follow-up studies that have been published since 1992 is provided, including women with first-onset postpartum psychosis within one year postpartum, and with clear numbers of patients with postpartum psychosis and relapse. These inclusion criteria resulted in nine retrospective studies and one prospective study, which estimated relapse rates after first-onset postpartum psychosis. The limitation is that the data in these studies is usually obtained through retrospective methods and some studies were conducted a long time ago using diagnostic criteria from an outdated version of the DSM-V. Of relevance, but not included in this table, because of a different study method, is a recent study by Munk-Olsen et al. [75]. They studied a large group of women with a first-time psychiatric contact within the first postpartum year. In patients with an onset of psychiatric complaints within one month postpartum, the Kaplan-Meier curve showed a 20% conversion in bipolar disorder after 15 years of follow-up [75].

Table 3. Summary of studies with follow-up of first-onset postpartum psychosis. Percentages of affective relapses are calculated on the entire group of patients with a relapse.

Author + year	Country + centre	Data collection	Follow-up period in years (range)	Inclusion	Number of patients	Design and follow-up percentage	Relapse percentage and percentage of affective relapse
Kapfhammer, 2014 [76]	Germany – University clinic	1975-1995	12 (7-24)	<4 Weeks postpartum	55	Retrospective	56% Affective: 61.3%
Blackmore, 2013 [77]	United Kingdom – Nationwide recruitment		11.9 (SD 8.9)	<6 Weeks postpartum	116 -> 99 FO (13 depression in history)	Retrospective	72% Affective: 100%
Kisa, 2007 [78]	Turkey – University clinic	1998-2006	4 (2-6)	<6 Months postpartum	23	Prospective 78%	65% Affective: 39.1%
Rohde, 1993 [79]	Germany – University clinics	1950-1979	26 (12-41)	<6 Weeks postpartum	61	Retrospective 87%	64% Affective: 62.3%
Benvenuti, 1992 [32]	Italy – University clinic	1973-1987	12 (4-18)	<8 Weeks postpartum*	30	Retrospective 79%	63% Affective: 90%
Terp, 1999 [80]	Denmark – Register Study	1973-1993	10	<2-91 Days postpartum	609	Retrospective	65% X
Kirpinar, 1999 [81]	Turkey- Clinical patients	1973-1994	11 (SD 3)	<3 Months postpartum	64	Retrospective 72% visited, 28% information from GP	81% Affective: 51,5%
Schopf, 1994 [82]	Switzerland – University clinics	1949-1990	23 (3-35)	<3 Months postpartum 54% depressions 46% PP	100	Retrospective 84%	69% Affective: 75.0%
Pfuhlmann 1999 [83]	Germany -University clinic	1981-1997	13 (6-26)	<6 Months postpartum*	39	Retrospective 81%	87% Affective: 53.8%
Videbech, 1996 [84]	Denmark- Register study	1973-1987	11 (median) (7-14)	<1 Year postpartum	50	Retrospective	58% Affective: 56.7%

Affective disorders: Depression, bipolar disorder, schizoaffective disorder bipolar type
X: Not specified
Inclusion: -First-onset postpartum psychosis
-Clear numbers of patients with postpartum psychosis and relapse
-Within one year postpartum
-Published since 1992

THE RELATIONSHIP BETWEEN IMMUNOLOGY AND PSYCHIATRY

Immune hypothesis

In the first decade of the 20th century, reports appeared about the involvement of the immune system in psychiatric disorders, and in the last decade of the 20th century, the first specified studies on the relationship between psychiatric disorders the immune system appeared. Smith postulated one of the first hypotheses in 1991, implicating that mood symptoms are related to the activation of the immune system in the "macrophage theory of depression" [85]. This theory pronounces that constantly activated macrophages (and their equivalents in the brain, the microglia) and T-cells generate cytokines and inflammatory compounds. These cytokines and compounds can pass the blood-brain barrier and influence the brain. This makes the brain vulnerable to mood symptoms that are determined by a person's genetic background and environmental risk factors.

It is assumed that there is a relationship between psychiatric diseases and the immune system for several reasons, which are listed below:

a. Several epidemiologic studies demonstrate a co-occurrence of mental disorders with autoimmune diseases and chronic inflammatory conditions such as diabetes, atherosclerosis, and Graves' disease [86]. A large Danish register study found that individuals with schizophrenia had an elevated risk of subsequent auto-immune diseases, and a family history of schizophrenia slightly increased the overall risk of developing autoimmune diseases [87].
b. Some general pathophysiological mechanisms of autoimmunity are similar to the characteristics of psychiatric diseases. Both diseases are generally multifactorial, require inheritance of at least multiple gene polymorphisms and exposure to one or more environmental factors, have the tendency to remit and relapse, have familial occurrence, show progression from subclinical to clinical disease, and have cyclical exacerbation-remission patterns [86].
c. Studies have found that some patients with psychiatric disorders demonstrate signs of immune dysfunction, which could be the triggers of the development and the progression of these psychiatric disorders [88]. In the introduction of this thesis we further describe these previously found disturbances.
d. Another reason for the assumed relationship between psychiatry and immunology are the discovered immune-modulating effects of antipsychotics and anti-depressants, and the mood altering effects of anti-inflammatory therapies [88].

The immune system

The immune system protects an organism against disease with a combination of biological structures and processes. To function properly, an immune system can detect a wide variety of agents and can differentiate them from their own healthy tissue. The immune system is divided into the innate immune system and the adaptive immune system (Figure 1). Problems with the immune system can cause cancer, autoimmune diseases, and inflammatory diseases. Immunodeficiency involves an immune system that reacts with less activity than normal and can cause dangerous infections. Immunodeficiency can be caused by obtained diseases such as HIV/AIDS, genetic deficiencies, or immunosuppressive medication. On the other hand, autoimmunity involves a hyperactive immune system, which attacks normal tissues as though they were foreign organisms. Examples of autoimmune diseases are rheumatoid arthritis, thyroid diseases, systemic lupus erythematosus (SLE), and diabetes mellitus type 1.

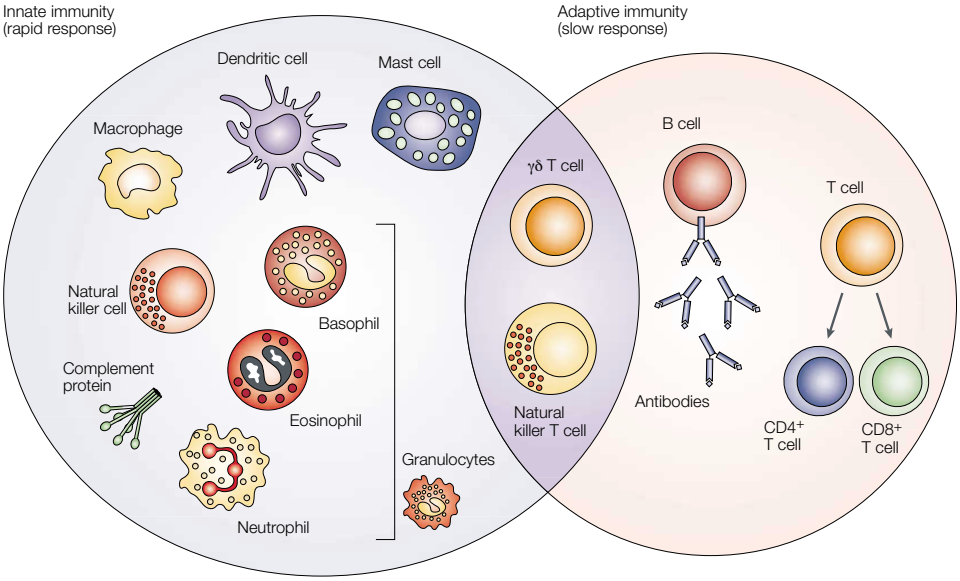

Figure 1. The innate and adaptive immune response [89].

Innate immunity

The innate immune system is a more ancient component of the immune system and it provides the first line of defense against pathogens. It generates a fast response with limited specificity. The innate immune system consists of barriers (mucus, saliva,

tears, and skin), defense cells (neutrophils, monocytes, macrophages, natural killer cells, and mast cells), and soluble factors (cytokines and chemokines). Cells of the innate immune system can be triggered by penetration of natural barriers such as the skin, or by recognition of molecules on a microbe through pattern recognition receptors. Signals of damaged and stressed cells can also activate immune cells. In this thesis we focus on the cells of the mononuclear phagocyte system (MPS).

Mononuclear Phagocyte System (MPS)

This system consists of three cell types: monocytes, macrophages, and dendritic cells. The classical function of MPS cells is to provide defense against foreign intruders through a process called 'phagocytosis'. This innate process consists of recognition, uptake, and full degradation of microorganisms. Another function of the MPS cells is to degrade foreign intruders into an array of antigenic peptides, which trigger T- cells and B-cells to generate an antigen specific immune response.

Monocytes

Monocytes are a subset of circulating blood cells with remarkable plasticity and diverse functions during infection, tumor formation, and chronic inflammation [90]. The monocyte residents in the blood and can infiltrate a target tissue, where it differentiates into macrophages and dendritic cells. There is also evidence that circulating monocytes are activated in several psychiatric diseases, similar to microglia (see below). Monocytes are not always the precursors of microglia, although they are members of the same cell development lineage. Monocytes circulate in the blood which makes them much better to study than microglia [91].

Macrophages

Macrophages are widely distributed innate immune cells that play central roles in host defense against invading pathogens and in maintaining immunological homeostasis. Their name is derived from the Greek word for glutton. Heterogeneity and plasticity are hallmarks of macrophages. Macrophages have been broadly characterized as either classically activated (M1) or alternatively activated (M2) based on surface receptors, gene signatures, and secretion of inflammatory mediators [92]. In the brain, a balance between the pro-inflammatory M1 and anti-inflammatory M2 macrophages is necessary to maintain homeostatic balance. During chronic episodes of mood disorders, the balance is shifted toward the M1 pro-inflammatory state, as defined by increased activity of cytokines (IL-1β, IL-6, TNF-α) and chemokines (CCL2), for example. Simultaneously, the system tries to reset by stimulating the M2 repair process, as indicated in Figure 2 (increased microglial phagocytosis, increased

synaptic pruning, release of anti-inflammatory cytokines). One of the current hypotheses of the etiology of psychiatric disorders is that the imbalance between the M1 and M2 (M1 >M2) states of microglial activation results in mood disorders, and that restoration of the balance (toward M2 by dampening M1 signaling) could be a therapeutic strategy for treating mood disorders [93].

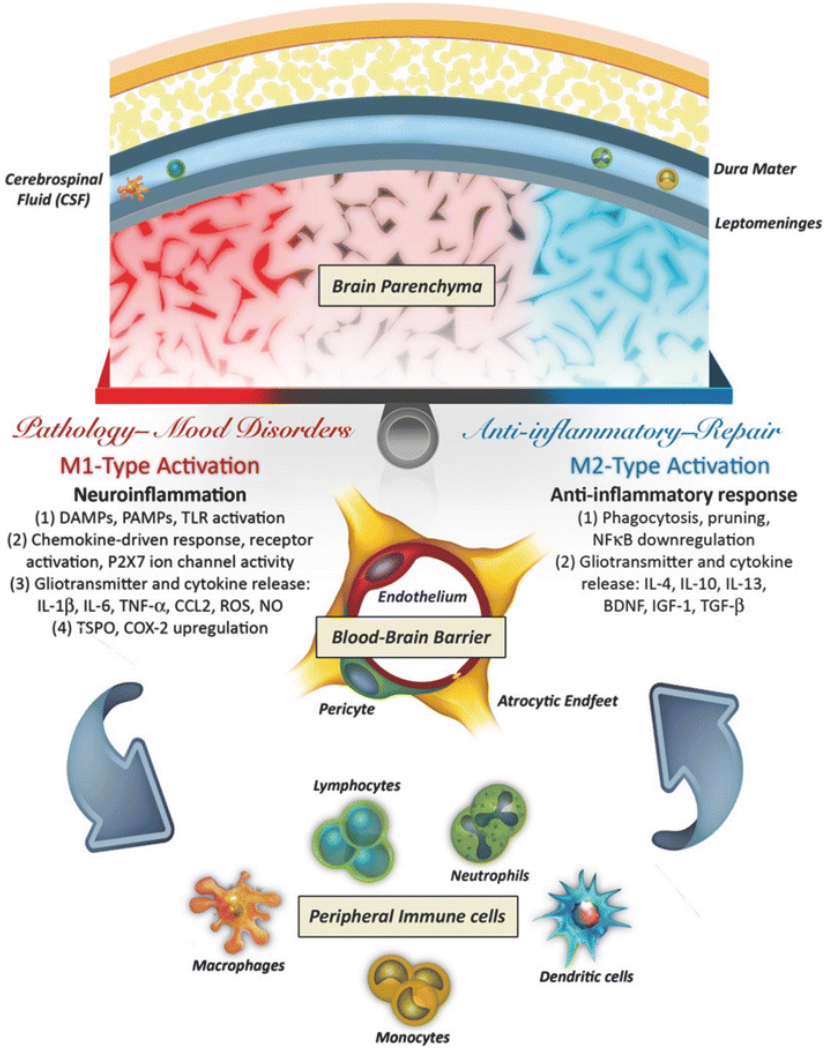

Figure 2. Schematic representation of the interplay between peripheral immune cells, the blood–brain barrier, and microglia–astrocytes within the brain to drive neuro inflammation [93].

Pro-inflammatory cytokines

Cytokines are large molecules that are mainly released from immune cells such as monocytes, macrophages, and lymphocytes in addition to microglia and astrocytes. Cytokines are activated during situations in which inflammation, infection, and/or immunological alterations occur and are mainly involved in the repair of damaged tissues and the restoration of homeostasis. Inflammatory cytokines activate macrophages to increase phagocytosis and killing, and to enhance the expression of inflammatory compound production and adhesion molecules [94].

Cytokines mediate signals between immune cells and are generally divided into pro-inflammatory (facilitating immune responses) and anti-inflammatory cytokines (inhibiting immune responses) [95].

It is assumed that pro-inflammatory cytokines have a crucial role in the pathophysiology of psychiatric illnesses such as depression [96]. Pro-inflammatory cytokines mediate and facilitate neural activities and inflammatory processes, and they are listed below with their effects on neurogenesis (adapted from Kim et al., 2016) [95]:

IL-1β: Decreased proliferation and differentiation, and decreased migration and increased proportion of astrocytes.

IL-6: Decreased proliferation and differentiation.

TNF-α: Decreased number of newly generated neurons, decreased proliferation and differentiation, and increased proportion of astrocytes.

CCL2: Modulator neural cell function and chemotactic and activating actions on monocyte/macrophages, T lymphocytes, and dendritic cells [97].

Microglia

Microglial cells are the mononuclear phagocytes of the brain and they fulfill roles on different levels: immune responses, neurodevelopment, and synaptic functioning [86]. Their role in immune regulation includes the production of pro-inflammatory cytokines and free radicals, as well as anti-inflammatory components. Microglia exist in the brain during early brain growth and contribute to various aspects of brain development, such as synaptogenesis and synaptic pruning, developmental cell death, and axon remodeling [98]. Microglia that are abnormal and inflammatory activated can cause problems with synaptogenesis and neurogenesis by deficiency of neuroprotective factors and cytokines, and neuronal growth factors [98].

Monocytes, cytokines, and microglia in patients with bipolar disorder

Higher numbers of CD14+ monocytes were not found in patients with bipolar disorder. Nor were there differences between the number of mature and immature circulating monocytes in bipolar disorder patients [98]. Studies that focused on the

gene expression of circulating monocytes found that the majority of patients with bipolar disorder showed an activated monocyte gene expression set-point involving cluster 1 and 2 genes [99-101]. The overexpression of monocyte activation genes was particularly evident in active cases (i.e., in patients with mania, active depression, or active psychosis) [99, 102].

In affective psychosis, during a manic episode, the cytokines IL-6, TNF- α, interleukin-1 receptor antagonist, IL-10, CCL2, and soluble tumor necrosis factor receptor 1 were raised, showing a robust stimulation of the inflammatory response system [86, 103]. However, the results are heterogeneous, with studies reporting normal or lower cytokine levels in bipolar disorder patients than in healthy controls. This may be due to the fact that peripheral cytokines are strongly influenced by lifestyle and disease factors [104, 105]. Microglia, that are observed with a positron emission tomography (PET) scan showed significantly increased binding potential, which is indicative of neuro-inflammation in the right hippocampus of bipolar disorder patients when compared to the healthy controls. Although the same trend was observed in the left hippocampus, this difference was not statistically significant [106].

Monocytes, cytokines, and microglia in patients with schizophrenia

In patients with schizophrenia, higher monocyte numbers were found than in patients with bipolar disorder [86, 107]. Another immunological difference between patients with schizophrenia and bipolar disorder is that the majority of patients with bipolar disorder showed an activated monocyte gene expression set-point involving cluster 1 and 2 genes, whereas the majority of the schizophrenia patients showed an activated monocyte set-point of cluster 1 genes only [99-101].

Cytokines in schizophrenia are described in a review that showed higher levels of IL-6, sIL-2R, and interleukin-1 receptor antagonists and a lower level of IL-2, with no significant results for other cytokines [108]. A recent meta-analysis found elevated levels of IL-6, IL-1β, and TGF-β, only in the acute phase (not after remission) of schizophrenia; the cytokines IFN-γ, TNF-α, sIL-2R, and IL-12 increased during the acute psychosis and after remission [109]. Microglial activity was elevated in patients with schizophrenia and in persons with subclinical symptoms who were at ultra-high risk of psychosis, and was related to at-risk symptom severity; this was measured with a PET scan [110-112]. In schizophrenia, some functions of the hippocampus are impaired, such as sensory-emotional integration and immediate memory. In this hippocampal area, microglia activation (and sometimes higher numbers of T-cells) are found only in acutely psychotic patients with prominent cognitive impairment, and not in patients who recovered from psychosis and showed a global brain inflammatory effect [99, 113].

Monocytes, cytokines, and microglia in patients with depression

The number of monocytes was similar in patients and controls before treatment [114]. Monocyte immune activation was only found in patients of 28 years and older [115]. Microglia and monocytes show a pro-inflammatory activation profile with increased expression of genes related to immune activation in patients who have several psychiatric disorders, including major depression [116]. A meta-analysis has shown that the pro-inflammatory cytokines TNF-α, IL-6, and C-reactive protein (CRP) are consistently elevated in the serum of patients with major depression [115]. The results from other studies are more heterogeneous; they found that the levels of pro-inflammatory cytokines, such as IL-1β and IL-6, were increased in patients with depression, although other cytokines, such as IL-1β, IL-2, IL-4, IL-10, and IFN-γ, were not significantly elevated [95, 117]. Another study found that the pro-inflammatory cytokines IL-2, IL-6, TNF-a, and IFN-ɣ increase in patients with depression and the anti-inflammatory cytokines IL-4 and IL-10 decrease [118].
A recent review shows that different PET imaging studies show different results with different ligands. One study revealed that there was no difference between depressed and control groups in any brain region. Another more recent study reported significant depression-associated elevation in volume distribution in the prefrontal cortex, insula, and anterior cingulate cortex (ACC) that correlated positively with the severity of depression [119].

Adaptive immunity

The adaptive immune system is antigen specific, contains a memory, and is activated 7-10 days after the innate immune system. The key players in this system are T-cells and B-cells. B-cells can transform into plasma cells and produce antibodies, which protect against viruses, bacteria, and toxins. In this thesis we focus on T-cells. T-cells are essential for antigen-specific cell-mediated immune responses. There are different subsets of T-cells with diverse functions, which can be distinguished on the basis of membrane bound 'cluster of differentiation' (CD) proteins and by the cytokines that they produce. T-cells can generate auto-immune diseases, which is the failure of the immune system to recognize its own cells, in diabetes type 1 for example [120].
T-cells can be divided into CD4+ and CD8+ T-cells. CD8+ T-cells are called T killer cells and are cytotoxic and important for killing other body cells that are infected with viruses, bacteria, or malignancy [121].
CD4+ cells are called T helper cells and these cells interact with and regulate the function of other immune cells. T helper cells develop after antigen stimulation from naïve T-cells, and they are capable of actively secreting cytokines upon (re)-activation [122]. The production of these small signaling proteins defines the functionality of the

T helper cells. The produced cytokines stimulate and/or inhibit various components of the immune reaction. A naïve T helper cell can differentiate into four T helper cell subtypes which are described in detail below:

Th1 cells: Production of IFN-ɣ and stimulating macrophages.

Th2 cells: Production of interleukin-4 (IL-4) and IL-5, which stimulate B-cells into plasma cells.
Counteracts the effects of IFN-ɣ, and the Th1/ Th2 cell balance and therefore reflects one of the pro/anti-inflammatory balances that are operative in the immune system.

Th17 cells: Production of IL-17, IL-21, and IL-22; these cytokines stimulate macrophages to protect the host against bacteria and fungi by activating macrophages.
In addition, Th17 cells are a factor in the pathogenesis of autoimmune diseases (Bettelli et al., 2008).

Treg cells: Dampen the inflammatory responses by dampening Th1, Th2, Th17 cells and prevent damage of auto-reactive T-cells with monocytes/ macrophages [121].

T-cell related cytokines

IFN-ɣ: Inhibits the Th2 response though negative feedback.

IL-4: Drives naïve T-cells in the direction of Th2 development.

IL-17: Function not entirely known, but likely has similar functions to IFN-ɣ.

IL-2: Acts as the autocrine proliferation factor for the effector T-cells [105].

T-cells and T-cell related cytokines in patients with bipolar disorder

Serum levels and percentages of anti-inflammatory Treg cells were higher in patients with bipolar disorder who were under 40 years old compared to healthy controls. Percentages of Th1, Th2, and Th17 cells were normal [105]. This study did not find higher or reduced levels of typical Th1 or Th2 cytokines in patients with bipolar disorder [105].

T-cells and T-cell related cytokines in patients with schizophrenia

Two studies found decreased numbers of T-cells in patients with paranoid schizophrenia, and this was normalized during treatment [113]. Our study group found lower numbers of circulating lymphocytes in patients with paranoid schizophrenia. However, within this reduced population, an increase in the percentage of TH1, TH17, and Treg cells was found [123]. Many studies found an increase in sIL-2R in the serum of patients with paranoid schizophrenia or with bipolar mania. This could be

a helpful phenomenon, neutralizing the high activity of the monocytes/macrophages in these patients [100]. In patients with schizophrenia, the function of the T-cells is affected; several studies found decreased IL-2 production by T-cells, and one study found decreased sensitivity to several antigens in the delayed hypersensitivity test [86, 124].

T-cells and T-cell related cytokines in patients with depression

The number of cytotoxic T-cells were similar in patients and controls, but patients with depression showed reduced percentages of Treg cells when compared to controls, accompanied by nearly significant reductions in the Th1 and Th17 subsets [114]. In patients with depression, increases in the pro-inflammatory cytokines IL-2, IL-6, TNF-a, and IFN-ɣ, and decreases in the anti-inflammatory cytokines IL-4 and IL-10 were found [118].

Tryptophan pathway

In this thesis we also focus on the serotonin (5-HT) pathway and its immunomodulatory effects. Serotonin is well known in the treatment of psychiatric diseases, mainly in depression. Important anti-depressive drugs such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MOAIs), and tricyclic antidepressants (TCAs) all influence the availability of serotonin by different mechanisms. Major depression, fibromyalgia, Alzheimer's disease, psoriasis, arthritis, allergies, and asthma are all associated with changes in the serotonergic system [125].

Consistent evidence supporting a role of the kynurenine pathway in depression comes from a series of studies in patients who were taking interferon-alpha (IFN-α) as a treatment for chronic viral hepatitis C. IFN-α frequently induces a number of psychopathological side effects, including depression and fatigue, which impair patients' quality of life. This cytokine has been suggested to induce depressive symptoms through direct effects on the brain and the modulation of the tryptophan-kynurenine pathway described above. Specifically, IFN-α up-regulates the expression of indoleamine 2,3 dioxygenase (IDO) [126]; the decrease of plasma tryptophan and the increase of kynurenine and neopterin during IFN-α treatment correlates with the development of depression [127, 128].

Indoleamine 2,3 dioxygenase (IDO)

Figure 3 shows the tryptophan pathway in which serotonin is involved, which makes it interesting for studying the etiology of mood disorders. Several enzymes control the tryptophan pathway, such as IDO and MAO. IDO catabolizes the first and rate-limiting

step in the degradation of tryptophan to a number of downstream metabolites, which together are identified as kynurenines. The pro-inflammatory status of patients with psychiatric disorders is described previously in this introduction. In the case of a pro-inflammatory state, there is also IDO activation because IDO is particularly induced in macrophages and monocytes, as well as in other tissues (e.g. placenta, brain) under the influence of pro-inflammatory cytokines [129] (e.g. during infections, mental or physical stress, and pregnancy). Under such circumstances IDO and tryptophan breakdown increases because of the function of IDO as a host defense; it limits the access to tryptophan, which is essential for bacteria to proliferate.

In the tryptophan pathway, IDO stimulates the formation of one of the first metabolites, kynurenine, which is broken down into two tryptophan pathways again: (1) a neuroprotective pathway with kynurenic acid and (2) a neurotoxic pathway with 3-hydroxy kynurenine (3-OH-KYN) and quinolinic acid [130]. Based on the evidence above, a hypothesis was proposed that an imbalance between the neurodegenerative and neuroprotective pathways leads to neurodegeneration and brings a person to a chronically depressed state. This imbalance might be due to a highly increased neurodegenerative pathway activity or a lack of sufficient neuroprotective factor activity [131]. There are several hypotheses about the relationship between the

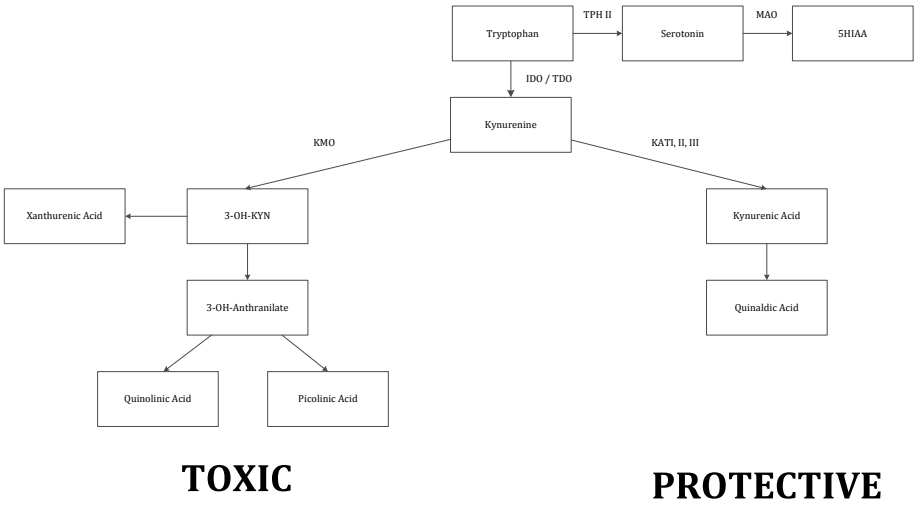

Figure 3. The tryptophan pathway.

IDO = indoleamine-2,3-dioxygenase, TDO = tryptophan 2,3-dioxygenase (TDO), KMO = kynurenine-3-monooxygenase, KAT = kynurenine aminotransferase, TPH = tryptophan hydroxylase, MAO = monoamine oxidase.

tryptophan pathway and T-cells. One hypothesis is that cells expressing IDO (in particular monocytes) regulate T-cell-mediated immune responses in inflammatory diseases [132]. A second hypothesis is that downstream metabolites that are produced by IDO+ monocytes/macrophages, such as the kynurenines, inhibit T-cell proliferation, promote T-cell death, and exert differential effects on helper T-cell responses by altering the Th1/Th2 balance [133].

Tryptophan pathway

Tryptophan pathway in patients with bipolar disorder

Reininghaus and colleagues showed increased blood kynurenine and an increased kynurenine/tryptophan ratio in euthymic bipolar disorder patients [134]. In patients with bipolar disorder, the serum kynurenic acid level and the neuroprotective serum ratio of kynurenic acid over kynurenine were normal, though the plasma tryptophan levels were significantly lower than healthy controls [135]. Regarding bipolar mania, increased expression of TDO2 was reported in the anterior cingulate gyrus of post-mortem brain tissues from bipolar patients [136, 137].

Tryptophan pathway in patients with depression

Based on the tryptophan breakdown hypothesis, a study was conducted on the tryptophan
breakdown pathway metabolites in 58 depressed patients and 189 normal controls who were recruited from Korea University Medical Centre [138]. Tryptophan levels and neuroprotective kynurenic acid significantly decreased in depressed patients. It was also observed in that study, that depressed patients with a first episode of depression showed significantly increased kynurenic acid levels after a six-week antidepressant treatment, and those with repeated episodes of depression did not. The ratio between kynurenine and kynurenine acid, which indicates how much of the kynurenine would be degraded into kynurenine acid, was significantly lower in depressed patients than in healthy controls [137]. In major depression, there is evidence of neurodegenerative changes and loss of astrocytes [139]. These changes may be partly due to the increased toxic kynurenine metabolites that result from the pro-inflammatory state induced imbalance between kynurenine metabolites with potentially toxic and protective effects [137, 140].

Tryptophan pathway in patients with schizophrenia

Elevated kynurenine acid is one of the most consistently observed deviations in patients with schizophrenia and with bipolar disorder with psychotic features [140]. It was hypothesized that accumulation of kynurenine acid may lead to schizophrenic

symptoms. A study of post-mortem brain tissue in different cortical regions revealed increased kynurenine acid levels in schizophrenic samples compared with a control sample, particularly in the prefrontal cortex [137, 141]. A recent study offers support for an over-activated and imbalanced kynurenine pathway, favoring the production of kynurenine acid over quinolinic acid in patients with schizophrenia [142].

The immune system during pregnancy and in the postpartum period

During pregnancy, it is not known how a mother tolerates a semi-allogeneic graft without rejecting it and without the immunosuppression that is necessary to accept an organ transplant [143]. Successful pregnancy is dependent on maternal tolerance of immune non-reactivity to paternal antigens. Maternal tolerance appears to be associated with the development of several specific mechanisms that protect the fetus from maternal cytotoxic immune attack [144]. There are features at the trophoblast maternal interface, at the site of initial implantation, and in the placenta that subvert the normal graft rejection immune response. These include expression of only non-polymorphic, non-classical HLA antigens on the trophoblast; local immune suppression mediated by infiltrating NK cells; monocytes and T regulatory cells; and inhibition of T-cell activation by tryptophan catabolism [143]. Around the time of implantation, a local inflammatory response sets up the stable placental site.

During pregnancy a decrease in T-cells; B-cells; and serum levels of IgM, IgG, and IgA is found [145]. Thus, pregnant women can show remission of autoimmune diseases, and are more susceptible to severe complications of influenza and other infections. This immune modulation, which is necessary for the well-being of the fetus, can occasionally be harmful to the mother [143]. There is evidence that the mother changes the balance of her T-cell responses to Th2 rather than Th1 [146]. This is also visible in the expression of the previously mentioned change in autoimmune diseases during pregnancy and the postpartum period. 'Th2-cytokine driven' auto-immune diseases such as systemic lupus erythematosus (SLE), autoimmune thrombocytopenic purpura (ATP), and auto-immune hemolytic anemia (AHA) tend to be exacerbated during pregnancy. By contrast, rheumatoid arthritis, autoimmune thyroid disease (AITD), and multiple sclerosis (MS) tend to remit during pregnancy and flare or develop initially during the postpartum period. These illnesses are usually considered 'Th1 - cytokine' dependent [86, 147, 148].

Pregnancy is related to lower Treg numbers, and therapies that generate better pregnancy outcomes result in a higher number of Treg cells. Studies found that Treg can control immune cell responses at the interface between mother and fetus; Treg constructs a tolerant microenvironment. This is done by expression of immune regulatory molecules directly at the fetal-maternal interface and by interacting

with other immune cells, such as DCs and NK cells [149]. The duration of the immunosuppression of pregnancy into the postpartum period has not been fully delineated. Although not all investigators have documented differences between T and B lymphocytes and natural killer (NK) cells from the third trimester of pregnancy through the first five postpartum months, most researchers have found that T-cell subset numbers decrease during pregnancy and return to normal in the postpartum period. However, there is disagreement about the time frame within which a return to non-pregnant immune baseline status occurs.

Some studies show that the immunological effects of pregnancy persist until approximately one year after delivery [145, 150]. In the postpartum period, percentages of Treg cells increased from the prenatal to the postpartum period, and these percentages of Treg cells may vary by time in relation to delivery, and by maternal atopic status, exposure to pets, and number of prior births [151]. It is hypothesized that paternal antigens play a role in the pregnancy-associated increase of Treg, although a hormonal explanation should not be rejected. The importance of Treg for a normal pregnancy situation was shown in pregnancies in mice; deficiency of Treg cells harmed the pregnancy while the transmission of Treg cells prevented fetal rejection [151].

Certain cytokines seem to increase during pregnancy, a study found that during the third trimester of pregnancy, monocytic IL-12 production was about three-fold and TNF-alpha production was approximately 40% lower than postpartum values [147]. During pregnancy, tryptophan metabolism is altered, with a decrease in total tryptophan and a shift in the proportion of free and bound tryptophan [152]. After pregnancy, free and bound tryptophan levels gradually return to pre-pregnancy levels [153-155].

OPPER STUDY

AIM AND OUTLINE OF THIS THESIS

1. What are the treatment responses and remission outcomes at nine months postpartum using a four-step treatment algorithm in women with first-onset postpartum psychosis?
2. How is the functional recovery process nine months postpartum after admission for a postpartum psychosis?
3. What are the longitudinal outcomes of women after first-onset postpartum psychosis after four years follow-up? Is it possible to identify risk factors for relapse or to find influence of medication use?
4. What are the changes in the immune system in patients with postpartum psychosis compared to healthy women in the postpartum period and healthy women outside of the postpartum period regarding: The inflammatory state of the immune system (monocytes and cytokines) and the numbers of T-cells?

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Chapter 2

Evaluation of a treatment algorithm in 64 patients with first onset postpartum psychosis

K. M. Burgerhout*
V. Bergink*
K.M. Koorengevel
A.M. Kamperman
W.J. Hoogendijk
M.P. Lambregtse-van den Berg
S.A. Kushner

**Authors contributed equally to this manuscript and share first authorship*

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ABSTRACT

Objective: Postpartum psychosis is a severe disorder that warrants acute clinical intervention. Unfortunately, little is known about what interventions are most effective. We present treatment response and remission outcomes at nine months postpartum using a 4-step treatment algorithm in patients with first-onset psychosis and/or mania in the postpartum period.

Methods: Sixty-four women consecutively admitted for postpartum psychosis were followed prospectively. Treatment was administered using a structured, sequential treatment algorithm involving 1) benzodiazepines, 2) antipsychotics, 3) lithium, and 4) ECT. Clinical remission was defined as the absence of psychotic, manic, and severe depressive symptoms for at least 1 week, including CGI ≤3, YMRS ≤8 and EPDS ≤10. Women who remitted on antipsychotic monotherapy were advised to continue this treatment as maintenance therapy, while women who required both antipsychotics and lithium to achieve remission were maintained on lithium monotherapy. We defined relapse as the occurrence of any psychiatric episode fulfilling DSM-IV-R criteria.

Results: Nearly all patients (98.4%) achieved complete remission within the first three steps of the treatment algorithm. None of the patients required ECT treatment. At nine months postpartum, sustained remission was observed in 51 of 64 women (79.7%). Patients treated with lithium had a significantly lower rate of relapse compared to those receiving antipsychotic monotherapy (P=0.002). Multiparity (P=0.03) and non-affective psychosis (P=0.05) were identified as risk factors for relapse.

Conclusion: A standardized treatment algorithm with the sequential addition of benzodiazepines, antipsychotics, and lithium resulted in high rates of remission in patients with first-onset postpartum psychosis. During the nine months postpartum follow-up period, lithium maintenance was superior to antipsychotics for relapse prevention.

CLINICAL VIGNETTE

A patient with first-onset postpartum psychosis

Mrs. B, a 28-year-old primiparous primigravid woman with no prior psychiatric history, delivered a healthy daughter after an unremarkable pregnancy. She breastfed her daughter every 2-3 hours without difficulty. On the third day postpartum, Mrs. B expressed concern that her husband wanted to kill their newborn. In response to her mother's suggestion that she discontinue breastfeeding to enable better sleep, Mrs. B became extremely violent and kicked her mother in the abdomen. Over the next 4 days (postpartum days 4-7), Mrs. B became progressively more impulsive, irritable, and disorganized.

On day 7 postpartum, Mrs. B was admitted with her daughter to the Mother-Baby Unit of the Erasmus MC. During the admission interview, she exposed her breasts while shouting: "Look at these! My breasts are great! I want to breastfeed 24 hours non-stop!" She was diagnosed as manic with psychotic features (Young Mania Rating Scale: 34). Physical examination and routine laboratory investigations, including thyroid screening were normal. During periods of clinical stability, Mrs. B was encouraged to perform daytime bottle feedings under the supervision of a nurse. Nighttime feedings were performed exclusively by nursing staff.

On admission, Mrs. B was treated with lorazepam monotherapy for three days without significant clinical improvement, after which haloperidol was initiated. Two weeks following the initiation of haloperidol, Mrs. B remained actively manic with psychotic features, requiring the addition of lithium. With a combination of lorazepam, haloperidol, and lithium, her manic and psychotic symptoms remitted over the next 3 weeks. Mrs. B and her daughter were discharged home from the hospital seven weeks after delivery, with close outpatient follow-up, lithium monotherapy, and mother-child interaction therapy. Lithium was discontinued after 9 months. Over the past 4 years of outpatient follow-up since discharge, Mrs. B has remained in full remission.

INTRODUCTION

Postpartum psychosis is a psychiatric emergency that requires immediate medical attention and mental health care referral. The prevalence in the general population is estimated to be 1-2 cases per 1000 childbirths [1, 2]. In the majority of cases, the onset is rapid and within 2 weeks postpartum. Early symptoms often include insomnia, mood fluctuation, and obsessive concerns regarding the newborn, followed by more severe symptoms such as delusions, hallucinations, and disorganized behavior.

Severe mood symptoms, such as mania, depression, or a mixed state are a hallmark of the disease. Clinical presentation, family history, and the longitudinal illness course are highly overlapping with bipolar disorder. Therefore, postpartum psychosis is generally considered a bipolar spectrum illness and not a primary psychotic disorder.

The initial clinical evaluation for postpartum psychosis requires a thorough medical and psychiatric history, physical and neurological examination, and comprehensive laboratory analysis to exclude known organic causes for acute psychosis. Differential diagnosis should include infectious diseases (e.g. mastitis, endometritis), eclampsia, postpartum thyroiditis [3], and less frequently paraneoplastic encephalitis [4, 5], primary hypoparathyroidism [6], vitamin deficiency, stroke, and drug-induced psychosis [7]. Case reports have documented misdiagnosis of postpartum psychosis revealing a late-onset urea cycle disorder [8] and citrullinemia type I [9]. Clinicians need to ensure the adequate safety of the patient and her children, considering the highly elevated risk of suicide and infanticide.

Because of the severity of the symptoms and the unpredictable nature of the disease, pharmacological treatment is typically initiated immediately, for which postpartum psychosis is widely considered among the group of bipolar affective disorders [7, 10, 11]. Unfortunately however, few standardized treatment recommendations are currently available for postpartum psychosis, as research has been limited and no randomized trials have been performed. The effects of lithium [12, 13], antipsychotics [14], ECT [12, 13], estrogen [15-17], progesterone [18] and propranolol [19] have been examined. In total, 21 treatment studies of postpartum psychosis can be found in the recent literature, of which sample sizes are very small: the majority involve case reports and few studies have included more than 10 patients [20, 21].

Therefore, in the absence of formal guidelines, treatment in clinical practice is typically based on the most prominent symptom dimensions. Benzodiazepines are used for insomnia and agitation, antipsychotics and mood stabilizers for psychotic and manic symptoms, and antidepressants for depressive symptoms. Electroconvulsive therapy (ECT) has been described as an effective treatment option in patients with severe catatonic features. Recently, ECT has even been proposed as a first-line treatment option [22-24].

Here we present the clinical outcomes of 64 women consecutively admitted for psychosis and/or mania limited to the postpartum period. We used a four-step standardized treatment algorithm developed with guidance from the extensive

literature on bipolar patients.
All patients were initially treated with benzodiazepines at bedtime for 3 days (Step 1). The purpose of starting with an initial period of benzodiazepine monotherapy was to evaluate if restoration of sleep resulted in clinical remission of manic and psychotic symptoms, as sleep loss has been considered an important etiologic factor for postpartum psychosis [25].

For those patients receiving benzodiazepine monotherapy with persistent manic and/or psychotic symptoms, antipsychotic medication was recommended beginning on day 4 (Step 2). Although the efficacy of antipsychotics in the absence of mood stabilizers has only been described in three case reports, antipsychotics are frequently used worldwide as first-line treatment for patients with postpartum psychosis and mania [14]. Furthermore, antipsychotics are often considered the preferred pharmacological treatment option for acute mania outside the postpartum period [26].

After 2 weeks of combination benzodiazepine/antipsychotic treatment, adjunctive lithium was recommended for those patients without a significant clinical response (Step 3). One small open-label study previously reported that the combination of lithium and antipsychotics is more effective than antipsychotic monotherapy in patients with postpartum psychosis [12, 13]. Furthermore, previous studies have demonstrated efficacy of lithium in the prevention of postpartum psychosis [27-30].

Finally, in those patients without a response after 12 weeks on the combination of benzodiazepine, antipsychotic and lithium pharmacotherapy, ECT was recommended (Step 4). Case reports and case series have described positive treatment outcomes with ECT in women with treatment refractory postpartum psychosis [24, 31].

Treatment response, acute remission, and sustained remission were monitored during the first 9 months postpartum in 64 women with postpartum psychosis.

METHODS

Participants

The study was approved by the Institutional Review Board of the Erasmus Medical Centre (Rotterdam, The Netherlands). All patients provided written informed consent. The study was performed at the Mother-Baby Unit (MBU) of the Department of Psychiatry in the Erasmus Medical Centre. This 5-bed inpatient unit is specialized for

the care of patients with severe psychopathology in the postpartum period. Women are given the option for admission together with their baby in a fully staffed nursery adjoining the unit [32]. Every patient admitted to the MBU between August 2005 and June 2011 was screened for study inclusion (n=200) and diagnosed using Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID – 1/P) [33].

Patients aged 18-45 years with a diagnosis of postpartum psychosis were eligible to participate. As postpartum psychosis is not described as a distinct disease entity in DSM-IV-R, we defined eligible subjects as those patients for whom the SCID interview generated any of the following diagnoses, and requiring the specifier "onset postpartum": depressive disorder with psychotic features, psychotic disorder not otherwise specified, brief psychotic disorder, or mania. Importantly, the specifier "onset postpartum" requires that the onset of symptoms must occur within 4 weeks postpartum.
Eighty-three (n=83) patients fulfilled the criteria for postpartum psychosis or mania. Fifteen (n=15) patients had a history of psychosis or mania outside the postpartum period, and therefore were excluded from our analyses. Further, one patient was excluded because of substance abuse, and two patients declined participation. One patient was lost to follow-up after remission; we describe her disease course separately. In total, sixty-four patients with psychosis or mania limited to the postpartum period were evaluated weekly during admission and at nine months postpartum.

Non-pharmacological treatment

All women received non-pharmacological interventions to optimize mother-baby interaction [34]. These interventions included feedback from nursing staff, video-interaction guidance, baby massage and a support group for mothers.

Pharmacological treatment

Step 1: All women were initially treated with lorazepam at bedtime for 3 days.

Step 2: For those women receiving lorazepam monotherapy with persistent manic and/or psychotic symptoms, antipsychotic medication was recommended beginning on day 4. Our primary recommendation for antipsychotic treatment was haloperidol 2-6 mg per day. In case of side effects, we switched to an atypical antipsychotic. Of note, for the limited subset of patients (n=11) that had already been treated with an antipsychotic for more than 2 days prior to admission (e.g. by acute services), we skipped Step 1 and continued treatment with the same antipsychotic.

Step 3: After 2 weeks of combination benzodiazepine/antipsychotic treatment, adjunctive lithium was recommended for those women without a significant clinical response. Lithium dosing was achieved based on plasma level (target: 0.8-1.2 mmol/L).

Step 4: In those women without a response after 12 weeks on the combination of benzodiazepine, antipsychotic and lithium pharmacotherapy, ECT was recommended. All psychotropic medications were tapered to discontinuation, prior to the initiation of ECT.

Maintenance treatment

After complete remission of symptoms, all women were advised to taper benzodiazepines to discontinuation. Women receiving antipsychotic monotherapy were advised to continue this treatment as maintenance therapy until nine months postpartum. Conversely, women requiring both antipsychotics and lithium to achieve clinical remission were advised to discontinue antipsychotic treatment, with maintenance lithium monotherapy until nine months postpartum. Lithium dosing for relapse prevention was achieved based on plasma level (target: 0.6-0.8 mmol/L).

Symptomatology and clinical course

In addition to the SCID-R, all participants and their relatives were interviewed by a psychiatrist (V.B. or K.K.). Duration of episode was defined as the number of days from the initial onset of psychiatric symptoms until remission. Phenomenology was quantified using the Bipolar Affective Disorder Dimension Scale (BADDS) [35]. The BADDS is a dimensional rating scale intended for use in clinical cohorts with a high incidence of bipolar spectrum illness. There are four identified dimensions: mania, depression, psychosis and mood incongruence. During hospitalization, clinical evaluation was performed weekly using the Young Mania Rating Scale (YMRS) [36], the Edinburgh Postnatal Depression Scale (EPDS) [37], and the Clinical Global Impression - Bipolar Disorder (CGI-BP). The CGI-BP is a modified version of the CGI-scale that allows the clinician to rate the global illness severity and time course in patients with bipolar spectrum disorders [38].

Clinical remission was defined as the absence of psychotic, manic, and depressive symptoms for at least 1 week, including CGI ≤3, YMRS ≤8, and EPDS ≤10 [39]. We defined relapse as the occurrence of any psychiatric episode fulfilling DSM-IV-R criteria and/or CGI-BP score >3. Accordingly, sustained remission was defined as having never experienced a DSM-IV-R mood or psychotic episode throughout the

entire follow-up period, as well as maintaining a CGI-BP score ≤3. Longitudinal assessment of mood episodes was performed using the NIMH Life-Chart Method (NIMH-LCM-R) at nine months postpartum [40].

Statistical Analysis

Categorical demographic variables were compared with the Fisher Exact Test (FET) and continuous demographic variables were compared with the Mann-Whitney U test. Categorical outcomes of relapse risks were examined using the Fisher Exact Test, logistic regression analysis, and Kaplan-Meier estimation of the log-rank test. Analyses were performed using SPSS 20.0. A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Table 1 shows the demographic, psychiatric, and phenomenological characteristics for the 64 enrolled patients. The phenomenological classification included manic-psychotic features (65.6%), mixed episode (17.2%), and depression with psychotic features (9.4%). Only five patients had a postpartum psychosis without prominent affective symptomatology (7.8%). The median onset of initial psychiatric symptoms occurred at eight days postpartum (IQR 5-14). The median duration until clinical remission was 40 days (IQR 26-65) (Table 1).

Complete remission

Four of the 64 women remitted at Step 1 of the treatment algorithm (n=4, 6.3%) (Figure 1). Two of these patients experienced remission of manic and psychotic symptoms after only three days of benzodiazepine treatment (median time to complete remission, 21 days). Furthermore, two patients declined to advance further in the treatment algorithm, despite having persistent symptoms at the end of the three-day Step 1 period. As expected, they had a substantially longer duration of illness, although they both ultimately achieved full remission (median time to remission, 161 days).

Twelve patients remitted during treatment with a combination of benzodiazepines and antipsychotics (Step 2; n=12, 18.8%) (Figure1). Of these 12 patients, seven received haloperidol, four were prescribed olanzapine, and one patient used quetiapine. Ten (n=10/12) patients experienced full resolution of manic and psychotic symptoms

within two weeks of treatment, despite a more persistent affective instability (median time to remission, 30 days; IQR 21-41). The remaining two patients were limited to Step 2, despite persistent symptoms: one declined adjunctive lithium, while in the other patient lithium was contraindicated secondary to psoriasis (median time to remission, 39 days).

Table 1. Demographic and Clinical Characteristics of Women with Sustained Remission or Relapse after Postpartum Psychosis.

	All women (n=64)		Sustained remission (n=51)		Without sustained remission (n=13)		P-value [a]
General demographics	N	%	N	%	N	%	
Dutch ethnicity	56	87.5	45	88.2	11	84.6	0.66
Education beyond high school	36	87.5	28	54.9	8	61.5	0.76
Married or living with partner	62	96.9	50	98.0	12	92.3	0.37
Multiparity	14	21.9	8	15.7	6	46.2	0.03
Mean age	31.9	SD 4.7	31.6	SD 4.7	32.8	SD 4.4	0.40
Psychiatric history	N	%	N	%	N	%	
No psychiatric history	46	71.9	37	72.6	9	69.2	1.00
Previous PP in history	10	15.6	6	11.9	4	30.8	0.19
Depression/anxiety in history	8	12.5	8	15.5	0	0.0	0.20
Phenomenology - Affective psychosis	N	%	N	%	N	%	
With manic-psychotic features	42	65.6	35	68.7	7	53.8	0.34
Depressed/mixed	17	16.6	14	27.4	3	23.1	1.00
Non-affective psychosis	5	7.8	2	3.9	3	23.1	0.05
Psychotic symptoms	N	%	N	%	N	%	
Mood incongruence	40	62.5	32	62.7	8	61.5	1.00
First-rank symptoms[b]	6	93.8	4	7.8	2	15.4	0.59
Days	Median	IQR	Median	IQR	Median	IQR	
Onset PP	8	5-14	7	5-14	10	5-16	0.54
Duration of episode	40	26-65	42	23-69	38	29-48	0.90
Treatment	N	%	N	%	N	%	
Step 1	4	6.3	4	7.8	0	0.0	0.57
Step 2	12	18.8	6	11.8	6	46.2	0.01
Step 3	48	75.0	41	80.4	7	53.8	0.07

[a] Women with sustained remission (N=51) were compared to women without sustained remission (N=13). Categorical variables were tested using the Fisher Exact Test. Continuous variables were tested using the Mann-Whitney U test.

[b] Thought echo, insertion, withdrawal or broadcasting, passivity experiences, hallucinatory voices giving running commentary, discussing subject in third person or originating in some part of the body, bizarre delusions, or catatonia.

Forty-eight women were treated with a combination of benzodiazepines, antipsychotics, and lithium. Forty-seven (n=47) women remitted under Step 3 of the treatment algorithm (n=47, 73.4%) (Figure 1). The antipsychotic usage included: 37 patients with haloperidol, 9 with olanzapine, and 1 with quetiapine. The remaining patient advanced from Step 1 directly to Step 3 after declining antipsychotics, and was therefore treated with only benzodiazepines and lithium. The median time until remission for patients treated under Step 3 was 44 days (IQR 26-69 days).

In total, sixty-three of the 64 patients achieved a full clinical remission within the first three steps of the clinical algorithm (98.4%) (Figure 1). The one remaining patient was discharged against medical advice during Step 3, and never achieved remission during the nine-month follow-up period. None of the 64 enrolled patients were treated with ECT (Step 4). However, the one patient lost to follow-up did not respond to the sequential addition of benzodiazepines, antipsychotics and lithium and only remitted after ECT treatment. This patient suffered from depression with psychotic features, and was without manic symptoms. Her psychiatric symptoms began at postpartum day 4 with a total duration until clinical remission of 186 days, after which she was discharged home and subsequently lost to follow-up.

We compared demographic and clinical characteristics of patients who achieved clinical remission at Step 1, 2, or 3. Women receiving a combination of benzodiazepines and antipsychotics (Step 2) were significantly older than women receiving adjunctive lithium treatment in Step 3 (Fisher Exact Test, $P<0.01$). No other differences were identified in demographics, psychiatric history, phenomenological characteristics, or postpartum latency to onset of symptoms.

Sustained remission and relapse rates after nine months

Sustained remission at nine months postpartum was observed in 51 of the 64 patients (79.7%) (Figure 1). Of the remaining 13 patients, twelve patients relapsed (18.8%) and one never remitted (1.6%). Among the 12 patients experiencing relapse, 10 had a depressive episode (83.3%), one had manic symptoms without psychosis (8.3%), and one had a non-affective psychotic episode (8.3%). Relapse occurred following a median of 54 days after full remission (IQR 23-101). The median duration of relapse was 61 days (IQR 30-73).

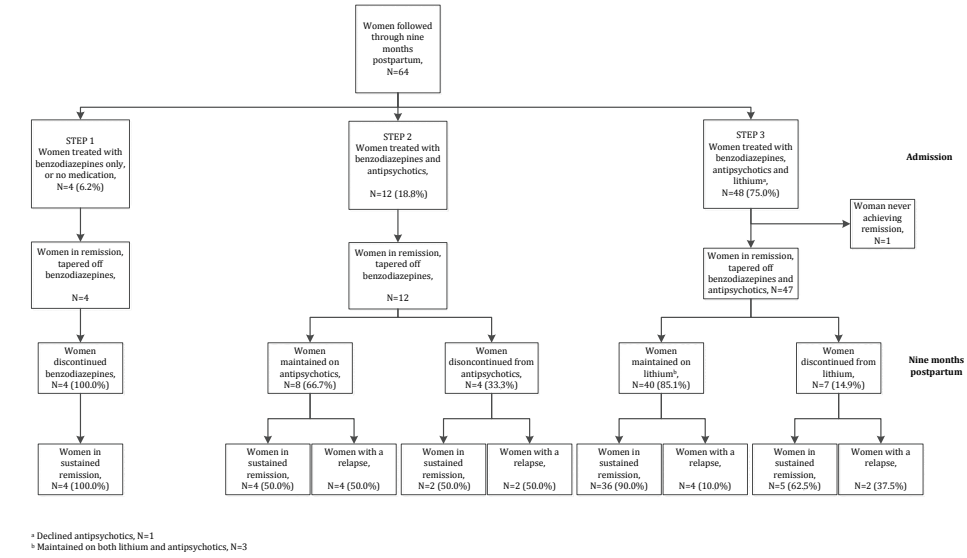

Figure 1. Flowchart of treatment outcomes in 64 women with postpartum psychosis.
[a] One patient declined antipsychotic medication.
[b] Three patients were maintained on both lithium and an antipsychotic.

There were no differences in age, ethnicity, education, psychiatric history, onset or duration of episode between patients with sustained remission (n=51), compared to patients without sustained remission (n=13) (Table 1). However, sustained remission was associated with parity, for which primiparous patients were more likely to achieve sustained remission (n=43/50, 86%) compared to multiparous patients (n=8/14, 57%) [P=0.03; FET, OR=4.6, 95% CI=1.2-17.4]. Among the six multiparous patients with relapse episodes, two had a single prior episode of postpartum psychosis, while four patients each had two prior episodes of postpartum psychosis.

With regard to phenomenology, patients with affective psychosis were more likely to achieve sustained remission (n=49/59, 83.1%) compared to those with non-affective psychosis (n=2/5, 40.0%) [P=0.05; FET, OR= 7.4, 95% CI=1.1-49.8]. Among patients with affective postpartum psychosis, sustained remission was not associated with manic, mixed, or depressed symptomatology, nor with the mood-congruence of psychotic symptoms.

Influence of medication on relapse rates

Treatment received upon admission was highly predictive of sustained remission (P=0.002; log-rank test) (Figure 2). None of the patients treated with benzodiazepines monotherapy relapsed (n=4). Patients treated with the combination of benzodiazepines and antipsychotics (Step 2) were significantly more likely to relapse (n=6/12, 50.0%) compared to those receiving adjunctive lithium in Step 3 (n=6/47, 12.8%) [P=0.01; FET, OR= 6.8, 95% CI=1.6-28.3].

Importantly, we also evaluated whether non-compliance or medication discontinuation might have influenced the significantly higher rate of sustained remission in patients treated with adjunctive lithium. Among the 12 patients who remitted with benzodiazepines and antipsychotics under Step 2, eight were continuously maintained on antipsychotics throughout the entire follow-up period, of which four relapsed (n=4/8, 50.0%). Similarly, of the four patients who discontinued antipsychotic treatment, two patients relapsed (n=2/4, 50.0%). Therefore, relapse was not associated with antipsychotic discontinuation during the follow-up period.

Among patients receiving adjunctive lithium (Step 3), the majority was continuously maintained on lithium throughout the entire follow-up period (n=40/48, 83.3%). Of these 40 patients, four relapsed (10.0%), for which their mean lithium level during follow-up (0.57±0.41 mmol/L) was similar to patients with sustained remission (0.58±0.27 mmol/L). Eight patients discontinued lithium treatment during the follow-up period, of whom one patient never achieved remission and two relapsed (37.5%, P=0.08, FET, OR=5.4, 95% CI=0.7-44.6).

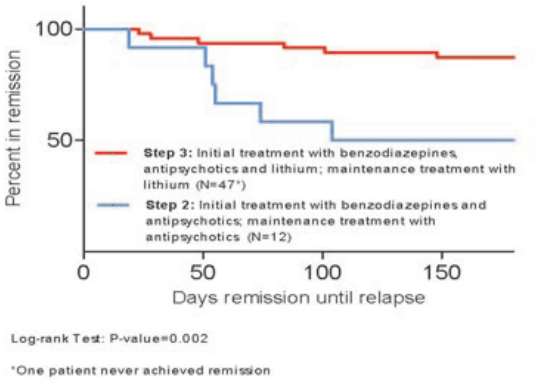

Figure 2. Kaplan-Meier curve of relapse after full remission of symptoms in women with postpartum psychosis using either antipsychotics of lithium maintenance monotherapy.

CONCLUSION

Given that postpartum psychosis is a severe, potentially life-threatening disorder during the acute phase, the prognosis is remarkably optimistic. In particular, using a four-step clinical treatment algorithm, we observed high remission rates in the acute phase (98.4%), and with a considerable proportion of patients who achieved sustained remission (79.7%). Overall, the majority of patients required combination treatment with a benzodiazepine, antipsychotic, and lithium to achieve clinical remission. Moreover, rates of sustained remission were superior in patients using maintenance monotherapy with lithium, compared to antipsychotics.

All but one patient achieved full clinical remission, defined as the absence of psychotic and affective symptoms for at least 1 week. The median duration of illness was 40 days, defined from the onset of postpartum psychosis until remission. Accordingly, this might suggest that the four-step treatment algorithm was highly effective. On the other hand, these findings might also be attributed to a spontaneously remitting disease course of relatively short duration. Notably, we and others have described a higher biological vulnerability during the postpartum period, including substantial alterations of immunological and endocrine setpoints [41, 42]. Consequently, when this window of vulnerability has passed, a natural recovery of symptoms might occur in the absence of structured treatment. Importantly however, previous studies of medication-free patients do not support this alternative hypothesis, given that in the absence of pharmacological treatment patients experience a substantially longer duration until clinical remission (8 months) [43]. In the present study, the two patients who declined antipsychotic and lithium treatment experienced a much longer duration of illness (>5 months), compared to the median duration of illness in the full cohort (40 days; Table 1).

Overall, the naturalistic design of our study warrants a cautious interpretation of the effectiveness of each treatment step. Allowing a 3-day period of benzodiazepine treatment (Step 1) prior to the initiation of antipsychotics (Step 2) enabled us to carefully evaluate the influence of sleep hygiene on the severity of symptomatology, given that restoration of sleep might lead to recovery in a small subgroup of patients. Indeed, two patients responded promptly to benzodiazepine monotherapy. Notably, if antipsychotic treatment would have been more rapidly initiated, the recovery of these two patients may well have been falsely attributed to the use of antipsychotics for which maintenance antipsychotic treatment would likely have been recommended.

Nine patients (n=9/64, 14.1%) experienced remission of manic and psychotic symptoms within the two-week duration of the combination of antipsychotics and benzodiazepines. Importantly however, we acknowledge the likelihood that more patients might have had a favourable response to antipsychotics during the acute phase if we had extended the duration of antipsychotic monotherapy.

The overwhelming majority of patients responded to adjunctive lithium treatment and achieved clinical remission. Importantly however, since nearly all patients were using antipsychotics in addition to lithium, no conclusions can be drawn regarding the therapeutic potential of lithium monotherapy for the treatment of acute postpartum psychosis. In contrast, lithium monotherapy was highly protective for sustained remission, compared to antipsychotic monotherapy. Although lithium has not been described previously as a first-line option for maintenance treatment after postpartum psychosis, there is extensive evidence of the benefits of lithium for the maintenance treatment of bipolar patients [44].

ECT has been previously reported to accomplish a swift reduction of symptoms for postpartum psychosis [22-24]. In our study, severe symptoms such as agitation, mania and psychosis responded well to pharmacotherapy, for which a prolonged disease course was mostly due to affective instability. Remarkably, only one patient with depression with psychotic features was refractory to pharmacotherapy, and therefore required ECT treatment.

Notably in our study, the majority of patients had already stopped breastfeeding prior to their inpatient admission. Furthermore, in the non-pharmacologic treatment protocol of our inpatient program, the integrity of sleep hygiene and a structured rhythm of feedings are supported by specialized nurses, thereby offering a variety of options to women admitted together with their newborns. Unfortunately, many regions in the world do not have MBU care within a reasonable travel distance for the patient. Therefore, the specialized care within an MBU in our case series might hamper generalization of our findings. When mother and baby are separated during admission, the understandable wish to reunite them might lead to discharge prior to a full clinical remission. In contrast, in our hospital, most women were released only after complete remission of all symptoms, which might have influenced relapse risk.

An overwhelming majority of our patients with postpartum psychosis were primiparous, consistent with previous studies describing primiparity as a significant covariate of postpartum psychosis [32, 45-47]. Unexpectedly, we identified multiparity

as a significant risk factor for relapse, as six of 14 multiparous women relapsed. Of note, this multiparous group included patients with a prior history of postpartum psychosis (n=10/14, of which 4 relapsed). Accordingly, the threshold for manifesting clinical mood symptoms might be reduced in these patients as a consequence of the occurrence of multiple episodes of postpartum psychosis, a phenomenon known as the "kindling hypothesis of mood disorders" [48]. However, the relapse rate of 50% in multiparous patients without previous postpartum episode is not explained by this hypothesis, but numbers are too small (2 out of 4 patients) to establish firm conclusions.

Psychotic symptoms in the absence of affective symptomatology were also identified as a significant risk factor for relapse. Notably, affective symptomatology was present in > 90% of patients. There was no difference in relapse risk for patients with manic-psychotic symptoms (N=42), compared to patients with depressed-psychotic or mixed-psychotic symptomatology (N=17). However, patients with non-affective psychosis (N=5) had a significantly poorer prognosis, with a 60% relapse rate compared to only 15% in patients with affective psychosis. Remarkably, affective symptomatology was present in 12 out of the 13 patients who relapsed (92.3%). Together, these findings contribute novel and compelling evidence to a broadening consensus that postpartum psychosis should be classified as an affective disorder and not a primary psychotic disorder [30, 46].

The illustrative case vignette presented above serves to make additional points about the diagnostic classification for patients with postpartum psychosis. This patient was primiparous, without a psychiatric history and with prominent affective symptoms (mania). After remission, she has remained stable throughout the entire four years follow-up period. According to both DSM-IV-R and DSM-V criteria, Mrs. B should be diagnosed as having Bipolar I Disorder. However, this diagnosis suggests a lifelong vulnerability for manic and depressive episodes. In contrast, some patients might have a biological vulnerability for severe affective psychosis that is limited to the postpartum period. The postpartum period is well established to have a dramatically elevated risk for affective instability and psychosis. Recent estimates have quantified this risk as approximately 20-25 times higher in the postpartum period [1]. Moreover, several studies have demonstrated that over long follow-up periods, a sizeable proportion of women have no evidence of mania or psychosis outside the postpartum period [10]. Therefore, we propose that Mrs. B would be better served by a distinct diagnostic category of 'Postpartum Mania', for which the need for lifelong mood stabilization remains currently unknown. Importantly however, her diagnosis should

indeed be converted to Bipolar Disorder if she would ever fulfill the diagnostic criteria outside the postpartum period.

In conclusion, patients with postpartum psychosis or mania achieved favorable treatment outcomes using a structured treatment algorithm during the acute phase of the illness. Following remission, maintenance with lithium monotherapy appears highly protective against relapse.

Treatment considerations:

Based on the observations from our case series and the previous literature, we propose the following recommendations for the treatment of patients with postpartum psychosis:

General Strategies:

- Inpatient psychiatric treatment is essential to ensure the safety of mother and baby. Admission to a mother-baby unit is associated with improved patient satisfaction and might help to reduce time to recovery [49].
- The clinician must inquire about thoughts of the patient of harming herself or her children.
- The initial clinical evaluation for postpartum psychosis requires a thorough medical and psychiatric history, including physical and neurological examination. Laboratory serum testing should include a complete blood count, electrolytes, blood urea nitrogen, creatinine, calcium, liver function tests, and glucose. Urine drug screen should also be performed. We suggest measuring TSH, fT4 and TPO antibodies, both at the time of diagnosis and 6 months postpartum. With proper clinical indication, brain CT or MRI, cerebrospinal fluid collection, limbic encephalitis antibody screening, serum vitamin B1, B12, and folate, and urinalysis should also be performed.
- Focus on the integrity of sleep hygiene and a structured rhythm of feedings. In clinical practice, this often means cessation of breastfeeding. Use of lactation inhibitors should be avoided.
- Mother-baby interaction deserves particular attention [34, 50, 51]. Moreover, support for the father is also an important aspect of successful treatment from the perspective of the family unit.

Pharmacotherapy

- Allowing a 2-3 day period of benzodiazepine treatment prior to the initiation of antipsychotics enables the clinician to carefully evaluate the influence of sleep hygiene on the severity of symptomatology, while also screening for somatic comorbidities. Restoration of sleep might lead to recovery in a small subgroup of patients.
- We discourage the use of antidepressants for the acute treatment of postpartum depression with psychotic features, particularly in the absence of appropriate mood stabilization, because of the risk of exacerbating mood instability [52, 53].
- Antipsychotic medication is recommended for acute treatment of psychotic symptoms.
- Lithium is highly recommended during the acute phase of the illness, unless otherwise contraindicated (e.g., due to impaired thyroid function, or impaired renal function), particularly in those patients without a significant clinical response to antipsychotic treatment.
- We recommend maintenance treatment using lithium monotherapy during the first nine months postpartum (blood level 0.6-0.8). After nine months, gradually tapering off lithium should be considered in patients that remain in full clinical remission.

ECT

- The choice between pharmacotherapy and ECT should be made in consultation with the patient, particularly regarding their preference for breastfeeding.
- ECT has been described as a very effective treatment option in patients with severe catatonic features [22-24].
- ECT should be considered for treatment of postpartum depression with psychotic features, given the relatively longer median duration of episode compared to postpartum mania [32].

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Chapter 3

Functional recovery after postpartum psychosis

K.M. Burgerhout
A.M. Kamperman
S.J. Roza
M.P. Lambregtse-Van den Berg
K.M. Koorengevel
W.J. Hoogendijk
S.A. Kushner
V. Bergink

Accepted by Journal of Clinical Psychiatry

ABSTRACT

Objective: Postpartum psychosis (PP) is an acute and severe mood disorder. Although the prognosis is generally good, it is a highly stressful life-event presumed to have a major impact on functioning and well-being beyond the acute stage of the illness. We studied functional recovery, including psychosocial functioning and the presence of psychological distress, in patients with a recent diagnosis of PP.

Methods: Seventy-eight patients with PP consecutively admitted for inpatient hospitalization between 2005 and 2011 were assessed nine months postpartum. Included were patients with DSM-IV diagnoses of psychotic disorder NOS, brief psychotic disorder, or mood disorder with psychotic features, each requiring the additional specifier "with postpartum onset". Functioning was assessed in four domains by the Range of Impaired Functioning Tool (LIFE-RIFT). Symptomatology was measured by the Brief Symptom Inventory (BSI) and compared to a matched population-based cohort.

Results: Nine months postpartum, 74% of women with PP reported good functioning on the domains work, interpersonal relations, recreation and global satisfaction. Moreover 88.5% of patients with PP had resumed their pre-morbid employment and household responsibilities. Compared to the general population, patients with PP reported a higher burden of depression and anxiety (effect sizes $r \leq 0.14$). Patients who had a relapse episode (18%) experienced considerable functional impairments across several domains.

Conclusion: Nine months postpartum, the majority of patients with PP reported good functional recovery. Our relatively improved functional outcomes compared to non-postpartum onset, could be attributed to the postpartum onset and/or more favorable risk factor profile.

Clinical Points

- Postpartum psychosis is an acute and severe mood disorder with substantial impairment in every aspect of daily life functioning during the acute episode. The prognosis is highly optimistic for achieving full clinical remission, but the impact on daily life functioning extends well beyond the acute stage of illness.
- 74% of patients with PP reported good functional recovery and 88.5% were able to resume their employment and household responsibilities within nine months postpartum. Compared to a matched population-based cohort, patients with PP reported only slightly more symptoms of depression and anxiety.
- 17% of women experienced a relapse within nine months postpartum, which resulted in considerable functional impairment and psychological distress.

INTRODUCTION

The birth of a child is a major life event, leading to profound changes in many aspects of daily life, especially for primiparous mothers [1, 2]. With an incidence of approximately 1:1000 childbirths, postpartum psychosis (PP) manifests as the acute onset of severe affective psychotic symptoms within 4-6 weeks after delivery, often in women without any prior psychiatric history [3, 4]. These symptoms of postpartum psychosis are very stressful for both the patient and her family and have a substantial impact on psychosocial functioning.

During the acute phase, patients frequently experience manic symptoms, severe depressive symptoms and/or purely psychotic symptoms. Given the predominance of the affective symptoms, PP is generally considered an affective disorder and not a primary psychotic disorder. Symptomatology, family history data and the longitudinal illness course, all support the notion of a strong link to bipolar disorder [5, 6].

Episodes of PP are typically severe, but limited in time [6, 7]. We previously described the complete remission of symptoms after a median episode of 40 days in 98% of patients receiving pharmacological treatment [8]. Notably, the median duration of illness in PP is similar to the duration of manic episodes reported for bipolar patients [9]. Although the short-term prognosis is very optimistic, following remission most patients describe their acute episode as very stressful and even traumatic [10, 11]. In addition, previous case series have revealed that patients often report feelings of guilt, anxiety, social vulnerability and difficulties in their personal relationships[10-12]. A comprehensive, prospective, longitudinal study of functioning and quality of life has never previously been conducted for women with PP, but will however provide a necessary base of evidence for clinicians to inform patients about their long-

term prognosis. The present study was designed to prospectively assess functional recovery nine months postpartum in 78 consecutive patients requiring psychiatric hospitalization for PP.

METHODS

Patient population

The medical ethical committee of the Erasmus MC approved this study. All patients provided written informed consent for their participation. All patients admitted to the Mother-Baby Inpatient Unit (MBU) of the Department of Psychiatry in the Erasmus Medical Centre between August 2005 and June 2011 were screened for eligibility. The MBU at the Erasmus MC is a 5-bed inpatient unit dedicated to the treatment of patients with severe psychopathology in the postpartum period. Diagnoses were obtained using the Structured Clinical Interview for DSM-IV Disorders (DSM-IV-R; SCID – 1/P research version)[13]. We included patients with mania or psychosis with an onset within 6 weeks after delivery. Since 'postpartum psychosis' is not described as a separate disease entity, we operationally defined 'postpartum psychosis' based upon any of the following DSM-IV diagnoses: psychotic disorder NOS, brief psychotic disorder or mood disorder (manic, mixed, or major depressive episode) with psychotic features, all requiring the specifier "with postpartum onset". Accordingly, patients with schizophrenia or schizoaffective disorder were excluded.

A total of 84 patients fulfilled the inclusion criteria for postpartum psychosis (Figure 1). Six patients were excluded from analysis: one patient was excluded due to cannabis dependence, three patients declined study participation and two patients were lost-to-follow-up. In total, we included 78 patients with postpartum psychosis in the final analyses. Of these 78 patients, 14 had a history of non-peripartum psychosis (n=4), mania (n=9) or hypomania (n=1).

In the remaining 64 patients, the psychotic or manic episode was limited to the postpartum period. Of these 64 patients, 54 were experiencing a first-onset psychotic or manic episode while the remaining 10 had a prior history of postpartum psychosis.

Treatment

Patients diagnosed with psychosis or mania limited to the postpartum period (n=64) were treated according to a structured treatment algorithm with sequential addition of a benzodiazepine, antipsychotic and lithium as described previously [8]. Remission was defined as the absence of psychotic, manic and severe depressive symptoms for at least 1 week including Clinical Global Impressions Scale (CGI) ≤3 [14], Young

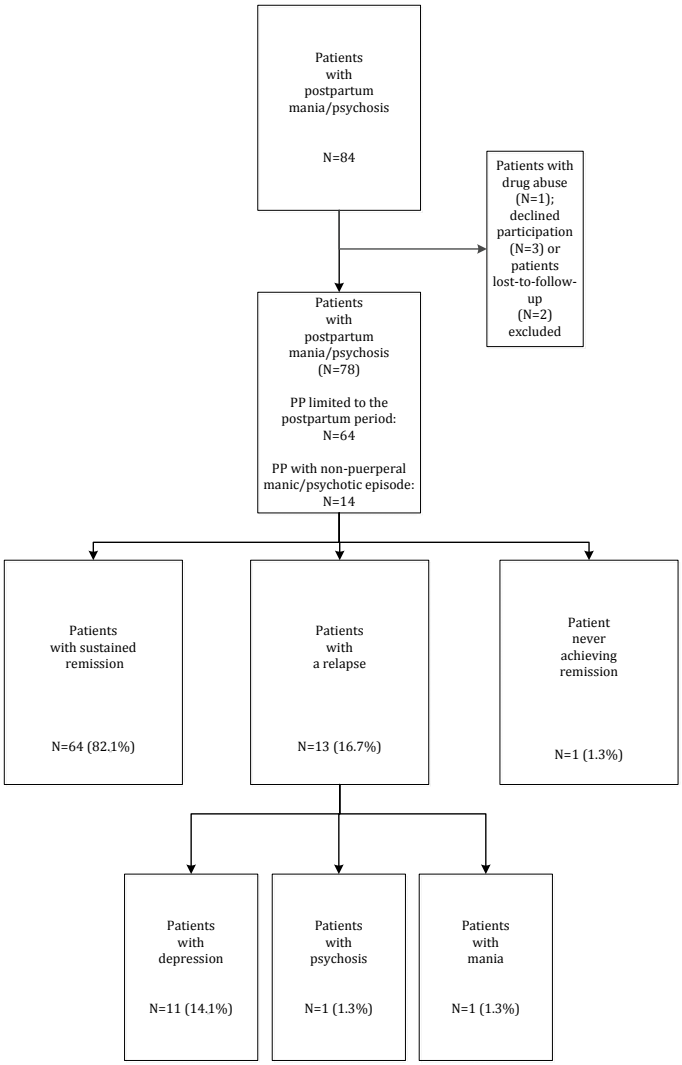

Figure 1. Flowchart of inclusion of patients with postpartum psychosis.

Mania Rating Scale (YMRS) [15] ≤8 and Edinburgh Postpartum Depression Scale (EPDS) ≤10 [16]. After complete remission, benzodiazepines were slowly tapered to discontinuation under medical supervision. Patients who remitted on antipsychotic monotherapy were advised to continue this treatment as maintenance therapy. Conversely, patients who required both an antipsychotic and lithium to achieve remission were maintained on lithium monotherapy.

Of the 64 patients with postpartum psychosis limited to the postpartum period, four patients remitted with benzodiazepines only, 12 patients remitted during treatment with a combination of benzodiazepines and antipsychotics and 47 patients remitted with a combination of benzodiazepines, antipsychotics and lithium. One patient never achieved remission. Nine months postpartum, 16 patients had discontinued their medication. The remaining 48 patients continued maintenance monotherapy throughout the full six months post-remission period, of which eight patients were using antipsychotic monotherapy and 40 patients were using lithium monotherapy.
Of the 14 patients with a history of non-peripartum mania or psychosis, nine patients were treated with the combination of benzodiazepines, antipsychotics and lithium, two patients with benzodiazepines and lithium, two patients with antipsychotics and valproic acid and one patient with benzodiazepines and an antipsychotic. Nine months postpartum, one patient had discontinued her medication, seven patients were maintained on lithium monotherapy, two patients were maintained on antipsychotic monotherapy and four patients were using combination therapy (antipsychotic and lithium, n=2; antipsychotic and valproic acid, n=2).

Assessments

Patients were evaluated weekly during inpatient hospitalization and at nine months postpartum. The mean follow-up period was 8.7 months postpartum (SD 7.5) and 6.1 months after remission (SD 7.4). The nine months postpartum evaluations were conducted in each patient's home, and included assessments of relapse and functional recovery, including psychosocial functioning and psychological distress. The researcher (KMB) met patients during the acute phase and invited them for the nine months postpartum visit. Importantly, KMB was not involved in the clinical care of the patients in this study.

Relapse

Relapse was defined as the occurrence of any psychiatric episode fulfilling DSM-IV-TR criteria and/or The Clinical Global Impression – Bipolar Disorder (CGI-BP) score >3 [14]. Sustained remission was defined as having never experienced a DSM-IV-TR mood or psychotic episode throughout the entire nine months postpartum follow-up period, as well as maintaining a CGI-BP score ≤3. Longitudinal assessment of mood episodes was performed by the NIMH Life-Chart Method (NIMH-LCM-R) [17].

Functional recovery - Psychosocial functioning

Psychosocial functioning was investigated using the Longitudinal Interval Follow-up Evaluation - Range of Impaired Functioning Tool (LIFE-RIFT, see supplementary material) [18].

The LIFE-RIFT is an observer-rated instrument that assesses the level of functional impairment in the past week across four domains: work, interpersonal relations, global satisfaction, and recreation (Supplemental Material) [18]. Results are scored on a five-point Likert scale, ranging from 1 to 5 [1: very good/no impairment, 2: good/satisfactory level 3: fair/mild impairment, 4: poor/moderate impairment, 5: very poor/severe impairment].

For the subscale work, the patients were asked to specify the degree to which their work (employment, household or student) activities have been impaired as a result of psychopathology. Similarly, for the 3 subscales regarding interpersonal relations (spouse/children/other relatives), patients were asked to specify the degree to which their interpersonal relations have been impaired as a result of psychopathology. With regard to satisfaction, patients were asked to rate their overall level of satisfaction. Finally, for the subscale recreation, patients were asked at what level they have been involved in recreational activities and if they were able to enjoy these activities [18].

LIFE-RIFT domain scores are summarized into a total psychosocial impairment score, ranging from 4 (no impairments) to 20 (impairments in all domains). The LIFE-RIFT composite score has been shown to have high reliability and validity in case-control cohort studies [19]. LIFE-RIFT total and subscale scores were analyzed as continuous and dichotomized variables. A dichotomous threshold score of 10 was defined for the total scale (score ≤ 10 indicates an overall good functioning in all domains) and a score of 2 was defined as the dichotomous threshold for each subscale (score ≤2 indicates minimal or no problems within a given domain).

Functional recovery - Psychological distress

Psychological distress was assessed using the Brief Symptom Inventory (BSI) [20]. The BSI is a self-report questionnaire of 53 items validated for assessment of psychological well-being [20]. The BSI covers nine psychological symptom dimensions, divided into the following subscales: interpersonal sensitivity, depression, anxiety, hostility, somatization, obsessive-compulsive traits, phobic anxiety, paranoid ideation and psychoticism [20]. Each item of the BSI is rated on a five-point scale of distress, ranging from “not-at-all” (score of 0) to “extremely” (score of 4). The BSI demonstrates strong concordance with clinician symptom assessment and exhibits high test-retest and internal consistency reliabilities [20].

Reference population

BSI scores of women with PP were compared to a matched reference group who participated in the Generation R Study [21]. All pregnant women living in Rotterdam, the Netherlands, with an expected delivery date between April 2002 and January 2006 were invited to participate in the Generation R Study.

Subjects from the Generation R cohort were matched to our patient sample (ratio 4:1) based on age (5-year categories), ethnicity (Dutch native versus non-native), educational level (high school versus postsecondary education) and parity (primiparous versus multiparous), resulting in a reference sample of 318 women. Within the matched reference group, four BSI-subscales were measured at six months postpartum: interpersonal sensitivity, depression, anxiety, and hostility.

Statistical Analysis

We compared demographic and clinical characteristics between women with versus without impairments in daily functioning at nine months postpartum. The following characteristics were handled as continuous variables in statistical analyses: age, duration of the PP episode (in days), and onset of PP symptoms (in days). Characteristics that were handled as dichotomous variables (yes/no) included Dutch ethnicity, education beyond high school, married or cohabitating, primiparity, psychiatric history (categories included no psychiatric history, previous PP, history of depression or anxiety, history of psychosis outside the peripartum period), phenomenology (categories included manic-psychotic features, depressive/mixed features, non-affective psychosis), and psychotic symptoms (categories included mood incongruence, first-rank symptoms).

Next, we compared functioning (LIFE-RIFT scores) between women with sustained remission versus those who relapsed. BSI scores were compared between women with sustained remission of PP, women who relapsed following remission of PP, and women in the matched reference cohort.

BSI scores were unavailable for 21 women with PP (27%; 16 PP-Sustained and 5 PP-Relapse), and 34 women from the matched reference group (11%).

Differences between subsamples were tested with the Mann-Whitney U test (MWU) for continuous variables, and Pearson Chi-square and Fisher's Exact test (FET) for categorical variables. Effect sizes were calculated to estimate the magnitude of the effect. Correlation coefficients (r) were calculated with respect to continuous outcomes (LIFE-RIFT and BSI) while an Odds Ratio (OR) was calculated with respect to dichotomized outcomes. Analyses were conducted using SPSS version 20.0.

RESULTS

Demographic characteristics

Patients with a postpartum psychosis were predominantly of Dutch origin (89.7%), had completed postsecondary education (53.8%) and were primiparous (79.5%). The mean (± SD) age of the total study group was 32.1 ± 5.0 years with a median onset of the first symptoms occurring seven days after delivery (Table 1). The majority of patients experienced manic-psychotic symptoms (n=45, 57.7%), while 28 patients were diagnosed with a mixed or depressed-psychotic episode (35.9%) and five with a non-affective postpartum psychosis (6.4%). Psychotic symptoms were predominantly mood-incongruent (n=46, 59.0%), of which eight patients experienced first-rank symptoms. After treatment, patients were in full remission, median 40 days postpartum (IQR 26-57).

Table 1. Demographic and clinical characteristics of 78 patients with postpartum psychosis. Patient without impaired functioning (LIFE-RIFT score ≤ 10) compared to patients with impaired functioning (LIFE-RIFT score >11).

	PP-All (n=78)		No impairment in functioning (LIFE-RIFT total score ≤ 10) (n=58)		Impaired functioning (LIFE-RIFT total score >11) (n=20)		
General demographics	%	n	%	n	%	n	P-value
Dutch ethnicity	89.7	70	91.4	53	85.0	17	0.416
Education beyond high school	53.8	42	58.6	34	40.0	8	0.196
Married or living with partner	97.4	76	100.0	58	90.0	18	0.063
Primiparity	79.5	62	81.0	47	75.0	15	0.537
Mean age (SD) (years)	32.1	5	32.1	5	31.8	4	0.591
Duration of PP: median days (IQR)	40.5	26-57	34.0	23-55	44.0	40-115	0.015
Onset PP: median days (IQR)	7	5-14	8	5-15	7.0	4-13	0.192
Psychiatric history							
No psychiatric history	59.0	46	56.9	33	65.0	13	0.604
Previous PP in history	12.8	10	13.8	8	10.0	2	1.000
Depression/anxiety in history	10.3	8	10.3	6	10.0	2	1.000
Non-postpartum psychosis or (hypo)mania	17.9	14	18.9	11	15.0	3	1.000
Phenomenology - Affective psychosis							
With manic-psychotic features	57.7	45	56.9	33	60.0	12	1.000
Depressed/mixed	35.9	28	36.2	21	35.0	7	1.000
Non-affective psychosis	6.4	5	6.9	4	5.0	1	1.000
Psychotic symptoms							
Mood incongruence	59.0	46	60.3	35	55.0	11	0.793
First-rank symptoms	10.3	8	10.3	6	10.0	2	1.000
Relape	17.9	14	8.6	5	45.0	9	0.0008

*Including one patient who never achieved remission during the follow-up period

Relapse

Nine months postpartum, 64 patients (82.1%) had a sustained remission (PP-sustained), 13 patients (16.7%) experienced a relapse (PP-relapse) and one patient never remitted (1.3%). The median period from complete remission to relapse was 53 days (IQR 28-94). Only three women (3.8%) relapsed within one month after full remission (on days 19, 23 and 28). Of the 13 patients who relapsed, 11 women experienced a depressive episode (14.1%), one woman experienced a non-affective psychosis (1.3%) and one woman had a manic episode (1.3%).

Among the 64 patients with psychosis limited to the postpartum period, the relapse rate was 20.3% (13/64). Of the remaining 14 patients with a history of non-peripartum mania or psychosis, the relapse rate was 7.1% (1/14) (p=0.28, FET).

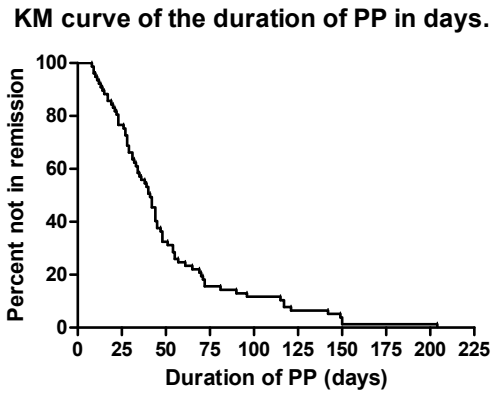

Figure 2. Kaplan-Meier curve showing the duration of postpartum psychosis (from acute onset to full remission). Remission was defined as the absence of psychotic, manic and severe depressive symptoms for at least 1 week including CGI ≤3, YMRS ≤8 and EPDS ≤10.

Psychosocial functioning

Nine months postpartum, 74.4% (58/78) of patients with PP exhibited good overall functioning based upon the total LIFE-RIFT score (Table 2). Patients with a relapse exhibited a significantly greater impairment of daily functioning (median total LIFE-RIFT score 11.0, IQR 8.8-13.5), compared to patients with sustained remission (median total LIFE-RIFT score 7.0, IQR 4.0-9.0; r=0.44, p<0.001). Of the 64 patients in sustained remission, 82.8% (53/64) had a score indicative of good functioning in all domains of the LIFE-RIFT, compared to only 35.7% (5/14) of patients with a relapse during follow-up. Patients with a relapse had significantly reduced functioning on both continuous and dichotomous scores across all four subscales (Table 2). Effect sizes showed medium to large effects on the continuous subscale scores (r values ranged

from 0.34-0.47) (Table 2). Moreover, the duration of the acute episode was predictive of impairment in daily functioning at nine months postpartum. Women with impaired functioning (n=20, LIFE-RIFT total score >11) had a significantly longer duration of episode (median 44 days, IQR 40-115), compared to women with good functioning (n=58, median duration of episode 34 days, IQR 23-55, MWU P=0.015). No significant difference in median total LIFE-RIFT score was observed for any of the other variables measured, including demographics, psychiatric history, or phenomenology. None of the other clinical or demographic characteristics were associated with impairment in functioning (Table 1).

Interpersonal relations

Most women (65/78, 83.3%) reported having good to very good interpersonal relations with their spouse, friends, and child(ren). Of the 13 women reporting problems with interpersonal relations, five women described problems with their spouse and friends, three women described problems with their spouse, child(ren), and friends, and five women reported problems limited to a single category (two with friends, two with children, and one with her spouse).

Resumption of work

Nine months postpartum, the vast majority of patients had fully resumed their pre-morbid employment and household responsibilities (69/78, 88.5%), with only a minority on medical leave (9/78, 11.5%). Notably, the rate of medical leave was similar between patients with sustained remission compared to those with a relapse (FET, p=0.66, OR=1.36). There was no significant difference in medical leave between patients with or without a history of mania or psychosis outside the postpartum period (FET, p=0.35, OR=4.96). In addition, the proportion of women engaged in paid work was similar in patients with or without a prior psychiatric history (FET, p=0.17, OR=2.68). On the subscale work on the LIFE-RIFT, 56.4% (44/78) of patients scored minimal or no problems at work and/or household responsibilities.

Lastly, overall good scores were given in the LIFE-RIFT subscales global satisfaction in 66.7% (52/78) and recreation in 71.8% (56/78).

Table 2. LIFE-RIFT scores in patients with postpartum psychosis.

LIFE-RIFT	PP-All (n=78)		PP- Sustained (n=64)		PP-Relapse (n=14)		PP-Sustained vs. PP-Relapse	
Percentage good functioning *	%	n	%	n	%	n	P-value	Effect size (OR)
Work	56.4	44	64.1	41	21.4	3	0.007	6.54
Interpersonal relations	82.1	64	87.5	56	57.1	8	0.012	5.26
Satisfaction	66.7	52	75.0	48	28.6	4	0.002	7.52
Recreation	71.8	56	81.3	52	28.6	4	<0.001	10.87
Total	74.4	58	82.8	53	35.7	5	0.001	8.70
Median scores (total)	Median	IQR	Median	IQR	Median	IQR	P-value	Effect size (r)
Work	2.0	1.0-3.0	2.0	1.0-3.0	3.0	2.8-4.0	0.002	0.34
Interpersonal relations	1.0	1.0-2.0	1.0	1.0-2.0	2.0	1.8-3.0	0.002	0.35
Satisfaction	2.0	1.0-3.0	2.0	1.0-2.8	3.0	2.0-4.0	<0.001	0.45
Recreation	2.0	1.0-3.0	2.0	1.0-2.0	3.0	2.0-4.0	<0.001	0.47
Total	7.0	5.0-11.0	7.0	4.0-9.0	11.0	8.8-13.5	<0.001	0.44

*Score ≤ 2 (subscale) or ≤ 10 (total score). A higher score indicates more functional impairment.

Psychological distress

Brief Symptom Inventory (BSI)

Patients with postpartum psychosis had significantly elevated BSI scores on two of the four subscales in comparison to the matched reference group (Table 3: depression and anxiety), but effect sizes were small (r, depression: 0.12 and anxiety: 0.14). No significant differences were observed between patients and the matched reference group on the subscales interpersonal sensitivity and hostility. Patients with sustained remission had significantly higher scores on the BSI subscales interpersonal sensitivity and depression compared to patients who relapsed (Table 3, median effect size). Notably, patients with sustained remission demonstrated no significant differences compared to the matched reference group on any of the BSI subscales (Table 3).

We examined the Spearman correlation coefficients between LIFE-RIFT scores and BSI items. Negative affect on the BSI was associated with functioning across several domains, most prominently satisfaction and recreation (Supplementary Table 1).

Table 3. Brief symptom inventory (BSI) scores of all patients with postpartum psychosis (PP-All), compared to a matched population based reference cohort group, Generation R (Gen R). PP patients in sustained remission (PP-Sustained) and patients with a relapse (PP-Relapse) compared to Gen R.

BSI subscale	PP-All (n=57) Median (IQR)	Gen R (n=284) Median (IQR)	P-value	Effect size (r)	PP-Sustained (n=48) Median (IQR)	Gen R (n=284) Median (IQR)	P-value	Effect size (r)	PP-Sustained (n=48) Median (IQR)	PP-Relapse (n=9) Median (IQR)	P-value	Effect size (r)
Interpersonal sensitivity	0.25 (0.00-0.50)	0.00 (0.00-025)	0.156	0.08	0.00 (0.00-0.50)	0.00 (0.00-025)	0.620	0.03	0.00 (0.00-0.50)	0.50 (0.25-0.75)	0.040	0.27
Depression	0.17 (0.00-0.33)	0.00 (0.00-0.21)	0.012	0.14	0.00 (0.00-0.33)	0.00 (0.00-0.21)	0.174	0.08	0.00 (0.00-0.33)	0.67 (0.17-1.33)	0.007	0.36
Anxiety	0.17 (0.00-0.50)	0.17 (0.00-0.33)	0.034	0.12	0.17 (0.00-0.50)	0.17 (0.00-0.33)	0.173	0.08	0.17 (0.00-0.50)	0.33 (0.17-0.92)	0.095	0.22
Hostility	0.00 (0.00-0.20)	0.20 (0.00-0.20)	0.238	-0.07	0.00 (0.00-0.20)	0.20 (0.00-0.20)	0.080	-0.10	0.00 (0.00-0.20)	0.20 (0.10-0.50)	0.070	0.24

Supplementary table 1. The Spearman correlation coefficients between the BSI subscales depression and anxiety and domains of functioning.

BSI (n=57)	Interpersonal sensitivity	Depression	Anxiety	Hostility	Total 4 BSI scales
LIFE-RIFT (n=78)					
Work	0.19	0.18	0.31*	0.20	0.29*
Interpersonal relations	0.29*	0.11	0.23	0.20	0.30*
Satisfaction	0.46**	0.47**	0.42**	0.26	0.54**
Recreation	0.39**	0.32*	0.39**	0.13	0.42**
Total LIFE-RIFT	0.38**	0.31*	0.41**	0.23	0.46**

DISCUSSION

Psychosocial functioning

All 78 women with postpartum psychosis and inpatient psychiatric treatment experienced a substantial impairment of every aspect of life functioning during the acute episode. Remarkably however, the majority exhibited substantial or complete recovery of life functioning within nine months postpartum. Nearly three-quarters of patients with PP reported functional recovery on the domains "work", "interpersonal relationships", "recreation" and "global satisfaction". Moreover, most patients had resumed their employment and household responsibilities nine months postpartum (88.5%). In our study, nine patients (11.5 %) described problems with their partner; none of the patients were separated from their partner during the first nine months postpartum. One previous study showed a divorce rate of 18% after a 12 years follow-up period [12]_ENREF_22.

As expected, functioning was more severely impaired in patients who experienced a relapse compared to those with sustained remission: only 28.6% of patients with a relapse reported being satisfied with their life, compared to 75.0% of patients in sustained remission. Though encouragingly, only two of the 14 patients who relapsed were still on medical disability leave at nine months postpartum, suggestive of a relatively short duration of the relapse episodes.

Similar to Blackmore et al, we also observed that the duration of the acute episode was significantly correlated with impairment in daily functioning [12].

Comparison to the general postpartum population

Women with a postpartum psychosis reported more depressive and generalized anxiety symptoms nine months postpartum compared to a population-based matched control group. Notably however, the effect sizes were generally small. Moreover, the majority of this difference was explained by the burden of affective symptoms in the subgroup of women who experienced a relapse (14/78, 17.9 %). In a retrospective cohort study from Blackmore et al., 26% of women reported ongoing symptoms 1 year postpartum [12].

Together, our findings suggest a generally optimistic prognosis for women with acute postpartum affective psychosis, for which a return to their prior level of functioning is highly likely within one year postpartum.

Comparison to first-onset bipolar disorder outside the postpartum period

We did not detect differences in psychosocial functioning between women with postpartum psychosis limited to the postpartum period compared to those with a

history of non-peripartum mania or psychosis. However, the small sample size of the group with a history of non-peripartum mania or psychosis (n=14) would have precluded us from detecting potential differences of small or medium effect size.

We compared our findings to the literature on psychosocial functioning of patients after their first episode of mania outside the postpartum period. A recent meta-analysis described pooled symptomatic recovery rates of 62% (CI 42-79%, 8 studies) following a first episode of mania outside the postpartum period [22]. Therefore, our results support previous reports suggesting a superior prognosis following postpartum mania or affective psychosis compared to non-postpartum onset [23, 24]. Several risk factors have been reported as associated with impaired functioning after a first-onset bipolar episode: family history of affective disorder, earlier age at onset, comorbid drug or alcohol use, mood-incongruent psychosis, symptom severity, non-adherence to medication, comorbid substance abuse, low socioeconomic status, poor premorbid function and treatment noncompliance [22, 25-29]. In the current study, most women had a high socio-economic status with good premorbid function, demonstrated good treatment compliance, and with minimal drug or alcohol use. Therefore, the relatively improved functional outcomes that we have observed could be attributed to the postpartum onset and/or more favorable risk factor profile.

Limitations

We recognize a number of limitations in our study. Data on the Brief Symptom Inventory (BSI) were unavailable for 27% (21/78) of the PP cohort, attributable to the data collection procedure by which we chose to minimize the length of the face-to-face interview by asking the patient to complete the BSI questionnaire afterwards and return it by postal mail. This procedure might have resulted in a selection bias among the returned BSI questionnaires, although we found no demographic characteristics or psychosocial functioning metrics that were significantly associated with completion of BSI questionnaires.

The specialized care within an MBU might hamper generalization of our findings to other psychiatric units. Unfortunately, many regions in the world do not have MBU care within a reasonable travel distance for the patient. When mother and baby are separated during admission, the understandable wish to reunite them might lead to discharge prior to a full clinical remission. In contrast, in our study, most patients were released only after complete remission of symptoms. This might have lowered relapse risk leading to better functional outcome. Moreover, specialized MBU treatment to improve bonding and mother baby interaction might have had a positive effect on psychosocial functioning in our patient group.

Conclusion

The current study demonstrates that psychosocial functioning was preserved in the vast majority of PP patients nine months postpartum. Psychosocial functioning of patients who relapsed after their initial remission were more impaired compared to patients in sustained remission, but even within this subgroup most women had largely resumed their premorbid function. Overall, the prognosis for PP patients is highly optimistic for achieving clinical remission and returning to their premorbid level of functioning.

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Chapter 4

Relapse after a first-onset postpartum psychosis: 4 years prospective follow-up

In preparation.

ABSTRACT

Objective: First-onset postpartum psychosis or mania (PP) is a rare but very severe psychiatric disease. Women with first onset postpartum psychosis or mania are at high risk of subsequent bipolar spectrum episodes outside the postpartum period. This prospective study was designed to describe the relapse risk and treatment during a four years follow-up period.

Methods: Seventy-one women admitted with a first-onset postpartum psychosis or mania were included at the Mother-Baby Unit of the Erasmus MC between 2005 and 2012. Four years postpartum women (median 46 months; IQR 40-53, follow-up rate 94.4) sixty-seven women were evaluated using the Structured Clinical Interview for DSM-IV (SCID), the Clinical Global Impression – Bipolar Disorder (CGI-BP) and the Life-Chart method. We defined a relapse as the occurrence of any mood or psychiatric episode fulfilling DSM-IV-TR criteria, including hypomanic episodes and a CGI-BP over this period >3.

Results: After four years, 26 of the 67 women (38.8%) experienced a relapse. Of these, twelve women had a depression, eight a manic episode and six a non-affective psychosis. The majority of relapses (23/26) were during the first 18 months after remission and related to medication withdrawal. More than half (16/26) of the women relapsed more than once during follow-up. Seven women (10.4%) were admitted during the follow-up period. We found no indication of any influence of illness episode, phenomenology, psychiatric family history and treatment on relapse. Sixty-one percent of the women were medication free at four years follow-up.

Conclusion: This study demonstrates that 61.2% of women are in sustained remission four years after a severe postpartum psychosis or mania. These women have psychosis and/or mania limited to the postpartum, which should be a distinct disease category. Clinicians should be aware of a high relapse risk particularly in the first 18 months after the initial disease episode and when medication is changed.

INTRODUCTION

Postpartum psychosis (PP) is the most severe form of childbirth related psychiatric illness with an estimated prevalence in the general population as 0.5-1 per 1000 deliveries [1-4]. Postpartum psychosis has an onset within 4-6 weeks after delivery [5, 6].

The onset of a postpartum psychosis is median 8 days after delivery and starts with symptoms like mood fluctuations, insomnia and sometimes obsessive concerns about the baby [7]. Little later more severe symptoms follow like serious mood symptoms, disorganized behavior, delusions and hallucinations. An important difference between a postpartum psychosis and a non-postpartum psychosis is the presence of severe mood symptoms like mania, depression or a mixed episode [8]. Psychotic symptoms almost exclusively occur within the setting of affective instability. Consequently, postpartum psychosis is generally considered a bipolar related mood disorder and not a primary psychotic disorder.

The initial clinical evaluation for postpartum psychosis requires a thorough physical and neurological examination, to exclude known organic causes for acute mania or psychotic depression. Moreover, clinicians need to ensure the adequate safety of the patient and her baby, considering the highly elevated risk of suicide and infanticide

We previously found that patients with first-onset postpartum psychosis can be successfully treated (98% remission during acute phase) with a combination of benzodiazepines, antipsychotics and lithium [9]. Moreover, we found that within nine months postpartum, the majority of patients with PP functioned well. Patients who experience a relapse remain moderately impaired and require ongoing support to achieve a complete return to their pre-morbid level of functioning and well-being [10].

Currently, most women with first-onset postpartum psychosis are often given a diagnosis of bipolar disorder (BD), because another classification is not possible within the current diagnostic system DSM-IV/V (Diagnostic Statistic Manual of Disease). Moreover, most women with postpartum psychosis are advised to use long-term maintenance pharmacotherapy after complete remission of their first episode. The traditional rationale underlying the recommendation for chronic pharmacotherapy is the prevention of subsequent psychotic and affective episodes. Importantly however, retrospective studies have documented that after long term follow-up, a substantial proportion of women with postpartum psychosis do not have episodes outside the postpartum period (3-9). More specifically, since 1992 ten studies have reported the relapse risk after first-onset postpartum psychosis. These studies estimated that 56-87% of the women after a postpartum psychosis experience a relapse after this initial

episode [11-22]. Accordingly, many women might not have a bipolar disease course with multiple manic and depressive episodes.
We previously proposed a model for the longitudinal course of first-onset postpartum psychosis in which for some women the vulnerability for mania and psychosis is limited to the postpartum period whereas for others postpartum psychosis is the start of a life-long course of bipolar disorder [23].
This study was designed to study the longitudinal outcomes of women following a first-onset episode of postpartum psychosis, and to identify prognostic factors regarding the risks and benefits of maintenance pharmacotherapy. In this prospective study we followed a group of 67 women with a first-onset postpartum psychosis over a four-year period. We assessed the relapse frequency and the moment of relapse and related these with patient and disease characteristics and the use of medication. In doing so, we hope to gain a better understanding in the women who are vulnerable for the development of bipolar disorders, and the women for whom their illness is a postpartum condition, and whether and when these groups of women could safely taper off medication.

METHODS

Participants

The study was approved by the International Review Board of the Erasmus Medical Centre (Rotterdam, The Netherlands). All patients provided written informed consent. The study was performed at the Mother-Baby Unit (MBU), a five-bed inpatient unit that specializes in the care of patients with severe psychopathology in the postpartum period, located in the Department of Psychiatry in the Erasmus Medical Centre (Erasmus MC) in Rotterdam, The Netherlands. Women are given the option for admission together with their baby in a fully staffed nursery adjoining the unit [24]. Every patient admitted to the MBU between August 2005 and June 2012 was screened for study inclusion (N=230) and diagnosed using the Structured Clinical Interview for DSM-IV Disorders (DSM-IV-TR; SCID – 1/P research version) [25]. Previous hypomanic and manic episodes were registered using the MDQ (Mood Disorder Questionnaire) [26].
Included were patients aged between 18-45 years with a diagnosis of first-onset postpartum psychosis. First-onset postpartum psychosis is operationalised as any of the following DSM-IV-TR diagnoses, and requiring the specifier “onset postpartum”: manic episode, mixed episode, depressive disorder with psychotic features, psychotic disorder not otherwise specified (NOS) or brief psychotic disorder, as assessed

with the SCID interview. The specifier "onset postpartum" requires that the onset of symptoms must occur within 4-6 weeks postpartum. Patients with a chronic psychotic disorder, mania or psychosis with onset during pregnancy or with a history of psychosis or mania outside the puerperal period were excluded.

Procedure

A total of 230 women were admitted to our MBU between August 2005 and June 2012, of whom 94 patients with a postpartum psychosis (Figure 1). Of these 94 women, four patients declined participation and 19 women were excluded (18 women with non-puerperal manic of psychotic symptoms, one woman with drug abuse). Accordingly, 71 patients fulfilled the criteria for psychosis limited to the postpartum period. Four patients were lost to follow-up (5.6%). Finally, 67 women were evaluated between 2010 and 2014. Median duration of follow up was 46 months (IQR = 40-53).

Figure 1. Flowchart of inclusion for patients with a first-onset postpartum psychosis.

* Including four women with anxiety disorders during follow-up

All participants and their relatives were interviewed during admission and follow-up by an intensively trained medical practitioner (K.M.B.) or a psychiatrist specialized in peripartum psychiatry (V.B.). Relapse criteria and the final diagnosis of each patient were made in consensus. All patients gave permission to the researchers to contact their General Practitioner and/or psychiatrist for additional information.

Symptomatology and clinical course of the initial episode

All participants and their relatives were interviewed by a psychiatrist (V.B. or K.M.K.) and a SCID was performed. A clinician-administered questionnaire provided information about general demographics, psychiatric history, psychiatric family history, phenomenology, illness episode and treatment during admission (described in Table 1) [9]. Phenomenology was quantified using the Bipolar Affective Disorder Dimension Scale (BADDS) [27].

During admission women with a first-onset postpartum psychosis were treated according to a standardised treatment algorithm, as described previously [9]. As a first step all patients were treated with benzodiazepines for 2-3 days. For those patients without a marked improvement on benzodiazepine monotherapy, antipsychotic medication was initiated as a next step within the first week of admission (step 2). After 2 weeks of combined antipsychotic/benzodiazepine treatment, adjunctive lithium was initiated for those patients without a significant clinical response (step 3) [24, 28]. In those patients who did not respond to the previous steps, electroconvulsive therapy (ECT) was started after tapering of medication (step 4) [29]. After complete remission, women were advised to taper off daily benzodiazepines.

All women were encouraged to continue maintenance monotherapy throughout the first 9 months postpartum. Women who remained clinically stable after 9 months were assisted in gradually tapering their medication to discontinuation.

Longitudinal course of the illness

Four years postpartum, women were evaluated using the structured clinical interview for DSM-IV (SCID) [30], the Clinical Global Impression - Bipolar Disorder [31] (CGI-BP) and the Life-chart method [31, 32].

The CGI-BP [31] is a modified version of the CGI-scale that allows the clinician to rate the global illness severity and change over time in patients with bipolar spectrum disorder. The US National Institute of Mental Health created the Life-chart Methodology (NIMH-LCM) [33]. The Life-chart assesses the level of depression based on functional impairment related to affective symptoms (from −1 slight or mild to −4 severe depression) and mania (from +1 mild to +4 severe mania), with 0 representing a balanced, well-functioning euthymic state. Additionally, medications, life events,

drug abuse, hours of sleep, irritability, and other co-morbidities are documented in the life-chart.

We defined relapse as the occurrence of any mood or psychotic episode fulfilling DSM-IV-TR criteria, including hypomanic episodes and a CGI-BP over this period > 3. Accordingly, sustained remission was defined as the absence of mood episodes severe enough to warrant treatment or fulfilling DSM-IV-R criteria and a CGI-BP score of 3 or less during the complete follow-up period. Specific questions were added to the interview to assess the moment of tapering off or stopping medication and the moment of relapse (if applicable). The patient's medical records were consulted to validate the information.

Statistical Analysis

Differences in socio-demographic characteristics, phenomenological characteristics and medication use of patients in sustained remission and of patients who experienced relapse were tested for significance using Mann-Whitney tests for continuous variables and the Fisher Exact tests for categorical variables. Relative risk (RR) is used as measure of association. In case of zero cell counts, 0.5 was added to all cells to calculate the relative risk [34]. Survival analysis using the Kaplan-Meier (KM) method is used to describe the time to relapse for the patients in the sample. SPSS 21.0 package for Windows (IBM corp.) and Graphpad were used to perform the analyses.

RESULTS

Baseline characteristics

Characteristics of all 67 patients with a first-onset postpartum psychosis and four years follow-up are shown in Table 1. The median onset of the postpartum psychosis was eight days postpartum (IQR 5-14)(Table 1).

Of all 67 women, 66 women achieved full remission with a median duration of episode of 40 days (IQR 26-65) (Table 1). Remission was defined as the absence of psychotic, manic or severe depressive symptoms for at least one week. The majority of our patients had a Dutch ethnicity (88.1%), was married or living with a partner (98.5%) and had no psychiatric history (74.6%) (table 1).

Table 1. Demographic, clinical, and phenomenological characteristics of women with first onset postpartum psychosis in the total sample (PP-All) and stratified by outcome: relapse (PP-Relapse) versus sustained remission (PP-Sustained).

	PP-All (n=67)		PP-Sustained* (n=41)		PP-Relapse (n=26)		PP-Sustained vs. PP-Relapse	
General demographics	N	%	N	%	N	%	Significance (MW/FET)	RR (95% CI)
Dutch ethnicity	59	88.1	38	92.7	21	80.8	0.245	0.58 (0.23-1.45)
Education beyond high school	38	58.2	22	53.7	16	61.5	0.526	1.13 (0.78-1.65)
Married or living with partner	65	98.5	40	97.6	25	96.2	0.999	0.81 (0.20-3.29)
Primiparity	54	80.6	35	85.4	19	73.1	0.215	0.71 (0.38-1.32)
Mean age	31.7	SD 4.7	31.7	SD 4.7	31.6	SD 4.6	0.770	0.96 (0.64-1.39)*
Psychiatric history								
No psychiatric history	50	74.6	31	75.6	19	73.1	0.816	0.95 (0.60-1.49)
Previous postpartum psychosis	7	10.4	3	7.3	4	15.4	0.417	1.48 (0.62-3.55)
Previous depression or anxiety	10	15.0	7	17.1	3	11.5	0.729	0.85 (0.54-1.35)
Psychiatric family history (1st degree)								
Bipolar disorder	6	9.0	4	9.8	2	7.7	0.999	0.79 (0.16-4.00)
PP episodes	11	16.4	6	14.6	5	19.2	0.517	1.42 (0.49-4.17)
Phenomenology - Affective psychosis								
-With manic-psychotic features	42	62.7	25	61.0	17	65.4	0.799	1.08 (0.73-1.58)
-Mixed features	11	16.4	6	14.6	5	19.2	0.738	1.15 (0.64-2.04)
-Depressed-Psychotic features	8	11.9	7	17.1	1	3.8	0.138	0.66 (0.47-0.93)
Non-affective psychosis	6	9.0	3	7.3	3	11.5	0.670	1.25 (0.55-2.84)
Ilness episode	Median	IQR	Median	IQR	Median	IQR		
Onset (days postpartum)	8	5-14	7	6-12	9	4-16	0.626	1.10 (0.75-1.62)*
Duration first episode (days)	40	26-65	42	18-56	40	28-73	0.686	0.92 (0.63-1.35)*

*Including four women with anxiety disorders during follow-up
RR calculated on the dichotomized variable (median split)

Four years follow-up - Relapse

Twenty-six women (38.8%) experienced a relapse during the four years follow-up (Figure 1). The median moment of relapse after full remission was 6.6 months (IQR 2.0-12.6). Moreover, 23 of the 26 (88.5%) women relapsed within 18 months after remission. The median duration from remission until medication stop was 6.9 months (IQR 4.8-11.6).

Ten women experienced a single relapse episode. Accordingly, sixteen women had a subsequent relapse-remitting disease course with more than one relapse during follow-up. Seven women were re-admitted during the follow-up period (Supplementary table 2).

Of the 26 women with a relapse, 12 women experienced a depressive episode, eight women a manic episode and six women a non-affective psychotic episode (Supplementary table 2).
Twelve women experienced a (first) depressive relapse (Figure 1 and Supplementary table 2). The median onset was 2.0 months (IQR 1.1-5.1) after remission and the median duration of this depressive episode was 2.0 months (IQR 1.1-3.2). Of these 12 women with an initial depressive relapse, five women experienced subsequent manic relapses after the initial depressive relapse. Three women were admitted for these episodes.
Eight women experienced a first manic relapse during the follow-up period (Figure 1 and Supplementary table 2). The median onset was 9.1 months (IQR 7.2-19.6) after remission and the median duration of the manic episode was 1.0 month (IQR 0.5-2.7 (Figure 2). In two women relapse could have been caused by somatic comorbidity (vitamin B12 deficiency and use of steroids).
Six women had a relapse with non-affective psychotic symptoms (Figure 1 and Supplementary table 2). The median onset was 9.5 months (IQR 3.6-15.4) after remission and the median duration of the psychotic episode was 2.5 months (IQR 0.3-10.2). None of the patients were re-admitted during follow-up. Four (4/6, 66.7%) women with a non-affective psychotic relapse experienced subsequent psychotic (n=3) or depressive (n=1) episodes during the four years follow-up.

In total 41 women (61.2%) did not experience severe mood or psychotic symptoms during the four years follow-up period of which 37 women did not experience any psychiatric symptoms. Four women (5.9%) suffered a transient episode of anxiety symptoms, (three women fulfilled criteria for a panic disorder (4.5%), now in remission and one woman (1.4%) had an anxiety disorder caused by hypothyroidism.

Potential predictors of relapse

In table 1 we compared women in sustained remission with women with a relapse after a first-onset postpartum psychosis. We did not find significant differences in ethnicity, education level, marital status, parity, gravidity, age, onset, psychiatric history, psychiatric family history, duration of postpartum psychotic episode, psychiatric history and phenomenology of postpartum psychosis.

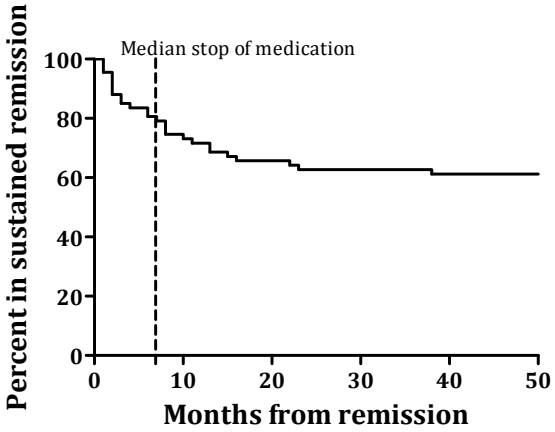

Figure 2. Kaplan-Meier Survival curves of the relapse rates four years after postpartum psychosis in first-onset postpartum psychosis.

Medication use

During admission, three women were treated with only benzodiazepines, and one woman remitted without medication. Benzodiazepines were tapered off in all four women and these four women remained stable during follow-up.

Fourteen women were treated with the combination of benzodiazepines and antipsychotics during the acute episode. These women tapered off benzodiazepines after remission and they were advised to use antipsychotic as maintenance therapy and encouraged to gradually taper off antipsychotics when they were stable at least 6 months after remission. Of these 14 patients, 3 patients did not taper off antipsychotics. Despite this long-term antipsychotic maintenance therapy, two of these three patients relapsed. Eleven patients tapered off antipsychotic monotherapy (median 4 months after full remission). Of these eleven, six patients relapsed and five patients remained stable without medication.

The majority of patients (N=49) were treated with a combination of benzodiazepines, antipsychotics and lithium during the acute phase. Benzodiazepines and antipsychotics were tapered off after the acute phase and women were maintained on lithium monotherapy and encouraged to taper this off when they were stable for at least 6 months after remission.

Ten out of 49 patients did not taper off lithium. Of these 10, four patients relapsed, despite lithium maintenance treatment. In total 39 patients tapered of lithium (median 7 months after remission). Of these 39 patients, 14 patients relapsed and 25

patients remained stable without medication. Taken together, in 67 women with a PP, 54 women (80.6%) tapered of medication, median 6.9 months after full remission. Of these 54 women, 34 women remained stable (63%), Accordingly, 20 women (20/54, 37%) experienced a relapse, 12 of these women relapsed during of directly after (within 2 weeks) medication discontinuation. The other 8 women relapsed median 6 months after medication discontinuation (supplementary table 1).
Together, in total thirteen women did not taper off their maintenance treatment (10 lithium, 3 antipsychotics). Of these thirteen, seven women were in sustained remission and six women experienced a relapse despite maintenance treatment with medication (lithium four women; antipsychotics two women). We compared the characteristics of table 1 of women who tapered off medication and not tapered off medication and we could not find any significant differences (not reported).

At the four years follow-up visit, 19 of the 26 women who had experienced a relapse during follow-up were still using medication (73.1%). Seven women were using lithium monotherapy, five women used lithium and an antipsychotic, one women used lithium and lamotrigine. Three women used antipsychotic monotherapy and one woman an antipsychotics with an antidepressant. One woman used a moodstabiliser and an antidepressant and one women used depakine. Seven women with a relapse during follow-up were treated for this episode with medication but had successfully tapered off this medication after full remission of their relapsed episode, median 12.6 (IQR 3.0-38.8) months after remission.

New pregnancies during follow-up

Sixteen women (16/67, 23.9%) gave birth to another child during the follow-up period. In addition, two women (2/67, 3.0%) experienced a miscarriage and two women (2/67, 3.0%) were pregnant during our follow-up visit. All women were included in our postpartum psychosis prevention program [36]. All women remained stable during the first three months postpartum.

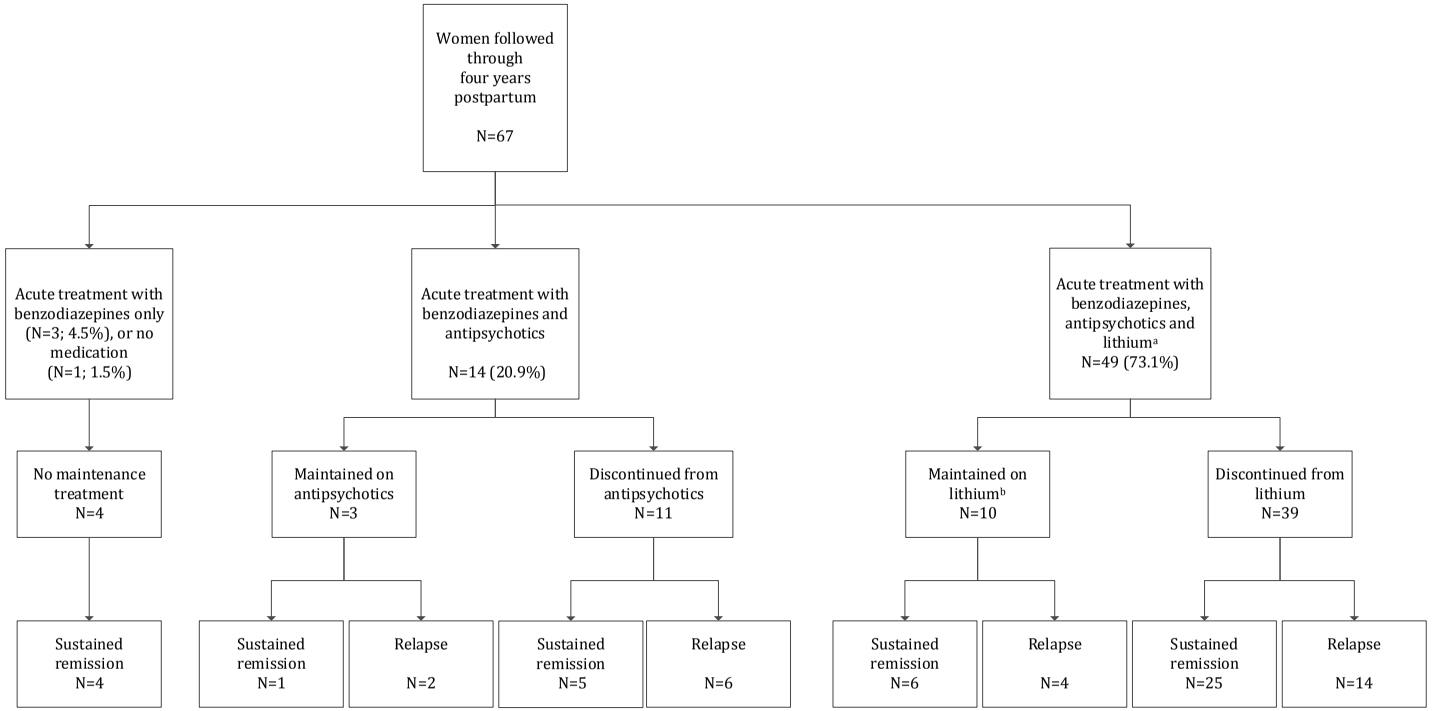

Figure 3. Treatment during four years follow-up related to relapse.

[a]Declined antipsychotics, N=1
[b]Maintaines on both lithium and antipsychotics, N=3

DISCUSSION

In this prospective study in 67 women with a first-onset postpartum psychosis we investigated the prognosis on longer term and the use of medication. We found that for 41 (61.2%) of the women first onset postpartum psychosis was a single event. Consequently, 26 women (38.8%)
relapsed and more than half of the women relapsed more than once during follow-up. Ten percent of the women were re-admitted during the follow-up period. Of the 38.8% of the women who experienced a relapse, the majority had a depression, which occurred earlier than a manic or psychotic relapse. Almost all relapses were in the first 18 months after remission (23 of 26), in conclusion, this seems to be the critical period for relapse.
Consistent with previous studies, we found that women who have an episode of postpartum psychosis have a good prognosis for recovery in the short term but remain at high risk of developing further episodes of affective disorder, both postpartum and at other times [37-39]
Like previous studies we found a majority of relapses within the affective spectrum (97.0%) [11-20]. The relapse rate of around 39% in our prospective study is lower than previously described in retrospective studies (relapse rates of 56% to 87%) [11-20, 40]. These differences could be due to substantial differences in our design compared to previous studies. Our study used a prospective design and almost all previous studies (9/10) used a retrospective method. The previous studies also had a longer follow-up period, ranging between four and 26 years [11, 14-16, 19, 20]. Although it is likely that a longer follow-up will lead to higher relapse percentages; we observed in our data that cumulative incidence of recurrent episodes is low after 2 years postpartum, (three women relapsed, 3/67, 4%). Further, in our study we used very stringent inclusion criteria: we only included women with a first onset of psychosis or mania within six weeks after delivery and without non-puerperal manic or psychotic episodes. Consequently, in our study we have exclusively focussed on early onset cases; the median onset of severe psychopathology was median eight days after delivery. These inclusion criteria were based on previous epidemiologic studies showing a specific peak of first onset severe psychopathology within the first 6 weeks after childbirth [4]. Previous studies included women up to 12 months postpartum and they screened for a history of psychopathology in retrospect and therefore these populations might be more heterogeneous. Another explanation for the difference in relapses rate between this study and previous studies could be the influence of our specialised treatment and prevention programs. We used a standardized and highly effective treatment algorithm consisting of benzodiazepines,

antipsychotics and lithium [9]. We advised to slowly taper of medication after being six months in remission and to do this under strict control of a clinician. Moreover, after a subsequent pregnancy all women were enrolled in a postpartum psychosis prevention program [36], which indeed prevented new episodes in all women (n=16). A next reason for the lower relapse rate in this study compared to previous studies could be a selection bias of our study population. Our cohort has a high likelihood of being ethnically Dutch, having postsecondary education and being married or living with a partner, compared to the catchment area. This is alarming because our findings suggest that there is a difference between psychiatric service utilization between native and immigrant residents in the Rotterdam area. For this study, the relatively stable educational, relational and work situation of our patients before postpartum psychosis, might have influenced their relapse rate by for example a higher therapy adherence which may influence relapse rate. In previous work on bipolar disorder it is found that the relapse rate is lower in "social stable patients" [41]. The last difference with previous studies is our low lost-to-follow-up percentage. We have a follow-up percentage of 94%, other studies have a follow-up percentage ranging from 78% until 87% [11-20].

Predictors of relapse

Previous studies identified risk factors for a more unfavorable disease course after first onset PP: being single or unmarried [22], older age [17], a longer episode of the postpartum psychosis [42] and a personal or family history of postpartum psychosis or bipolar disorder [5, 17, 43]. In contrast, we could not identify predictors for relapse, which might be a power problem.

Diagnosis of postpartum psychosis and the relation with bipolar disorder

In this study we found a 38.8% relapse rate. Only 2 patients had only non-affective episodes, both during their initial postpartum episode and during relapse. Our findings add to evidence that women with first-onset PP have one of two disease courses: PP limited to the postpartum period or a more chronic bipolar spectrum disorder.

Based on these data and other studies there are many arguments to give these women with first onset postpartum psychosis including mania and psychotic depression an official status as a discrete gender-specific diagnostic entity. This can aid in reducing stigma as women will not immediately be diagnosed with a life-long illness such as bipolar affective disorder, but instead be diagnosed with "a postpartum only condition".

Implications for treatment

Our findings have consequences for treatment recommendations. Specifically, if not all psychotic or manic episodes postpartum convert to bipolar disorder during lifetime, use of long-term mood stabilizers is not required for all women who experience postpartum psychosis. This would also suggest that psychotropic medications could be slowly withdrawn after the acute symptoms have come under control. This is particularly important during next pregnancies. If women have successfully tapered off medication without relapse, women with only PP are not at elevated risk of psychiatric episodes during pregnancy, offering an important clinical advantage by avoiding in utero foetal exposure to prophylactic medication [36].

Limitations of this study

The most important limitation of our study is the sample size. Another limitation of the present study is the naturalistic design, which does not allow us to draw causal conclusions about the associations. This naturalistic design allows for the possibility that some of the outcomes were influenced by patients' preferences. Lastly, our cohort was recruited from a single, inpatient site, which may limit the ability to generalize our findings.

In conclusion, our study demonstrates a lower relapse rate (38.8%) than earlier found after four years follow-up after a first-onset postpartum psychosis. Almost all relapses occurred within 18 months postpartum and the majority of relapses were related to tapering off or stopping medication use. Most women experienced a depressive relapse that occurred earlier after remission than manic or psychotic relapses. The majority of the women (61.2%) was medication free after four years follow-up. We argue that women in sustained remission after a PP could try to taper off medication. This should be done under meticulous supervision of a psychiatrist, because it is a moment with a high vulnerability for relapse.

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Supplementary table 1. Characteristics of women a first onset postpartum psychosis who experienced a relapse during a four years follow-up period.

Age	Phenomenology	History	Initial treatment	Time to tapering off	Time from remission to relapse	Morbidity 1st Relapse	Medication use relapse	More relapses?	Diagnosis after 4 years	Medication at follow-up visit	Potential trigger of relapse
26	Manic-psychotic	-	AP	3	3	Depression	During tapering off	-	Bipolar spectrum disorder	-	X
29	Manic-psychotic	-	AP + Li	1	1	Depression	During tapering off	Panic disorder without agorarphobia	Bipolar spectrum disorder	Li + MS	X
35	Manic-psychotic	-	AP	2	2	Depression	During tapering off	-	Bipolar spectrum disorder	AP	Work stress
32	Manic-psychotic	-	AP + Li	5	6	Depression	2 Weeks after stopping	-	Bipolar spectrum disorder	Li	Graves and deceased baby
30	Manic-psychotic	-	AP + Li	1	1	Depression followed by mania[a]	2 Weeks after stopping	(Hypo)mania 2x	Bipolar I disorder	Li + AP	X
27	Manic-psychotic	Other	AP + Li	-	2	Depression	During medication use	(Hypo)mania 2x, Depression 2x	Bipolar I disorder	MS + AD	X
41	Manic-psychotic	-	AP	-	2	Depression	During medication use	Mania	Bipolar I disorder	-	X
29	Manic-psychotic	-	AP + Li	3	38	Depression	3 Months after stopping	-	Bipolar spectrum disorder	Li + AP	Giving birth
27	Mixed	Anxiety	AP + Li	-	1	Depression	During medication use	(Hypo)mania 6x	Bipolar I disorder	Li+ AP	X

Supplementary table 1. Continued

Age	Phenomenology	History	Initial treatment	Time to tapering off	Time from remission to relapse	Morbidity 1st Relapse	Medication use relapse	More relapses?	Diagnosis after 4 years	Medication at follow-up visit	Potential trigger of relapse
38	Mixed	-	AP	4	3	Depression	During tapering off	-	Bipolar spectrum disorder	-	X
33	Only psychotic	-	AP	-	2	Depression followed by mania[a]	Directly after stopping	Mania 2x	Schizoaffective disorder	MS	Forgotten medication
32	Psychotic depression	Postpartum	AP + Li	8	13	Psychotic depression[a]	During tapering off	-	Bipolar spectrum disorder	-	Abortion
32	Manic-psychotic	Postpartum	AP + Li	2	8	Mania	6 Months after stopping	(hypo) Mania	Bipolar 1 disorder	-	X
26	Mixed	Anxiety	AP + Li	10	13	Mania[a]	2 Months after stopping	-	Bipolar I disorder	Li	X
24	Mixed	-	AP + Li	-	22	Steroid induced mania[a]	Long period after stopping	(Hypo)mania	Bipolar I disorder	Li	Steroid use.
33	Manic-psychotic	-	AP + Li	-	8	Mania[a]	During medication use	Mania[a] + depression[a]	Bipolar I disorder	Li + benzo	Work stress
29	Manic-psychotic	-	AP + Li	-	23	Mania	Long period after stopping	-	Bipolar 1 disorder	Li	Vit B12 deficience
33	Manic-psychotic	-	AP	-	7	Mania + psychosis	During medication use	Depression	Bipolar I disorder	AP + AD	Social stress

Supplementary table 1. Continued

Age	Phenomenology	History	Initial treatment	Time to tapering off	Time from remission to relapse	Morbidity 1st Relapse	Medication use relapse	More relapses?	Diagnosis after 4 years	Medication at follow-up visit	Potential trigger of relapse
31	Manic-psychotic	Anxiety	AP + Li	5	10	Manic- + psychosis	5 Months after stop stopping	Year later medication stop: Mania	Bipolar 1 disorder	AP	Dead of friend
28	Manic-psychotic	Postpartum	AP + Li	5	6	Mixed[a]	During tapering off	Depression [a] 3x Mania[a] 3x	Bipolar I disorder	Li + AP	Deceased baby
39	Manic-psychotic	Postpartum	AP + Li	-	4	Non-affective psychosis	During medication use	-	Bipolar spectrum disorder	-	After surgery
21	Manic-psychotic	-	AP + Li	2	2	Non-affective psychosis	Directly after stopping	-	Schizoaffective	-	X
34	Mixed	-	AP	7	15	Non-affective psychosis	8 Months after stopping	Non-affective psychosis 2x, Depression	Schizoaffective disorder	Li + AP	X
35	Only psychotic	-	AP + Li	8	8	Non-affective psychosis	During tapering off	Non-affective psychosis 2x Specific phobia	Psychosis NOS	Li + AP	X
36	Only psychotic	-	AP	7	16	Non-affective psychosis	During tapering off	Non-affective psychosis	Psychosis NOS	AP	Divorce and work stress
30	Manic-psychotic	-	AP + Li	6	11	Non-affective psychosis	4 Months after stopping	Non-affective psychosis 2x	Schizoaffective	Li	After patients day

Supplementary table 1. Continued

Age	Phenomenology	History	Initial treatment	Time to tapering off	Time from remission to relapse	Morbidity 1st Relapse	Medication use relapse	More relapses?	Diagnosis after 4 years	Medication at follow-up visit	Potential trigger of relapse
37	Mixed	Anorexia	-	25	2	Anxiety	-	-	Panic disorder with agoraphobia	-	X
34	Manic-psychotic	Anxiety	AP + Li	7	39	Anxiety	During tapering off	-	Panic disorder without agorophobia	-	Finishing thesis
35	Mixed	-	AP + Li	6	1	Anxiety	-	-	Panic disorder with agoraphobia	-	X
27	Manic-psychotic	-	AP + Li	6	1	Anxiety	Not related to medication changes	-	Anxiety disorder by somatic illness	-	Hashimimoto hypothyroidism

[a] Required inpatient psychiatric admission.
AP = antipsychotic
AD = antidepressant
Li = lithium
MS = moodstabiliser (not lithium)
Schizoaffective: Schizoaffective disorder, bipolar type
Time to begin tapering off and time to relapse: From remission

Chapter 5

Immune system dysregulation in first-onset postpartum psychosis

V. Bergink
K.M. Burgerhout
K. Weigelt
V.J. Pop
H. De Wit
R.C. Drexhage
S.A. Kushner
H.A. Drexhage

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ABSTRACT

Objective: Accumulating evidence suggests that dysregulation of the immune system represents an important vulnerability factor for mood disorders. Postpartum psychosis (PP) is a severe mood disorder occurring within 4 weeks after delivery, a period of heightened immune responsiveness and an altered endocrine set point. Therefore, the aim of this study was to examine immune activation in patients with first-onset PP at the level of monocytes, T-cells, and serum cytokines/chemokines.

Methods: We included 63 women admitted with first-onset PP. Control groups included healthy postpartum (n = 56) and non-postpartum (n = 136) women. A quantitative-polymerase chain reaction monocyte gene expression analysis was performed with 43 genes previously identified as abnormally regulated in non-postpartum mood disorder patients including the isoforms of the glucocorticoid receptor. Peripheral blood mononuclear cells percentages were measured by fluorescence-activated cell sorter analysis, whereas serum cytokines/chemokines were determined with a cytometric bead array.

Results: In healthy women, postpartum T-cell levels were significantly elevated compared with non-postpartum. Patients with PP failed to show the normal postpartum T-cell elevation. In contrast, these patients showed a significant elevation of monocyte levels and a significant upregulation of several immune-related monocyte genes compared with control subjects postpartum and non-postpartum. Furthermore, the glucocorticoid receptor a/b gene expression ratio was decreased in monocytes of PP patients, strongly correlating with their immune activation.

Conclusion: This study demonstrates a robust dysregulation of the immuno-neuro-endocrine set point in PP, with a notable over- activation of the monocyte/macrophage arm of the immune system.

INTRODUCTION

Postpartum psychosis is an acute psychiatric emergency and considered the most severe of the postpartum mood disorders. The acute onset of mood symptoms and psychosis occurs within the first four weeks postpartum [1]. Remarkably, the majority of patients admitted with postpartum psychosis have no prior diagnosis of a psychiatric disorder [2]. While some patients experience symptoms only during the postpartum period, postpartum psychosis will often in retrospect be appreciated as the incipient presentation of bipolar disorder [3].

Thus far, neurobiological research in postpartum psychosis has been principally focused on neurosteroid pathways because of the dramatic changes occurring in hormone levels in the early postpartum period. Further, sleep deprivation has been described as a possible causal trigger for postpartum psychosis [4]. However, the precise underlying mechanisms have remained elusive [5-7].
Although little is known about the biological mechanism underlying postpartum psychosis, there is accumulating evidence that an abnormal activation of the immune system might be central to the pathogenesis of bipolar disorder [8]. This activation is reflected by an elevation of serum cytokines and chemokines [9-14], an activation of circulating monocytes demonstrated through profiling of inflammatory gene expression and activation of the T-cell system [15, 16]. Given the overlapping clinical characteristics with bipolar disorder, postpartum psychosis might also be characterized by immune activation, especially because the postpartum period is considered as a period of elevated immune responsiveness. During pregnancy, changes in the maternal immune system are necessary to induce tolerance of the mother towards the histo-incompatible fetus. However, following delivery the relative immunologically-suppressed state of pregnancy shows a rebound, during which many immune diseases are well-described to become clinically exacerbated or have their initial onset [17-24].

Here, we perform a detailed and comprehensive analysis of immune activation in a cohort of patients with first-onset postpartum psychosis and no prior psychiatric history. Further, we included both healthy postpartum and non-postpartum women as control groups, given that the healthy postpartum period is a period of immune activation. We have investigated inflammatory gene expression in circulating monocytes, focusing on those genes previously found to be significantly up-regulated in bipolar disorder, schizophrenia, and major depression [15, 16]. We also included genes related to autoimmune thyroid disease and glucocorticoid receptor

signaling, to specifically evaluate the hypothesis that postpartum psychosis is the psychopathological endpoint of a dysregulated neuro-immuno-endocrine axis [6, 25-27]. In addition to monocyte gene expression, we also determined the percentages of circulating monocytes, lymphocytes, and their cellular subsets using detailed FACS analysis. Lastly, we determined the levels of monocyte and T-cell related cytokines/chemokines in serum.

METHODS

Participants

This study protocol was approved by the institutional review board of the Erasmus Medical Center, Rotterdam. After receiving a complete description of the study, all patients and their authorized legal representatives provided written informed consent. Sixty-three (n=63) patients with first-onset postpartum psychosis (PP) were recruited from the Mother-Baby Inpatient Unit of the Department of Psychiatry of the Erasmus University Medical Centre in Rotterdam, the Netherlands between August 2005 and May 2012. All patients were diagnosed according to DSM-IV-TR [28] using the Structural Clinical Interview for Disease (SCID – 1/P research version). The clinical characteristics of this cohort have been described in detail [29].

Briefly, we have included patients with any of the following diagnoses, including the specifier "onset postpartum": depressive disorder with psychotic features, mania with psychotic features, mixed episode with psychotic features, or brief psychotic disorder. Importantly, the specifier "onset postpartum" requires that the onset of symptoms must occur within 4 weeks postpartum. Patients with a history of prior psychotic episodes and/or bipolar disorder were excluded. Physical examination and routine laboratory screening were performed at the time of study enrollment to confirm the absence of infection. All patients were in an acute disease state at moment of blood withdrawal.

The postpartum control cohort consisted of 56 healthy postpartum women recruited between 2008-2012 through the Department of Obstetrics & Gynaecology (Erasmus MC, Rotterdam), with an EPDS score <10 at the time of 4 week postpartum blood sampling. One hundred thirty-six (n=136) healthy age-matched non-postpartum women were also included. Inclusion criteria for both postpartum and non-postpartum controls included the absence of any medical, neurologic, psychiatric, or autoimmune disorders, as well as having no current or recent clinical evidence of acute infection.

Blood collection and preparation

Blood was collected in clotting tubes for serum preparation (stored at -80°C) and in sodium-heparin tubes for immune cell preparation. From the heparinized blood, peripheral blood mononuclear cell (PBMC) suspensions were prepared by low-density gradient centrifugation, as described previously in detail [30], within 8 hours to avoid activation of the monocytes (erythrophagy). PBMCs were frozen in 10% dimethylsulfoxide and stored in liquid nitrogen. This enabled us to test patient and control immune cells in the same series of experiments later.

Gene expression of monocytes

Isolation of monocytes, RNA isolation and RT-qPCR. CD14 positive monocytes were isolated from frozen PBMCs by magnetic cell sorting system (Miltenyi Biotec). The purity of monocytes was >95% (determined by morphological screening after Trypan Blue staining and FACS). RNA was isolated from purified monocytes using RNAeasy columns according to the manufacturer's instructions (Qiagen, USA) [31].

One μg RNA was reversed-transcribed using High Capacity cDNA Kit (Applied Biosystems, Nieuwerkerk a/d Ijssel, The Netherlands) for 120 min at 37 C, while RT- qPCR was performed using a preloaded Taqman Low Density Array (TILDA) for real-time amplification and relative mRNA qualification (Applied Biosystems, Foster City, CA). A TaqMan Low Density Array is an Array of 384 reaction wells for two-step RT-qPCR. Each cDNA sample (40 μL) was added to 50 μL 2x TaqMan universal PCR master mix (Applied Biosystems) and 10 μLRNase free water was added to get an total volume of 100 μL. After gentle mixing and centrifugation, the sample was transferred on a TLDA card. The card was sealed and PCR amplification performed using an Applied Biosystems Prism 7900HT sequence detection system (equipped with a TaqMan low density array upgrade). Thermal cycler conditions were: 2 min at 50 C, 10 min at 94.5 C, 30 s at 97 C, and 1 min at 59.7 C for 40 cycles. Expression values were calculated using the comparative threshold cycle (CT) method [32].

For the monocyte gene expression analysis, we included in a first TLDA card run 23 patients and 17 matched postpartum controls, in a second TLDA card run 25 patients versus 29 matched postpartum controls. Together, we have analyzed monocyte gene expression of 48 PP patients and 46 controls postpartum (CP), compared to all healthy age matched female healthy non-pregnant/ non-postpartum controls samples (n=136) collected over the last years.

Percentages of Peripheral Blood Mononuclear Cells (PBMC's)

We determined the percentages of various subgroups of circulating Peripheral Blood Mononuclear Cells (PBMC's) in 63 women with PP, 56 CP, and 59 HC using fluorescence-activated cell sorting (FACS) analysis, as described previously [33, 34]. Specifically, we determined the percentages of Monocytes, B-cells, Natural Killer cells (CD3-CD56+ NK cells), total T-cells (CD3+ T-cells), cytotoxic T-cells (CD3+CD8+ T-cells) and T-helper cells (CD3+CD4+ T-cells). The latter group was subdivided in the effector T helper cells,Thelper-1 (Th1), Thelper-2 (Th2) and Thelper-17 (Th17), and in T-regulatory cells. The effector subgroups are identifiable by the panel of cytokines they secrete. T-helper 1 cells (Th1) and T-helper 17 cells (Th17) are involved in the activation of macrophages and secrete IFN-γ and IL-17, respectively. T-helper 2 cells (Th2) cells secrete IL-4 and IL-5, involved in the activation of B-cells. The regulator subgroup is formed by the natural T-regulatory cells, which dampen the activity of Th1, Th2, and Th17 cells.

In a membrane-bound approach and strategy (8 colour FACS) to identify Monocytes, B-cells, NK cells, total T-cells, cytotoxic T-cells and T-helper cells membrane-staining was done on thawed non-cultured PBMC with anti-CD3 PerCP-Cy5.5, anti-CD4 Pacific Blue, anti-CD8 PC7 (Beckman Coulter, California, USA), anti-CD19 APC, anti-CD45 Pacific Orange (Invitrogen, California, USA) and anti-CD56 PE (Dako, Denmark). The gating strategy enabled us to enumerate monocytes, lymphocytes, NK cells, T-cells, B-cells, CD4+ and CD8+ T-cell (Supplementary figure 1A: gating strategy and the dot plots of the staining).
In an intracellular approach and strategy to identify TH1, Th2, Th17 and natural T regulatory cells intracellular staining was performed and as hallmark intracellular cytokines we used: IFN-γ, IL-4 and IL-17A. To enable the enumeration of regulatory T-cells we intracellularly stained for FoxP3. Membrane-staining was done for CD3, CD4 and CD25. This enabled us to assign the cytokine staining to the enigmatic Th1, Th2 and Th17 cells and CD4+CD25highFoxP3+ T-cell population in the total population of CD4+ cells. For this approach PBMCs were suspended in complete culture medium. Cell suspensions were then stimulated with PMA (Sigma Aldrich, Missouri, USA), ionomycin (Sigma Aldrich, Missouri, USA) in the presence of Golgistop (Becton Dickinson, New Jersey, USA) for 4 hours in 37 C under a 5% CO2 environment. Cells were harvested; membrane staining was done with anti-CD3 APC-H7, anti-CD4 PerCP-Cy5.5, anti-CD25 APC and anti-CD45RO FITC (Dako, Denmark) according to standard protocol. Following membrane staining, the cells were fixed and permeabilized according to the manufacturers instructions (eBioscience, California, USA) and then stained with anti-FoxP3 PE, anti-IL-4 PE-Cy7 (eBioscience, California, USA), anti-

IFN-γ Horizon™ V500 and anti-IL-17A Brilliant Violet 421™ (BioLegend, California, USA). Stained cell samples were analyzed by eight-colour flow cytometry (LSR II, BD Biosciences, California, USA) as described previously and analyzed using FlowJo (Tree Star Inc. Ashland, Oregon, USA) research software (Supplementary figure 1B: gating strategy, dot plots of the staining and the definition of the cell populations).

Serum cytokine determination

Multiple serum cytokines were measured using an array approach: the Cytometric Bead Array kit (CBA, BenderMedSystems, California, USA) according to the manufacturer's protocol. Samples were analyzed in a FACS flow cytometer (BD Biosciences, California, USA) with the FlowCytomix Pro 2.3 Software (BenderMedSystems, California, USA). Using subjects enrolled in the study exclusively within the previous two years, we determined serum levels of the monocyte/macrophage cytokines CCL2, IL-1β, IL-6, the pro-inflammatory T-cell cytokine IL-22, and the anti-inflammatory cytokine IL-10.

Statistical Analysis

Statistical analysis was done with the SPSS software package (20.0). For sample characteristics, categorical data were evaluated using Fisher's exact test and continuous variables using a two-sample t-test. Continuous variables are expressed as the mean ± standard error, unless otherwise indicated. The Mann-Whitney U test was used to compare levels of nonparametric parameters. The Holm–Bonferroni correction was used to control for multiple comparisons. Correlations were determined via Spearman rank correlation coefficients.

RESULTS

Sample Characteristics

There were no significant differences in age, weight, gravidity, vacuum extraction, and mean time of blood withdrawal between women with postpartum psychosis (PP) and healthy postpartum women (CP) (Table 1). Significantly more healthy postpartum women were multiparous and had their delivery by caeserian section, compared to women with postpartum psychosis. At the time of blood sampling, the majority of PP patients were being treated with benzodiazepines (51 patients; 6.5 ±1.5 days) and/or antipsychotics (39 patients; 6.8 ± 1.8 days). CP women were more likely to be breastfeeding at the time of blood withdrawal ($P < 0.01$), given that all women with postpartum psychosis were advised to stop breastfeeding upon admission.

Table 1. General and obstetric characteristics of patients with first onset postpartum psychosis and controls postpartum.

	Healthy Controls N=136	Controls postpartum N=56		Postpartum Psychosis N=63		Difference between groups
		Mean	S.E.M	Mean	S.E.M	P
Age (years)	30.3 (0.7)	32.8	(0.5)	32.0	(0.6)	0.07
Weight		73.3	(2.5)	72.2	(1.8)	0.73
Bloodwithdrawal, days postpartum		29.3	(2.0)	30.9	(3.5)	0.68
		N	%	N	%	
Primiparity		34/56	60.7	52/63	82.5	0.01
Primigravidity		32/56	57.1	46/63	73.0	0.08
Caeserian section		14/56	25.0	6/63	9.5	0.03
Vacuum extraction		7/56	9.3	6/63	9.5	0.77
Breastfeeding at time of bloodwithdrawal		37/56	66.1	3/63	4.8	< 0.01

Activation state of monocytes

We included a group of 48 consecutive PP women, 46 CP women from the same hospital, and 136 HC women. We determined the monocyte gene expression of 43 genes, including 25 genes examined previously in patients with bipolar disorder, 5 genes identified as up-regulated in schizophrenia [16], 6 genes identified in studies of major depressive disorder [35], 4 interferon-inducible genes [36], 1 gene from studies of autoimmune thyroid disorder [37], as well as the transcripts for both the active and inactive isoforms of the glucocorticoid receptor (GR).

We performed a cluster analysis for monocyte gene expression in postpartum psychosis (Figure 1). Two main clusters were identified – Cluster 1 and 2. Cluster 1 genes included most of the wellknown pro-inflammatory mediators (IL1A, IL1B, IL6, PTX3, TNF, and PTGS2). Cluster 2 genes included many chemotaxis, motility, metabolic and cell adhesion functions (CCL2, CCL7, EMP-1, DHRS3, CD9 and FABP5). Notably, the gene clusters extensively overlapped with the previously identified monocyte gene expression clusters of bipolar patients [15, 16].

Table 2. RT-qPCR analysis of monocytes in two cohorts of patients with first onset postpartum psychosis (PP) compared to healthy controls (HC) and healthy controls postpartum (CP).

	Healthy Controls	Controls Postpartum		Postpartum Psychosis		
	N=136	N=46	P-value CP vs HC	N=48	P-value PP vs HC	P-value PP vs CP
Cluster 1	**Median FC**	**Median FC**		**Median FC**		
IL1A	0,007	0,003	0,030	0,005	0,966	0,052
IL1B	6,615	7,958	0,841	9,298	0,167	0,300
CCL20	0,026	0,023	0,837	0,046	0,013	0,041
IL6	0,010	0,021	0,007	0,036	0,000	0,253
PTX3	0,531	0,569	0,247	0,794	0,001	0,012
IRAK2	0,136	0,097	0,009	0,121	0,858	0,051
TNF	1,535	1,332	0,464	1,232	0,390	0,472
BCL2A1	7,844	8,764	0,674	11,51	0,001	0,003
CXCL2	1,003	1,150	0,111	2,733	0,000	0,005
PTGS2	1,377	1,769	0,044	2,363	0,000	0,079
ADM	0,812	0,816	0,405	1,505	0,000	0,000
BTG3	0,141	0,137	0,979	0,214	0,000	0,001
SERPINB2	0,136	0,151	0,544	0,204	0,000	0,016
PDE4B	2,149	2,490	0,638	4,138	0,002	0,005
TNFAIP3	4,256	2,540	0,000	2,468	0,005	0,486
ATF3	1,513	1,822	0,061	2,015	0,008	0,392
CDC42	0,648	0,654	0,354	0,987	0,000	0,005
MAFF	0,247	0,346	0,060	0,578	0,000	0,002
DUSP2	1,241	1,606	0,232	2,168	0,000	0,022
Cluster 2						
CCL7	0,007	0,005	0,026	0,018	0,050	0,000
FCAR	2,922	3,716	0,026	4,884	0,000	0,003
PTPN7	0,117	0,143	0,008	0,168	0,000	0,116
THBD	2,171	1,750	0,014	2,774	0,028	0,000
RGC32	1,778	1,250	0,000	1,383	0,000	0,204
STX1A	0,007	0,007	0,801	0,012	0,002	0,003
EMP1	0,377	0,294	0,289	0,560	0,004	0,000
NAB2	0,175	0,143	0,045	0,314	0,011	0,000
MAPK6	2,075	1,625	0,006	2,358	0,347	0,001
DHRS3	0,048	0,054	0,207	0,054	0,279	0,994
MXD1	4,324	3,833	0,230	5,842	0,000	0,000
IL1R1	0,122	0,085	0,006	0,159	0,047	0,000
CCL2	0,193	0,147	0,636	0,268	0,322	0,253
EGR3	2,577	2,730	0,161	4,762	0,000	0,078
CD9	0,757	0,982	0,062	0,944	0,050	0,946
FABP5	4,081	3,576	0,025	3,804	0,124	0,581

Table 2. Continued

	Healthy Controls	Controls Postpartum		Postpartum Psychosis		
	N=136	N=46	P-value CP vs HC	N=48	P-value PP vs HC	P-value PP vs CP
Cluster 1	Median FC	Median FC		Median FC		
Interferon cluster						
IFI44	1,407	1,737	0,105	1,683	0,158	0,832
IFI44L	1,175	1,335	0,318	1,353	0,443	0,892
IFIT3	0,417	0,472	0,124	0,399	0,652	0,112
HSP70	9,964	11,822	0,162	9,171	0,120	0,009
ADAM17	0,797	0,803	0,397	0,735	0,741	0,201
IFI27	0,013	0,013	0,705	0,012	0,778	0,494
Glucocorticoid receptor genes						
NR3C1-GR-alpha	2,085	2,045	0,573	1,720	0,000	0,001
NR3C1-GR-beta	0,002	0,003	0,008	0,003	0,001	0,850

Significant dysregulation compared to healthy controls after bonferroni correction is given in bold (P1). Significant dysregulation in patients with postpartum psychosis compared to controls postpartum after bonferroni correction are highlighted in grey (P2).
The quantitative value obtained from qPCR is a cycle threshold (CT). The fold change values between different groups were determined from normalized CT values (CT gene- CT housekeeping gene), by the widely used ΔΔCT method (2-ΔΔCT, User Bulletin 2, Applied Biosystems, Foster City, California). Data were given as logtransformed lineair data [32].

Healthy postpartum women

Monocytes of CP women showed hardly alteration of gene expression, compared to HC women (Table 2). Some genes were up-regulated and some were down-regulated, expression levels were only significantly down-regulated for 2 genes.

Postpartum psychosis

In women with PP, monocyte gene expression was consistently up-regulated, compared to both the HC and CP women (Table 2). Compared to HC, 17 immune-related genes were significantly up-regulated after Holm-Bonferroni correction for multiple comparisons. The up-regulated genes were found within both cluster 1 (12/19 genes) and cluster 2 (5/16 genes). Compared to controls postpartum (CP), 9 immune-related genes were significantly up-regulated after correction for multiple testing – mainly in cluster 2 (7/16 genes), with only two genes in cluster 1 (2/19). None of the interferon-inducible genes had significantly altered expression levels compared to either control group.

The expression of the active glucocorticoid receptor (GR)-α was significantly reduced in women with PP compared to each of the control groups (PP vs. HC, P <0.0001; PP

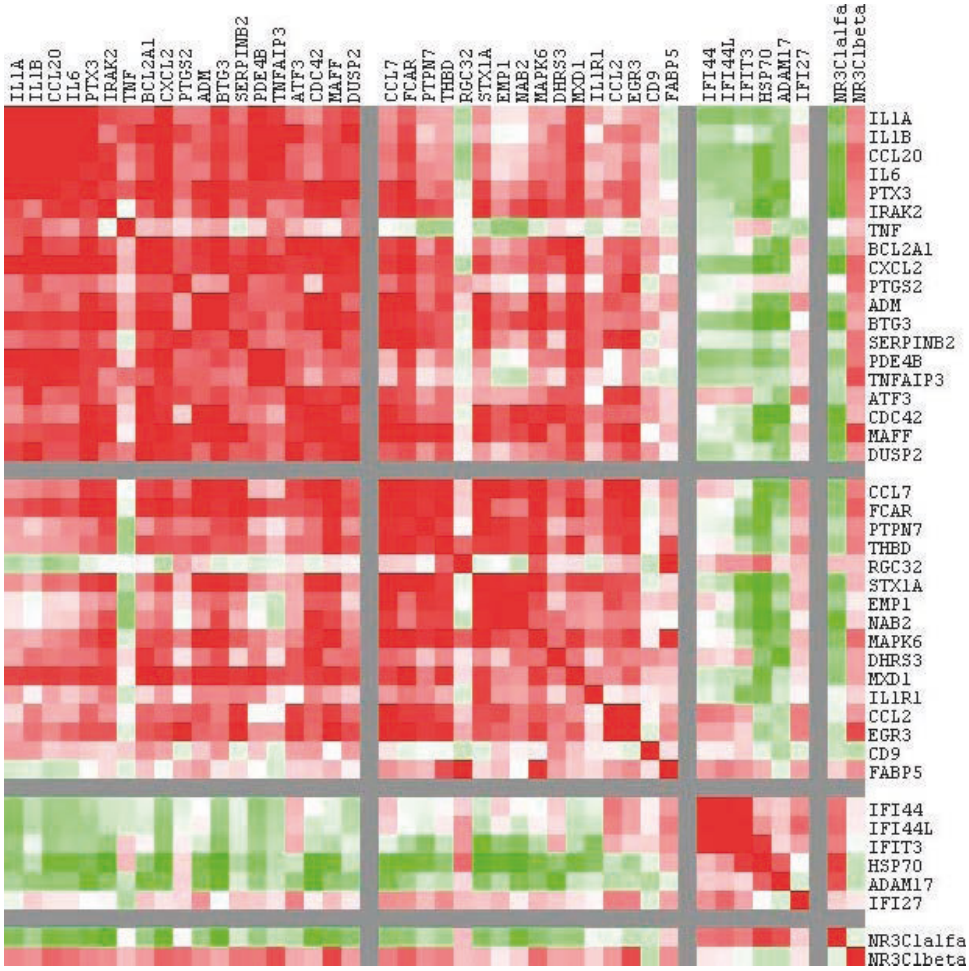

Figure 1. Heat map of gene correlation. Correlation of expression of the various genes; data represent Spearman's correlation coefficients, tested on the relative mRNA expression of the genes in 48 postpartum psychosis patients. The correlations of all tested genes to each other are shown. Significant positive correlations ($p<0.05$) are given by the red scale (darkest red are correlations >0.50), significant negative correlations are given by the green scale. Lighter fields are not significant.

vs. CP, P =0.001). In contrast, the inactive GR-β was significantly up-regulated in PP compared to HC, but not CP. Importantly, the coincident down-regulation of active GR-α expression and up-regulation of the inactive GR-β were significantly correlated with the observed alterations in monocyte gene expression from clusters 1 and 2 (Figure 1).

Regarding serum cytokine/chemokine levels, CP subjects showed significantly higher levels of the pro-inflammatory cytokine IL-1β compared to HC (P=0.026). Women with PP showed significantly higher expression levels of CCL2 compared to both HC (P=0.040) and CP (P=0.036) (Supplementary Figure 2).

Percentages of Peripheral Blood Mononuclear Cells

Monocyte, B-cell and T-cell counts were measured in 63 consecutive patients with PP, 56 CP and 59 HC (Figure 2).

Healthy postpartum women

There was no change in monocyte numbers in the healthy postpartum women. Circulating Natural Killer cells and B-cells were reduced in the postpartum period ($P = 0.003$ and $P < 0.001$), while percentages of circulating T-cells were elevated ($P < 0.001$). This elevation in T-cells was due to a significant rise in CD4+ T helper cells ($P = 0.008$). Within the CD4+ helper compartment, not only were the Th1 and Th17 cell percentages increased ($P = 0.008$ and $P < 0.001$), but also the percentages of T-regulatory cells ($P < 0.001$), suggesting a balance between effector and regulator forces despite T-cell activation.

Postpartum psychosis

Monocytes were significantly elevated in women with postpartum psychosis, compared to both control groups ($P < 0.001$). Further, women with postpartum psychosis did not show the normal reduction in natural killer cells or B-cells as found in the healthy postpartum period. Therefore, both NK cells and B-cells were reduced in PP, compared to controls postpartum ($P = 0.021$ and $P = 0.007$). Further, women with postpartum psychosis did not show the higher percentages of total T-cells or Th1 cells observed in the healthy postpartum period. Consequently, there were significantly reduced levels of T-cells ($P < 0.001$) and Th1 cells ($P = 0.003$), compared to healthy postpartum controls.

Relationship of monocyte activation and PBMC numbers to medication use, disease status, mode of delivery and breastfeeding

The majority of patients were on medication for just a few days at the time of blood sampling. Antipsychotic and/or benzodiazepine use did not result in a significant change in gene expression, PBMC numbers or cytokine/chemokine levels.

Patients with symptoms of psychotic depression showed a significantly lower gene expression level for the TNFAIP3 gene ($r=0,50$, $P=0.001$), compared to patients with manic-psychosis. Further, there were no differences observed in monocyte expression,

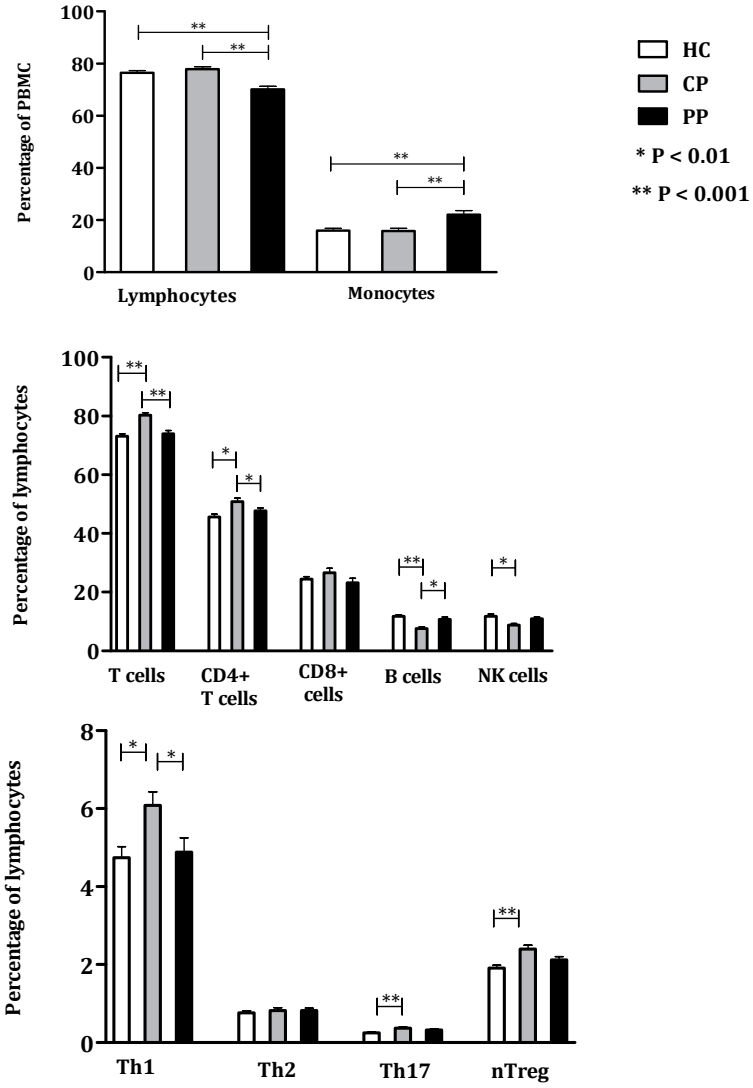

Figure 2. Percentage of different Peripheral Blood Mononuclear Cell (PBMC) subsets in 59 female healthy controls (HC), 57 healthy controls postpartum (CP) and 63 patients with first onset postpartum psychosis (PP) using FACS analysis. Bars=means, whiskers=standard errors.

2.1 Total Monocyte and Lymphocyte population 2.2 Lymphocytes are set at 100%: T-cells (subdivided in CD4+ T- helper cells and CD8+ cytotoxic T-cells), B-cells and Natural Killer (NK) cells.2.3 T-helper cell subsets: T-helper 1 cells (Th1), T-helper 2 cells (Th2) cells, T-helper 17 cells (Th17) and natural T-regulatory cells (nTreg).

PBMC percentages or cytokines/chemokine levels between patients with depressive or manic-psychotic symptoms.

There was no significant correlation between mode of delivery and any of the inflammatory genes. However, there was a significant increase of the monocyte/macrophage chemokine CCL2 (r=0.27, p=0.04) in patients with a caesarean section. Among healthy postpartum women, those who delivered by caesarean section showed higher percentages of Th1 helper cells (r=0.44, p=0.001) and Th2 helper cells (r=0.53, p=0.001) compared to those with vaginal delivery. In contrast, there was no significant correlation between the duration of delivery or the incidence of breastfeeding on any of the measured immune parameters.

DISCUSSION

Our study confirms that the normal postpartum period is a time of substantial immune system alteration. Our findings show a modest alteration of gene transcription in monocytes, an increase in serum IL-1β and circulating T-cell numbers across multiple T-cell subtypes, but a decrease in NK and B-cell numbers. The fact that both the percentages of T-effector and T-regulatory cells were increased in the postpartum period confirms a previously hypothesized balance between inflammatory and anti-inflammatory T-cell forces [38]. The observation of low NK cell numbers during the normal postpartum period is also consistent with previous reports [39]. Therefore, our data support the concept that the immune system reaches a distinct activation set point of particularly the T-cell arm in the postpartum period. It is therefore not surprising that across the lifespan of women, the risk of immune disease exacerbation is elevated during the postpartum period [40-42].

There are several reports suggesting that the activated T-cell system is specifically responsible for many postpartum immune syndromes (e.g. postpartum thyroiditis) [18]. Further, an activated T-cell system has also been associated with susceptibility for mood disorders [33, 43-45]. Surprisingly however, we did not find evidence of T-cell activation in women with postpartum psychosis. On the contrary, the percentages of circulating T-cells were significantly decreased compared to the normal postpartum period. Interestingly, a decrease in T-helper cells has also been described in schizophrenia patients with acute psychosis and in patients with major depression [46, 47].

With regard to monocyte function, we found that monocyte cell counts were elevated in women with postpartum psychosis compared to either control group. Further, monocytes in patients with PP showed an immune-related gene expression profile robustly up-regulated compared to controls. A similarly high level of transcriptional activation of immune genes has been previously described for bipolar disorder and schizophrenia [8]. Further, we found that CCL2 was increased in the serum of PP patients compared to CP. Notably, a higher serum level of CCL2 is consistent with previous reports in bipolar patients [11]. CCL2 is produced by monocytes during tissue infiltration, potentially representative of an ongoing mild inflammatory monocyte/macrophage response.

The majority of our patients were using benzodiazepines and antipsychotics for just a few days at the time of blood sampling. Antipsychotics are generally anti-inflammatory in character and known to down-regulate inflammatory gene expression [48, 49]. Notably, however, we did not find evidence of anti-inflammatory effects of medication, which is most likely due to the very short treatment duration at the time of blood sampling.

In theory, alterations in the stress axis and lactational hormones of breastfeeding women have the potential to influence maternal immune status. However, studies showing clear immune differences between women choosing to breastfeed versus bottle-feed are scarce. Groer et al. reported that immune differences between breastfeeding and bottle-feeding were relatively mild compared to the striking immune differences between postpartum women and non-postpartum controls [50]. Accordingly, in our study, we found no significant correlation between either monocyte or T-cell activation and breastfeeding in the postpartum period. Therefore, the robust increase in monocyte activation during postpartum psychosis does not seem to be significantly influenced by breastfeeding.

During pregnancy and the postpartum period, the physiology of the hypothalamic-pituitary-adrenal (HPA) axis undergoes substantial changes. Several reports suggest a causal relationship between these HPA-axis alterations and the occurrence of postpartum mood disorders [26, 51-56]. We found that blocking GR-β was up-regulated in monocytes of postpartum women, both healthy controls postpartum and women with postpartum psychosis, in comparison to that of non-postpartum women. However, in women with postpartum psychosis, the activating isoform GR-α was significantly reduced compared to healthy controls postpartum and non-postpartum, leading to a significantly lower GR-α/ β ratio compared to either control group. This

pattern of GR-α down-regulation, GR-β up-regulation, and the correlation patterns of this low GR α/ β ratio to the expression level of inflammation related genes together indicate that steroid resistance is an integral aspect of the monocyte activation state in postpartum psychosis. Therefore, our data strongly underscore the close link between disturbances in the endocrine and immune systems during postpartum psychosis.

Collectively, our data highlight a model for postpartum psychosis by which an abnormal set point of the neuro-immuno-endocrine axis leads to increased activity of macrophages and a reduction in T-cell numbers. Macrophages and their analogous cells in the brain, the microglia, are well-documented in animal models to regulate the growth, development, and function of neurons [57]. Further, an activated immune set point of microglia has been observed in acute schizophrenia patients for which animal models have demonstrated robust causal influences of microglial function on psychopathology [58-60]. Together, we hypothesize that an altered postpartum set point of the immune-endocrine system is the ultimate trigger for the acute onset of psychosis in women with an underlying genetic susceptibility for bipolar disorder or psychosis.

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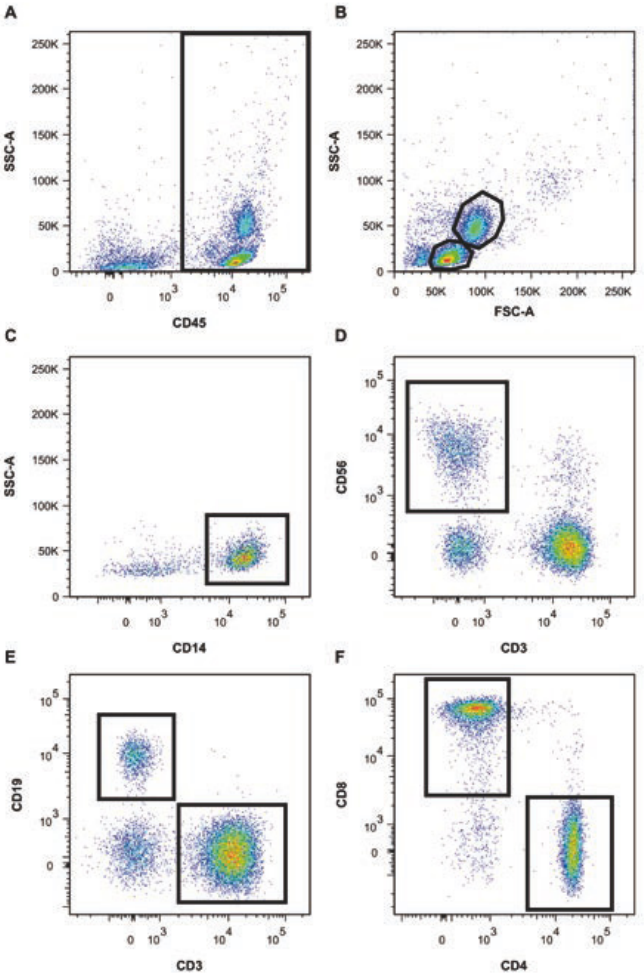
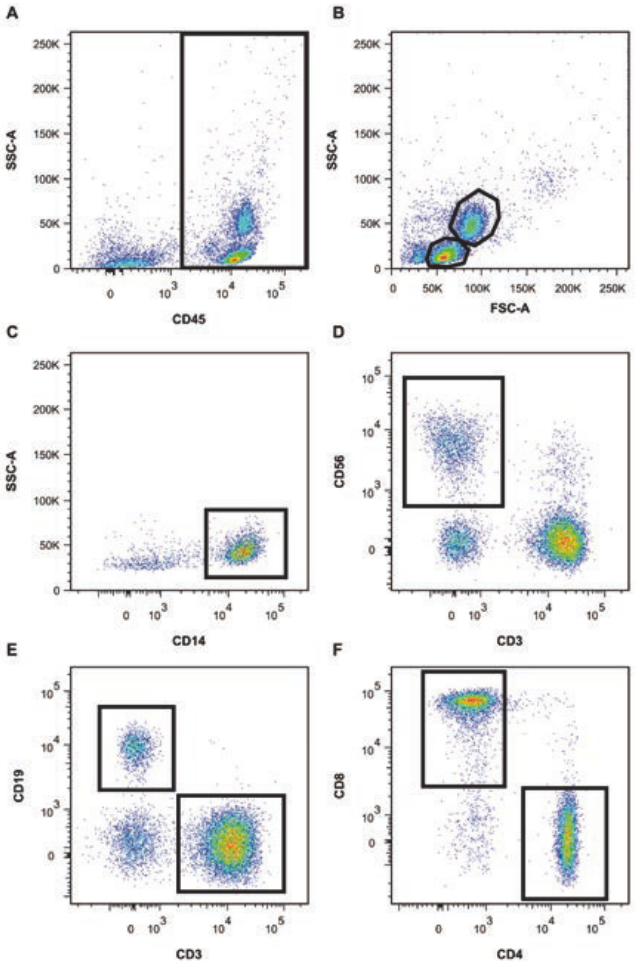


Supplementary Figure 1A. Definition of PBMC subsets and gating strategy.

Examples of gating in flow cytometry to detect the different PBMC subsets in a patient.

A. Selection of leukocytes. Gating was performed on $CD45^+$ events, excluding platelets, erythrocytes and cell debris.
B. Selection of lymphocytes and monocytes within the leukocyte gate (see point A). Lymphocytes (lower gate) and monocytes (upper gate) could be distinguished on the basis of forward scatter (FSC: proportional to cell size) and side scatter (SSC: proportional to cellular granularity).
C. Selection of $CD14^+$ monocytes within the monocyte gate (see B). Cells positive for CD14 were selected.
D. Selection of NK cells within the lymphocyte gate (see B). $CD3^-CD56^+$ cells were selected.
E. Selection of T and B-cells within the lymphocyte gate (see B). T-cells ($CD3^+$ events, lower right gate) could be distinguished from B-cells ($CD19^+$ events, upper left gate).
F. Selection of helper T-cells and cytotoxic T-cells within the T-cell gate (see D). $CD8^+$ cytotoxic T-cells (upper left gate) could be distinguished from $CD4^+$ helper T-cells (lower right gate).

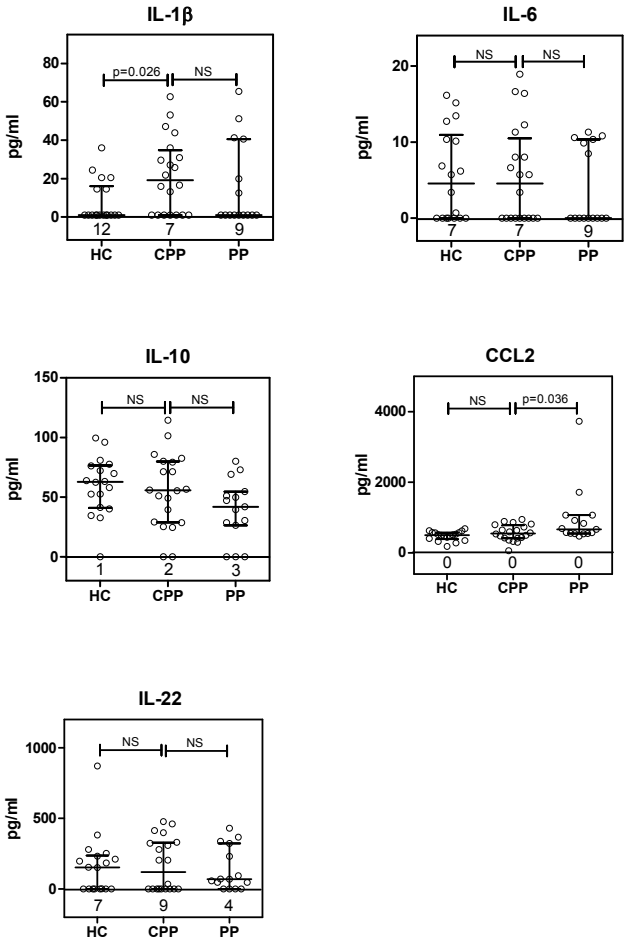


Supplementary Figure 1B. Definition of T-cell subsets by intracellular staining and gating strategy.

Examples of gating in flow cytometry to detect the different T-cell subsets in a patient.

First, single cell events were selected by gating out cell aggregates on the basis of event area versus event height (not shown). Within the single cells, further analysis was performed.

A. Selection of lymphocytes by forward (FSC: proportional to cell size) and side scatter (SSC: proportional to cellular granularity).
B. Selection of T-cells within the lymphocytes (see A). Cells positive for CD3 were selected.
C. Selection of total helper T-cells and the memory helper T-cell subpopulation. Within the T-cells (see B) memory helper T-cells (CD4+CD45RO+, upper gate) could be distinguished amongst the total T helper cell population (CD4+ events).
D. Selection of Foxp3+CD25high regulatory T-cells (Treg) within helper T-cells (see C). Treg are represented in pink. Within the helper T-cells, CD25high cells were selected and in this subset FoxP3+ were designated regulatory T-cells.
E. Selection of T helper 1 (Th1) and T helper 17 (Th17) cells within the helper T-cells (see C). Cells expressing intracellular IFN-γ (upper left gate) represent Th1 cells, cells expressing IL-17A+ (lower right gate) represent Th17 cells.
F. Selection of T helper 2 cells within the helper T-cells (see C). The gated, IL-4+IFN-γ- cells represent the Th2 cells.



Supplementary Figure 2. The serum cytokine/chemokine levels in pg/ml serum in 18 female healthy controls (HC), 20 healthy controls postpartum (CP) and 33 patients with first onset postpartum psychosis (PP). Individual data are given for the indicated cytokines. Bars represent the median, given p values are calculated by Mann-Whitney for non-linear data.

Chapter 6

Tryptophan pathway alterations in the postpartum period and in acute postpartum psychosis and depression

C. Veen
A.M. Myint
K.M. Burgerhout
M.J. Schwarz
G. Schutze
S.A. Kushner
W.J. Hoogendijk
H.A. Drexhage
V. Bergink

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ABSTRACT

Objective: Women are at very high risk for the first onset of acute and severe mood disorders the first weeks after delivery. Tryptophan breakdown is increased as a physiological phenomenon of the postpartum period and might lead to vulnerability for affective psychosis (PP) and severe depression (PD). The aim of the current study was to investigate alterations in tryptophan breakdown in the physiological postpartum period compared to patients with severe postpartum mood disorders.

Methods: We included 52 patients (29 with PP, 23 with PD), 52 matched healthy postpartum women and 29 healthy non-postpartum women. Analyses of serum tryptophan metabolites were performed using LC-MS/MS system for tryptophan, kynurenine, 3-hydroxykynurenine, kynurenic acid and 5-hydroxyindoleacetic acid.

Results: The first two months of the physiological postpartum period were characterized by low tryptophan levels, increased breakdown towards kynurenine and a downstream shift toward the 3-OH-kynurenine arm, away from the kynurenic acid arm. Kynurenine was significantly lower in patients with PP and PD as compared to healthy postpartum women ($p=0.011$ and $p=0.001$); the remaining tryptophan metabolites demonstrated few differences between patients and healthy postpartum women.

Limitation: Low prevalence of the investigated disorders and strict exclusion criteria to obtain homogenous groups, resulted in relatively small sample sizes.

Conclusion: The high kynurenine levels and increased tryptophan breakdown as a phenomenon of the physiological postpartum period was not present in patients with severe postpartum mood disorders. No differences were observed in the levels of the 'neurotoxic' 3-OH-kynurenine and the 'neuroprotective' kynurenic acid arms between patients and healthy postpartum women.

INTRODUCTION

After childbirth, women are at increased risk of severe mood disorders, such as postpartum psychosis and postpartum depression. Postpartum psychosis (PP) is the most severe childbirth related mood disorder. Although the prevalence is low (1-2 per 1000 childbirths), women are approximately 22 times more likely to experience the onset of a manic or affective psychotic episode in the first month postpartum than at any other time in their lives [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 [2-4]. Affective phenomenology is a hallmark of the disease and therefore, postpartum psychosis is generally considered a bipolar spectrum disorder and not a primary psychotic disorder [5]. In some women postpartum psychosis is a first manifestation of a life long bipolar disorder, but in other women affective psychosis is entirely restricted to the postpartum period [6]
Postpartum depression (PD) refers to a non-psychotic depressive episode that affects approximately 10% of mothers after childbirth [7]. 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 both psychosocial status and stressful life events are important risk factors. Half of women with postpartum depression have their onset during pregnancy. Severe depression with an acute onset within the first months postpartum is thought to be a more homogenous subtype within the bipolar spectrum [8].
The occurrence of first onset acute and severe episodes (mania, depression, psychotic depression) in the postpartum period is intriguing for both clinicians and researchers, but the underlying mechanism is largely unknown. Mood disorders in general have been associated with monoaminergic neurotransmitter alterations, such as decreased availability of serotonin. A few studies have suggested that the occurrence of postpartum mood symptoms could be related to increased tryptophan breakdown (Figure 1), a physiological phenomenon of pregnancy and the postpartum period [9, 10]. During pregnancy, tryptophan metabolism is altered, with a decrease in total tryptophan and a shift in the proportions of free and bound tryptophan [11]. After pregnancy, both free and bound tryptophan levels gradually return to pre-pregnancy levels [12-14]. The downstream tryptophan pathway beyond the degradation to kynurenine has never been investigated in women with severe postpartum mood disorders, but there is evidence for major alterations in severe mood disorders outside the postpartum period [15-19]. Increased breakdown via the tryptophan-kynurenine pathway augments serotonin deficiency, which could serve as a potential etiological

factor for mood disorders. In addition, tryptophan breakdown leads to an increased formation of kynurenine and downstream products, some of which are known to have neurotoxic properties [20, 21].

Tryptophan-2,3- dioxygenase (TDO) and indoleamine-2,3-dioxygenase (IDO) are enzymes in the degradation of tryptophan to kynurenine (Kyn). TDO is mainly induced by glucocorticoids [22] and IDO is particularly induced under the influence of pro-inflammatory cytokines [23] (Figure 1). Further downstream, Kyn is either metabolized to kynurenic acid (KynA) by the kynurenine aminotransferases (KAT) enzymes, or to 3-OH-kynurenine (3HK) under the influence of the enzyme kynurenine-3-monooxygenase (KMO). Similar to IDO, KMO is activated by pro-inflammatory cytokines [24, 25]. Several products in the 3HK pathway are toxic for neurons: 3HK contributes to neurodegeneration by inducing neuronal apoptosis [21] and quinolinic acid is a well-known excitotoxin [20]. KynA protects against the neurodegenerative excitotoxic action of quinolinic acid, balancing the two arms of the system [26]. Activation of the inflammatory response system can lead to an imbalance in the tryptophan degradation pathway including high tryptophan breakdown (due to activation of IDO) and a shift towards the more neurotoxic pathway (due to KMO activation).

The aim of the current study is to investigate if alterations in tryptophan degradation in the postpartum period are associated with the occurrence of severe depression and postpartum psychosis. We measured tryptophan pathway metabolites in both healthy postpartum and healthy non-postpartum women to examine the normal physiological changes that occur during the postpartum period. Moreover, we investigated the association of tryptophan metabolism with postpartum psychosis and postpartum depression compared to healthy postpartum women. We hypothesized that the physiological enhancement of the tryptophan breakdown pathway is aggravated in patients with postpartum psychosis and severe depression, considering their previously demonstrated inflammatory character [27-29].

METHODS

Participants

This study protocol was approved by the institutional review board of the Erasmus Medical Center, Rotterdam (original protocol number MEC-2005226). After receiving a complete description of the study, all patients provided written informed consent.

Fifty-two (n=52) patients with a severe postpartum onset psychiatric disorder (PP or PD) were recruited from the Mother-Baby Inpatient Unit of the Department of

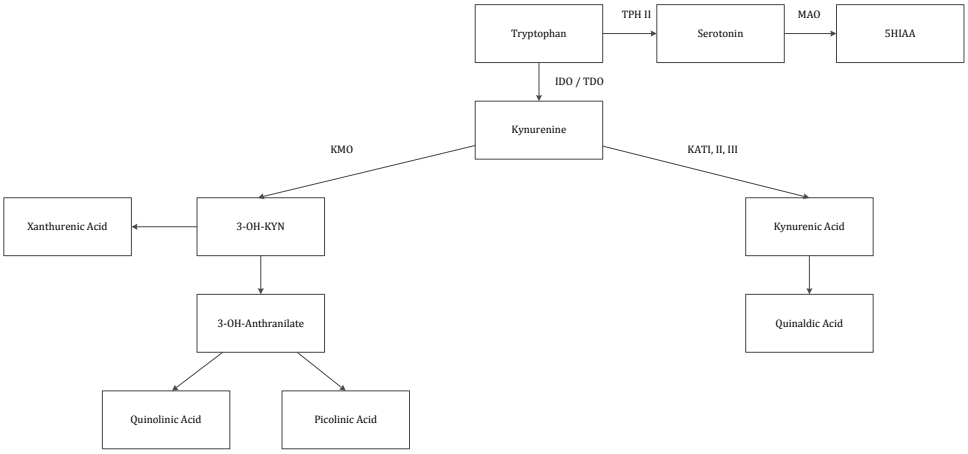

Figure 1. The tryptophan pathway- The pathways underlying tryptophan metabolism. The main branches are towards the 'neuroprotective' kynurenic acid arm, towards the 'neurotoxic' 3-OH-kynurenine arm and towards the serotonin arm.

Legend; IDO = indoleamine-2,3-dioxygenase, TDO = tryptophan 2,3-dioxygenase (TDO), KMO = kynurenine -3-monooxygenase, KAT = kynurenine aminotransferase, TPH = tryptophan hydroxylase, MAO = monoamine oxidase.

Psychiatry of the Erasmus University Medical Center in Rotterdam, the Netherlands between December 2006 and December 2011. All patients were diagnosed according to DSM-IV-TR [30] using the Structural Clinical Interview for Disease (SCID – 1/P research version). The clinical characteristics of this cohort have been previously reported [31].

Twenty-nine (n=29) patients were diagnosed with PP based upon any of the following DSM-IV-TR diagnoses: mania with psychotic features (n=18), mixed episode with psychotic features (n=5), depressive disorder with psychotic features (n=2) or brief psychotic disorder (n=4), all of whom met the criteria for the specifier "onset postpartum", defined by an onset within four weeks postpartum. Patients with PP with depressive features (Patients with mixed episodes and patients with depressive disorder with psychotic features) had a median Edinburgh Postnatal Depression Scale (EPDS) score of 14 (IQR 9.5-20). Patients with mania had a median Young Mania Rating Scale score of 16.5 (IQR 2-24.5). None of these 29 women had previous episodes of mania or psychosis outside the postpartum period. Six women had a single previous episode of a postpartum mood disorder and six women previously experienced non-

puerperal depressive or anxiety symptoms. The median onset of severe symptoms occurred on day seven (IQR 4-10) and median time of blood collection at day 21. At the time of blood withdrawal, almost all women used benzodiazepines (25/29, median two days), 17 women received antipsychotics (median three days), of these 17, one woman used adjunctive lithium for six days. None of the patients were using SSRIs or other antidepressant medication at the time of blood withdrawal.

Twenty-three (n=23) inpatients were diagnosed with PD with a median Edinburgh Postnatal Depression Scale (EPDS) score of 19 (IQR 14-22.5). The relevant DSM-IV-TR diagnoses included both major depressive disorder (n= 11), and anxiety disorders with comorbid depression (n=12). All women had a postpartum onset within three months following delivery. The median onset of severe symptoms occurred at day 10 (IQR 2,5- 41). Median time of blood collection occurred at day 63. Of these 23 patients, nine were using benzodiazepines (median two days) and two patients were using antipsychotics (seven and nine days) at the time of blood collection, none of the patients were using antidepressant medication. Patient admitted to our ward with depressive symptoms have an antidepressant free observation period, which enabled us to enroll patient before the start of antidepressant treatment. Eleven patients had a previous history of non-puerperal depressive or anxiety symptoms.

Patients with a history of bipolar disorder, non-puerperal psychotic episodes, substance abuse, or psychiatric symptoms during pregnancy were excluded from the study. Physical examination and routine laboratory screening were performed at the time of study enrolment to confirm the absence of infection or other hematological abnormalities. All patients were in an acute disease state at moment of blood withdrawal.

The postpartum control (CP) group consisted of 58 healthy postpartum women recruited between June 2008 and August 2012 (Erasmus MC, Rotterdam), with an EPDS score <10 at the time of postpartum blood sampling. Each healthy postpartum control was matched for a patient with severe postpartum psychiatric disorder by ethnicity, method of delivery and postpartum interval of blood collection. The healthy postpartum control group for the postpartum psychosis (CPP) cohort had a median at 22 days postpartum, and the healthy postpartum control group for the postpartum depression (CPD) cohort had a median time of blood collection at 40 days postpartum. Twenty-nine (n=29) healthy non-postpartum women were included as an additional control group (HC). Inclusion criteria for both healthy postpartum and healthy non-postpartum women included the absence of any medical, neurologic, psychiatric, or autoimmune disorders, as well as having no current or recent clinical evidence of acute infection.

Analysis of Tryptophan Metabolites

Serum samples were collected strictly between 08.00h and 11.00h and immediately stored at -80°C. Analyses of serum tryptophan metabolites were performed using LC-MS/MS system for tryptophan, kynurenine, 3-hydroxykynurenine, kynurenic acid, 5-hydroxyindoleacetic acid [32].

We calculated the tryptophan breakdown index to estimate the activity of the IDO and TDO enzymes (Figure 1, box below). Next, the ratio between serum levels of kynurenic acid and kynurenine estimates activity of the KAT enzymes. An increase in this ratio reflects higher activity of these enzymes. In addition, the ratio between serum levels of 3-OH-kynurenine and kynurenine estimates the activity of the KMO enzymes. An increase of these ratios reflects higher activity of these enzymes. Lastly, the ratio between 5-HIAA and kynurenine provides information about the balance of tryptophan metabolism between the kynurenine and serotonergic pathways.

Tryptophan breakdown index = plasma kynurenine (ng/mL) / plasma tryptophan (μg/mL)

KynA/Kyn ratio = 100 X plasma kynurenine acid (ng/mL)/plasma kynurenine (ng/mL)

3HK/Kyn ratio = 100 X plasma 3-OH-kynurenine (ng/mL)/ plasma kynurenine

5-HIAA/Kyn ratio = 100 X plasma 5-HIAA (ng/mL) / plasma kynurenine (ng/mL)

Statistical Analysis

Statistical analysis was performed using SPSS version 20.0. All metabolic data were examined using non-parametric statistics. Sample characteristics were evaluated using Fisher's exact test and the Mann-Whitney U test, and expressed with median and interquartile range (IQR). To compare parameters which demonstrated a skewed distribution, we used the Mann-Whitney U test and reported data as median values. Correlations were examined with Spearman rank correlation coefficients. The Bonferoni correction was applied for multiple testing, using α=0.05.

RESULTS

Characteristics of the study subjects

Characteristics of patients and controls are shown in Table 1. No significant differences were observed for age, weight, or the median time of blood collection between patients with postpartum psychosis (PP) and patients with postpartum depression (PD) compared to matched healthy postpartum women (CPP and CPD respectively). Healthy non-postpartum women (HC) were younger ($p<0.001$, MWU) and had a lower weight compared to all other groups (significant compared to CPP ($p=0.018$, MWU) and PD ($p=0.026$, MWU). No significant differences were observed for parity, gravidity, or obstetric complications (FET). As expected, healthy postpartum women were significantly more likely to be breastfeeding at the time of blood collection ($p<0.001$, MWU), given that most patients discontinued breastfeeding upon inpatient psychiatric admission.

Tryptophan pathway

Physiological postpartum period

All healthy postpartum women (CPP/CPD) had a significantly lower serum level of tryptophan (both $p<0.001$, MWU), and higher level of kynurenine ($p=0.001$, $p=0.002$ respectively, MWU) (Figure 2), compared to healthy non-postpartum women (HC). Consequently, the tryptophan breakdown index was significantly increased ($p=0.001$, $p<0.001$ respectively, MWU) (Table 2).

With regard to the downstream tryptophan metabolites, all healthy postpartum women had significantly lower serum levels of kynurenic acid, compared to healthy non-postpartum women ($p<0.001$, MWU). In addition, we found that all healthy postpartum women had significantly higher levels of 3HK, compared to healthy non-postpartum women ($p<0.001$, $p=0.011$ respectively, MWU) (Figure 2). Accordingly, the KynA/Kyn ratio was significantly decreased in all healthy postpartum women (both $p<0.001$, MWU), indicating a strong inhibition of the KAT enzymes during the first two months postpartum. The 3HK/Kyn ratio was significantly increased in healthy postpartum women with a median time of blood collection 22 days postpartum (CPP) ($p=0.021$, MWU), but not in healthy postpartum women with a median time of blood collection 40 days postpartum (CPD). This result suggests an increased activity of the KMO enzymes in the first month of the physiological postpartum period, gradually returning to normal levels. (Table 2)

With regard to the serotonergic pathway, 5HIAA levels were not significant altered. However, due to higher Kyn levels, the 5HIAA/Kyn ratio was significantly decreased in

all healthy postpartum women, indicating that the breakdown of tryptophan is biased towards the kynurenine pathway and away from the serotonergic pathway in the physiological postpartum period (Table 2). No significant differences in tryptophan metabolites were observed on repeat sampling for all healthy postpartum women.

Postpartum psychosis and postpartum depression

No differences in tryptophan levels were observed for patients (PP and PD) in comparison to matched healthy postpartum women (CPP and CPD). In contrast, kynurenine was significantly lower in patients as compared to healthy postpartum women (PP compared to CPP, p=0.011; PD compared to CPD, p=0.001, MWU). Accordingly, both PP and PD had a significantly reduced tryptophan breakdown index, compared to healthy postpartum women (Table 2).

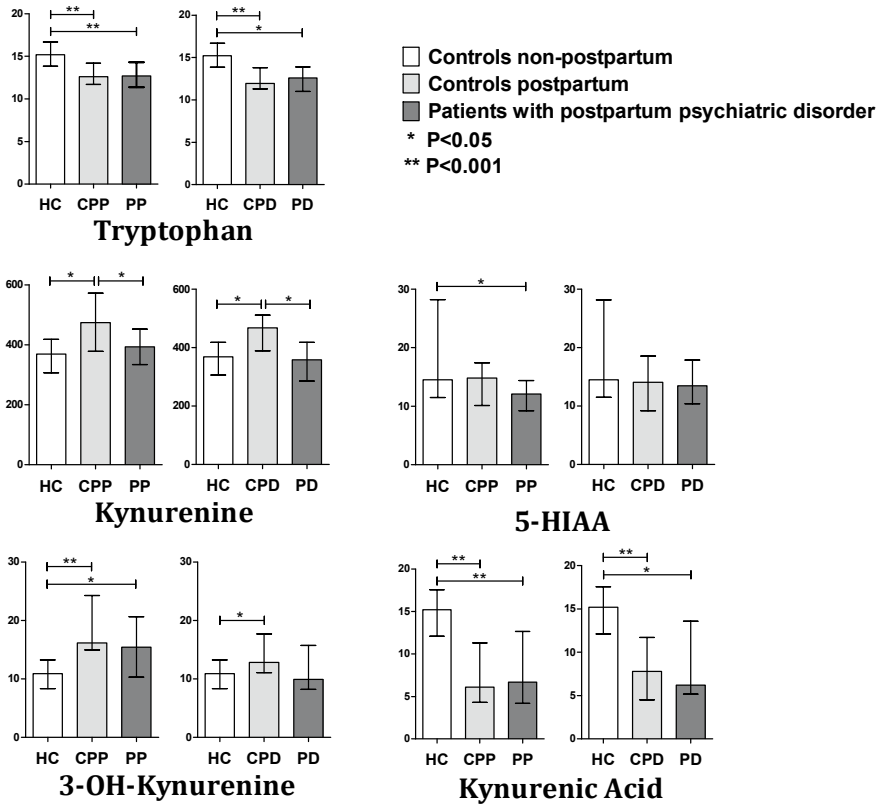

Figure 2. Serum levels of tryptophan pathway metabolites (ng/mL) in healthy non-postpartum women (HC), patients with a postpartum psychosis (PP) or severe postpartum depression (PD), and matched healthy postpartum women (CPP and CPD, respectively).

No differences were observed in kynurenic acid levels or the KynA/Kyn ratio between patients and healthy postpartum women, indicating that KAT enzymes were inhibited in both patients and healthy postpartum women (Table 2). No significant differences were observed in 3-HK levels and 3-HK/Kyn ratio between patients and healthy postpartum women (Table 2).
No significant difference was observed in serum levels of 5-HIAA between patient and healthy postpartum women.

Confounder analyses

No significant associations were observed between the levels of tryptophan metabolites compared to age or weight for any group (HC, CP, PP, CPD, and PP, Spearman rank) after correction for multiple testing. No association was observed between the levels of tryptophan metabolites and breastfeeding. The majority of patients were on medication for just a few days at the time of blood collection. There was no correlation between short term use of antipsychotics and/or benzodiazepines and the levels of tryptophan metabolites.

Table 1. General and obstetric characteristics of healthy non-postpartum women (HC), patients with a postpartum psychosis (PP) or severe postpartum depression (PD), and their matched healthy postpartum women (CPP and CPD, respectively).

	HC (n=29)	CPP (n=29)	PP (n=29)	CPD (n=29)	PD (n=23)
Age (years) – median (IQR)	23,9* (22-26)	31,8 (29-36)	32,6 (30-36)	33,1 (30-36)	31,6 (28-36)
Weight – median (IQR)	65,5† (60-72)	76,0 (63-82)	69,0 (65-78)	67,0 †(64-70)	72,0 (65-82)
Blood withdrawal, days postpartum – median (IQR)	-	22 (17-33)	21 (14-47)	40 (30 – 95)	63 (22-95)
		N (%)	N (%)	N (%)	N (%)
Primiparity	-	17 (58.6)	20 (69.0)	19 (65.5)	19 (82.6)
Primigravidity	-	17 (58.6)	20 (69.0)	17 (58.6)	14 (60.7)
Caesarian Section	-	2 (6.9)	4 (13.8)	8 (27.6)	5 (21.7)
Vacuüm Extraction	-	3 (10.3)	3 (10.3)	8 (27.6)	3 (13.0)
Breastfeeding at Time of Blood collection	-	21‡ (72.4)	2 (6.9)	18‡ (62.1)	0 (0)

*The HC group was significantly younger than CPP, PP, CPD and PD groups ($p<0.001$).
†The HC groups had significantly lower weight than CPP ($p=0.018$) and PD ($p=0.026$). The CPD group had significantly lower weight than PD ($p=0.035$).
‡ The CPP and CPD groups had a significant higher proportion of breast-feeding than PP and PD (both $p<0.001$).

Table 2a. Tryptophan metabolite ratios (median) of healthy non-postpartum women (HC), patients with postpartum psychosis (PP), and matched healthy postpartum women (CPP). Statistical testing was performed using the Mann-Whitney U test.

	HC (n=29)	CPP (n=29)	PP (n=29)	P-value (Z) HC vs. CPP	P-value (Z) HC vs. PP	P-value (Z) CPP vs. PP
Tryptophan breakdown index	25.87	35.92	30.60	0.001 (-4.845)	0.001 (-3.382)	0.016 (-2.402)
KynA/Kyn ratio	4.17	1.09	1,50	<0.001 (-5.124)	<0.001 (-4,549)	0.106 (-1.615)
3-OH-Kyn/Kyn ratio	2.92	3.61	3,56	0.021 (-2.304)	0.003 (-2.985)	0.625 (-0.488)
5-HIAA/Kyn ratio	4.58	2.90	2.99	0.013 (-2.478)	0.021 (-2.309)	0.800 (-0.253)

Table 2b. Tryptophan metabolite ratios (median**)** of healthy non-postpartum women (HC), patients with severe postpartum depression (PD), and matched healthy postpartum women (CPD). Statistical testing was performed using the Mann-Whitney U test.

	HC (n=29)	CPD (n=23)	PD (n=29)	P-value (Z) HC vs. CPD	P-value (Z) HC vs. PD	P-value (Z) CPD vs. PD
Tryptophan breakdown index	25.87	39.17	29.82	<0.001 (-5.272)	0.035 (-2.111)	0.002 (-3.156)
KynA/Kyn ratio	4.17	1,52	1.70	<0.001 (-5.075)	0.004 (-2.910)	0.099 (-1.648)
3-OH-Kyn/Kyn ratio	2.92	3,22	3.24	0.507 (-0.664)	0.608 (-0.514)	0.673 (-0.422)
5-HIAA/Kyn ratio	4.58	3.02	3.53	0.009 (-2.615)	0.458 (-0.742)	0.051 (-1.950)

DISCUSSION

Tryptophan breakdown into kynurenine

The physiological postpartum period is characterized by highly significant physiological changes in tryptophan metabolism. Our study confirms the earlier reports of physiological postpartum reductions in tryptophan levels and increased tryptophan metabolism to kynurenine [9, 12-14, 33]. However, our findings do not support the idea of an increased tryptophan metabolism as an etiological mechanism for severe postpartum mood disorders [9, 10]. In contrast, the substantial increase in kynurenine as seen in the physiological postpartum period was not present in patients with postpartum psychosis and postpartum depression. In these patients, we found significantly reduced kynurenine levels compared to healthy postpartum women, suggestive of an attenuated tryptophan metabolism into kynurenine.

One possible candidate mechanism for lower kynurenine levels in postpartum psychiatric patients could be a lower activity of the enzyme indoleamine-2,3-dioxygenase (IDO). In the physiological postpartum period increased tryptophan metabolism suggests an elevated activity of the enzyme IDO one of the enzymes

converting tryptophan into kynurenine (figure 1). Our data suggests that patients lack the physiological postpartum increase of this enzyme. Notably, the strongest-known inducer of IDO is interferon gamma (IFNγ), for which lymphocytes, and T-cells in particular, are the primary source [34]. The physiological postpartum period is characterized by an increase in the level of T-cells, but much to our surprise we previously found a severely blunted T-cell response in patients with PP, despite the pro-inflammatory state of circulating monocytes [29].
We postulate that the pro-inflammatory state of the physiological postpartum period may be responsible for the increase in tryptophan breakdown towards kynurenine. [23-25]. As an extend of this idea, we posit that the blunted T-cell response and consequent reduction of IFNγ production could explain the lower IDO activity and attenuation of tryptophan metabolism in patients with postpartum psychosis and postpartum depression.

Kynurenine pathway

In the physiological postpartum period, we describe two novel downstream alterations of the kynurenine pathway. Specifically, we found low level of 'neuroprotective' kynurenic acid (KynA) and higher levels of 'neurotoxic' 3-OH-kynurenine (3HK) in healthy postpartum women compared to healthy non-postpartum women. These findings are suggestive for a strong inhibition of the kynurenine aminotransferases (KAT) enzymes and a mild induction of the kynurenine-3 monooxygenase (KMO) enzymes during the physiological postpartum period.
This strong reduction of KynA in the physiological postpartum period has not been described before and the underlying mechanism remains elusive. Notably, kynurenic acid has anti-inflammatory qualities [35] and therefore, low levels of KynA further stresses the physiological pro-inflammatory state postpartum. In accordance, KMO enzymes are highly activated by pro-inflammatory cytokines and physiological the pro-inflammatory state of the postpartum period may be responsible for the increase in 3HK.
These increased levels of 3HK in healthy postpartum women, may serve an important homeostatic function during the energy demanding postpartum period. By entering the 3HK arm also adenosine-triphosphate (ATP) and nicotinamide-adenine-dinucleotide (NAD) are likely to be elevated and they provide energy for cells (Figure 1) [36, 37]. Together, in the physiological postpartum period the strong reduction of the 'neuroprotective' KynA levels and increase of the 'neurotoxic' 3HK levels could be seen as a contributor to the increased vulnerability for psychiatric disorders after delivery.

Unexpectedly, patients with postpartum psychiatric disorders did not have an increase in 'neurotoxic' 3HK or a reduction of 'neuroprotective' KynA compared to healthy postpartum women. There was no shift in this pathway. This is in contrast with finding in psychiatric disorders outside the postpartum period. Reduced levels of kynurenic acid have been observed in patients with major depressive disorder, bipolar disorder and schizophrenia [18, 19, 38]. This strong reduction of the protective KynA has been described as an important etiological mechanism [15-17]. In addition, higher 3HK levels have been found in patients with schizophrenia [15, 16, 39] and similar findings have been observed in IFNα induced depression [40-42]. Together, our negative findings in this downstream pathway suggest that the underlying neurobiological mechanisms are distinct in postpartum psychiatric disorders compared to non-postpartum psychiatric disorders.

Limitation of our study

In an effort to obtain highly homogenous groups with minimal confounding factors, we used strict exclusion criteria resulting in relatively small sample sizes. We have included a cohort of severely ill, antidepressant-free patients, with a well-specified onset of symptoms in the postpartum period. Healthy postpartum women were well matched to postpartum patients, but healthy non-postpartum women were not matched for age.

Another limitation is that our study design was limited to a matched case-control study due to the low prevalence of PP and severe PD, which rendered impractical a prospective longitudinal design with pre-morbid sampling.

Furthermore, the peripheral changes in tryptophan metabolites remain difficult to interpret with respect to the tryptophan metabolism in the brain. Tryptophan, kynurenine and 3-OH-kynurenine directly cross the blood brain barrier and high levels could have neurotoxic action. In contrast, kynurenic acid has, at best, very limited ability to cross the blood brain barrier [43]. Interestingly, increased kynurenic acid levels in the cerebrospinal fluid have been reported in patients with bipolar disorder and schizophrenia [44-46] and it would therefore be interesting to measure cerebrospinal fluid levels in postpartum patients in future studies. Lastly, we did not investigate the correlation between the tryptophan pathway and cortisol or sex-steroids. Although the two systems are known to interact [47], a single measurement would not have been informative in this highly fluctuating hormonal period.

Conclusion

Our current findings strengthen the view that tryptophan metabolism is highly altered during the physiological postpartum period. In particular, we demonstrated for the first time the downstream alterations with strong decrease of 'neuroprotective' KynA and increase of 'neurotoxic' 3HK in the physiological postpartum period. These alterations in tryptophan metabolism can be reasonably envisaged as contributing to the high risk of psychiatric disorders in the postpartum period. Remarkably, tryptophan metabolism to kynurenine was not increased, but rather attenuated, in PD and PP patients compared to healthy postpartum women. The remaining tryptophan metabolites evaluated demonstrated few, if any, differences between patients and healthy postpartum women, particularly compared to the striking alterations in the physiological postpartum period. Taken together, our findings suggest a physiologically complex mechanism underlying postpartum psychiatric disorders in which additional mechanisms are likely to contribute to the overall pathophysiology.

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Appendix 1

Laboratory Method for quantification of Kynurenine Pathway Metabolites

Instrumentation

The chromatographic system was composed of a Waters Acquity UPLC separations module connected to a Xevo TQ MS triple-quadrupole mass spectrometer, equipped with a Z-spray ESI ion source (Waters Corp., Milford, MA, U.S.). Separation was carried out using a Kinetex XB-C18, 2.6 µm, 2.1 x 150 mm colomn (Phenomenex, Torrance, California, U.S.).

Chemicals

Reagents for protein precipitation, derivatisation, and chromatography were purchased from Sigma-Aldrich (St. Louis, MO, U.S.), and Biosolve (Valkenswaard, NL).

Standards and control samples

Tryptophan, kynurenine, 3-hydroxykynurenine, kynurenic acid, 3-hydroxyanthranilic acid, quinaldic acid, and 5-hydroxyindoleacetic acid were purchased from Sigma-Aldrich (St. Louis, MO, U.S.). Standards and controls were established by adding defined volumes of the stock solutions to a human serum obtained from a blood bank. Quality control samples were generated to obtain low and high amounts of the analytes.

Sample extraction

A total sample volume of 300 µl serum was used. Analytes were extracted from samples and calibrators/controls by adding 50 µl of 2.0 M urea and 50µl of internal standard solution containing KYNA-D5, PIC-D4 and TRP-D5. Two precipitation steps by subsequently adding methanole/ethanol and CAN were carried out. The supernatant was separated into two portions, which were evaporated separately. One of these portions was directly reconstituted in mobile phase, while the other portion was used for derivatisation by addition of HCl/Butanol. After evaporation to dryness, this portion was reconstituted in mobile phase, too.

Chromatographic conditions

7.5 µl of the reconstituted samples/calibrators/controls were loaded onto the LC-MS/MS system. 3-HK, QUIN and PIC were analysed from the derivatized sample, while all other analytes were determined from the underivatized sample. A gradient method with a total duration of 7.5 min was used for chromatographic separation. Mobile

phase A was composed of 0.1% formic acid and 0.01% HFBA in water; mobile phase B was methanol. Flow rate was set at 0.25 ml/min, column temperature was set at 30.0 °C. Retention times for the analytes were between 3.1 and 6.0 min**.**

MS condition

The Xevo TQ MS was operating in atmospheric pressure electrospray ionization (ESI) positive mode (ESI+). Ion source settings were: capillary voltage, 1.00 kV; desolvation temperatures, 650 °C; source temperature, 150 °C; nitrogen was used as desolvation gas with a cone gas flow rate of 1200 l/h; argon was used as collision gas at a flow rate of 0.15 ml/min. The analytes and internal standards were detected using multi reaction monitoring (MRM) technique. System operation, data acquisition and data processing were controlled using MassLynx V4.1 software (Waters, Milford, USA).

Appendix 2

Supplementary Table 1a. Median values of the metabolites from the tryptophan pathway of healthy non-postpartum women (HC), patients with postpartum psychosis (PP), and matched healthy postpartum women (CPP). Statistical testing was performed using the Mann-Whitney U test.

	HC (n=29) Median (IQR)	CPP (n=29) Median (IQR)	PP (n=29) Median (IQR)	P-value (Z) HC vs. CPP	P-value (Z) HC vs. PP	P-value (Z) CPP vs. PP
Tryptophan	15.2 (13.8-16.7)	12.6 (11.7-14.2)	12.7 (11.4-14.3)	<0.001 (-3.805)	<0.001 (-3.694)	0.948 (-0.066)
Kynurenine	369.0 (306.5-418.5)	474.0 (378.0-572.0)	393.0 (334.5-452.5)	0.001 (-3.247)	0.213 (-1.244)	0.011 (-2.550)
3-OH-kyn	10.9 (8.3-13.3)	16.2 (15.0-24.3)	15.4 (10.3-20.7)	<0.001 (-3.542)	0.004 (-2.842)	0.312 (-1.010)
Quinolinic Acid	15.2 (12.1-17.5)	6.1 (4.3-11.3)	6.7 (4.2-12.7)	-	-	0.078 (-1.765)
Kynurenic Acid	14.5 (11.5-28.2)	14.8 (10.1-17.4)	12.1 (9.3-14.4)	<0.001 (-4.469)	<0.001 (-4.269)	0.806 (-0.246)
Quinaldic Acid	15.2 (13.8-16.7)	12.6 (11.7-14.2)	12.7 (11.4-14.3)	-	-	0.006 (-2.761)
5-HIAA	369.0 (306.5-418.5)	474.0 (378.0-572.0)	393.0 (334.5-452.5)	0.332 (-0.969)	0.012 (-2.512)	0.212 (-1.248)

Supplementary Table 1b. Median values of the metabolites from the tryptophan pathway of healthy non-postpartum women (HC), patients with postpartum depression (PD), and matched healthy postpartum women (CPD). Statistical testing was performed using the Mann-Whitney U test.

	HC (n=29) Median (IQR)	CPD (n=23) Median (IQR)	PD (n=29) Median (IQR)	P-value (Z) HC vs. CPD	P-value (Z) HC vs. PD	P-value (Z) CPD vs. PD
Tryptophan	15.2 (13.9-16.7)	11.9 (11.3-13.8)	12.6 (11.0-13.9)	<0.001 (-4.479)	0.001 (-3.424)	0.845 (-0.196)
Kynurenine	369.0 (306.5-418.5)	468.0 (389.0-512.0)	359.0 (286.5-418.0)	0.002 (-3.083)	0.697 (-0.390)	0.001 (-3.427)
3-OH-kyn	10.90 (8.4-13.3)	12.9 (11.1-17.7)	9.95 (8.2-15.8)	0.011 (-2.530)	0.962 (-0.048)	0.065 (-1.847)
Quinolinic Acid	15.2 (12.1-17.6)	7.8 (4.5-11.7)	6.2 (5.2-13.6)	-	-	0.814 (-0.235)
Kynurenic Acid	14.5 (11.5-28.2)	14.1 (9.1-18.2)	13.5 (10.4-17.9)	<0.001 (-4.608)	0.003 (-3.005)	0.992 (-0.010)
Quinaldic Acid	15.20 (13.9-16.7)	11.9 (11.3-13.8)	12.6 (11.0-13.9)	-	-	0.105 (-1.620)
5-HIAA	369.0 (306.5-418.5)	468.0 (389.0-512.0)	359.0 (286.5-418.0)	0.171 (-1.369)	0.287 (-1.065)	0.920 (-0.101)

Chapter 7

General discussion

One of the prime targets of this study was to unravel the follow-up of postpartum psychosis, clinically and immunologically. Women who were admitted to the mother-baby unit of Erasmus MC were prospectively followed over four years (OPPER study), and this is still occurring. Women are intensively followed during admission (Chapters 2, 3 and 4) and are visited at nine months postpartum (Chapter 2 and 3) and four years postpartum (Chapter 4).

Conclusions regarding the clinical aspects of postpartum psychosis:

- Every woman with postpartum psychosis should be admitted with her baby. The addition of lithium to the treatment of postpartum psychosis may be most beneficial for relapse prevention during the first nine months postpartum (Chapter 2).
- Postpartum psychosis is an acute and severe mood disorder with substantial impairment in every aspect of daily life functioning during the acute episode. The prognosis is highly optimistic for achieving full clinical remission.
- At nine months postpartum, the majority of women (74%) with postpartum psychosis reported good functional recovery. Compared to a matched population-based cohort, women with postpartum psychosis reported slightly more symptoms of depression and anxiety. Women who experienced a relapse also experienced considerable functional impairments across several domains (Chapter 3).
- In our study, the prognosis after four years postpartum is more optimistic than previously thought. 61.2% (41/67) of women were in sustained remission four years after severe postpartum psychosis, and 38.8% (26/67) of the women experienced a relapse. During follow-up, 12 women had depression, eight had a manic episode, and six had non-affective psychosis (Chapter 4).
- Clinicians should be aware of a high relapse risk, particularly in the first 18 months after the initial episode and when medication is tapered off (Chapter 4).
- A subgroup of women is vulnerable to severe mood disorders in the postpartum period only. Postpartum psychosis should be classified as a distinct disease entity, not as a primary psychotic disorder or directly as bipolar disorder in the next DSM-VI (Chapter 4).

Conclusions regarding the immunopathology of postpartum psychosis:

- The normal postpartum period is characterized by:
  - Normal numbers of monocytes with a slightly altered inflammatory gene signature (Chapter 5)
  - Higher levels of the cytokine Il-1β compared to healthy non-postpartum women (Chapter 5)

  - An increase in T-cells; particularly in CD4+ T helper cells, and within this population an increase in the pro-inflammatory Th1 and Th17 and the anti-inflammatory natural T regulatory cells (Chapter 5)
  - Increased tryptophan breakdown that results in high kynurenine levels, which suggests a higher activity of either the immune enzyme indoleamine-2,3-dioxygenase (IDO) or of the liver enzyme TDO (Chapter 6)
  - An increased skewing towards toxic 3-HK in the tryptophan catabolism pathway, suggesting that KMO enzyme activity is > than KAT enzyme activity (Chapter 6)
- The postpartum psychosis period is characterized by:
  - Higher numbers of monocytes with a consistently upregulated inflammatory gene signature (Chapter 5)
  - Higher levels of the cytokine CCL2 compared to healthy postpartum women (Chapter 5)
  - A lack of the normal postpartum T-cell increase (Chapter 5)
  - A lack of the normal postpartum increase in tryptophan breakdown (Chapter 6)

Together, postpartum psychosis might represents a T-cell defect that is uncovered by the postpartum period. This T-cell defect would be compensated by higher immune activity of the monocyte/macrophage arm, and it coincides with the inability to induce IDO (or TDO). The skewing in the trypcat pathway towards the toxic metabolite KMO is intact (Chapters 5 and 6).

Limitations of this study:

Small patient numbers

One of most important limitations of our studies is the relatively small number of women who were analyzed. This was caused by the severity and rare incidence of postpartum psychosis, and thus far, no randomized clinical trials have been conducted. However, our four-year follow-up rate is high (97.5%) and we believe that our study is the largest cohort of prospective follow-up women with PP.

Naturalistic design

The naturalistic design of our study warrants a cautious interpretation of the effectiveness of the given treatment. Because of the treatment algorithm, the effectiveness of medication may be falsely attributed due to the duration of treatment before the next step is added. The naturalistic design also allows for the possibility that patients' preferences influenced certain outcomes.

Patient recruitment from one mother-baby-unit

Another limitation is the consideration of whether the patient recruitment from a

single, inpatient, mother-baby-unit (MBU) might hamper the generalization of our findings. Unfortunately, many regions in the world do not have MBU care within a reasonable travel distance for women. When mother and baby are separated during admission, the understandable wish to reunite them might lead to discharge prior to full clinical remission. In contrast, in our hospital, most women were only released after complete remission of all symptoms, which might have influenced the relapse risk.

Comparison with a reference population

Another discussion point of this study could be the comparability of our women with the 'Generation R' population, as the population and the moment of evaluation differ. We performed a sensitivity analysis to investigate the influence of the difference in populations, and we conclude that the different characteristics between our PP cohort and the Generation R population do not interfere with the psychological functioning scores. The Generation R control group completed a questionnaire at a different time point than the postpartum psychotic women. This could lead to potential bias for our comparisons since it is generally assumed that all women experience more psychosocial symptoms in the early postpartum phase [1].

No monitoring during relapse

Most women did not receive visits during their relapse. Women and psychiatrists retrospectively obtained almost all of the information about the relapses. Some women were still in care or were referred again to the Erasmus MC. In that case, we could directly diagnose the type and duration of relapse. This limitation could be prevented by obtaining information about the follow-up care of all postpartum psychotic women at Erasmus MC. However, because of the national distribution of women this is not a convenient option.

No IDO determination in monocytes

In our study we did not determine IDO in monocytes directly; rather, we calculated a ratio between the enzymes.

Our clinical results compared with previous studies

In Table 1 (also in the introduction of this thesis) a summary of the previous follow-up studies is provided. Previous studies estimate that 56% to 87% of women with first-onset postpartum psychosis had a subsequent non-puerperal episode; our study is now included in Table 1. We found a lower percentage of women experiencing a subsequent non-puerperal episode (38.8%).

Table 1. Summary of studies with follow-up of first-onset postpartum psychosis. Percentages of affective relapses are calculated on the entire group of patients with a relapse.

Author + year	Country + centre	Data collection	Follow-up period in years (range)	Inclusion	Number of patients	Design and follow-up percentage	Relapse percentage and percentage of affective relapse
Current study	The Netherlands – University clinic	2005-2014	4 (3-5)	<4 Weeks postpartum *	67	Prospective 94%	39% Affective: 97.0%
Kapfhammer, 2014 [76]	Germany – University clinic	1975-1995	12 (7-24)	<4 Weeks postpartum	55	Retrospective	56% Affective: 61.3%
Blackmore, 2013 [77]	United Kingdom – Nationwide recruitment		11.9 (SD 8.9)	<6 Weeks postpartum	116 -> 99 FO (13 depression in history)	Retrospective	72% Affective: 100%
Kisa, 2007 [78]	Turkey – University clinic	1998-2006	4 (2-6)	<6 Months postpartum	23	Prospective 78%	65% Affective: 39.1%
Rohde,1993 [79]	Germany – University clinics	1950-1979	26 (12-41)	<6 Weeks postpartum	61	Retrospective 87%	64% Affective: 62.3%
Benvenut, 1992 [32]	Italy – University clinic	1973-1987	12 (4-18)	<8 Weeks postpartum*	30	Retrospective 79%	63% Affective: 90%
Terp, 1999 [80]	Denmark – Register Study	1973-1993	10	<2-91 Days postpartum	609	Retrospective	65% X
Kirpinar, 1999 [81]	Turkey- Clinical patients	1973-1994	11 (SD 3)	<3 Months postpartum	64	Retrospective 72% visited, 28% information from GP	81% Affective: 51,5%

Table 1. Continued

Author + year	Country + centre	Data collection	Follow-up period in years (range)	Inclusion	Number of patients	Design and follow-up percentage	Relapse percentage and percentage of affective relapse
Schopf, 1994 [82]	Switzerland – University clinics	1949-1990	23 (3-35)	<3 Months postpartum 54% depressions 46% PP	100	Retrospective 84%	69% Affective: 75.0%
Pfuhlmann, 1999 [83]	Germany -University clinic	1981-1997	13 (6-26)	<6 Months postpartum*	39	Retrospective 81%	87% Affective: 53.8%
Videbech, 1996 [84]	Denmark- Register study	1973-1987	11 (median) (7-14)	<1 Year postpartum	50	Retrospective	58% Affective: 56.7%

Affective disorders: Depression, bipolar (spectrum) disorder, schizoaffective disorder bipolar type
X: Not specified
Inclusion: -First onset postpartum psychosis
-Clear numbers of women with postpartum psychosis and relapse
-Within one year postpartum
-Published since 1992

The observed differences could be influenced by several possibilities. First, in contrast to our study almost all of the previous studies used a retrospective design and had a follow-up period ranging between 4 and 26 years with a mean of 12.7 years [4, 10, 12-15]. A retrospective design is more vulnerable to selection and recall bias, which can lead to a higher estimation of relapse. In addition, we had a relatively short follow-up period; it is possible that more relapses will occur after four years. Because almost all of the relapses that we found occurred in the first 18 months after remission, it is unclear whether a longer follow-up period will generate a higher relapse rate.
Second, in this study we used stringent inclusion criteria, especially regarding the onset and psychiatric history. An SCID [16] was performed on every mother with postpartum psychosis, to exclude women with previous non-puerperal (hypo) manic or psychotic episodes. Women with an onset of postpartum psychosis during pregnancy or more than six weeks after delivery were also excluded. In our study, the onset of the postpartum psychosis was soon after delivery (median eight days). In previous studies, the inclusion period ranges from six weeks postpartum up to twelve months postpartum. This generates a heterogeneous study population, increasing the possibility of including psychiatric disorders other than postpartum psychosis. In summary, our study population is homogenous.
A third possible explanation of the difference in relapse rates between this study and previous studies could be due to the treatment that our study population received. The treatment algorithm consisting of benzodiazepines, antipsychotics, and lithium has proven to be effective during the nine month follow-up [17]. We advised slowly tapering off medication after being in remission for six months, and doing this under the strict control of a clinician. In addition, during a new pregnancy, the postpartum psychosis prevention protocol [18] prevents a new episode. Almost all pregnant women with a history of first-onset postpartum psychosis (16 of 19 pregnancies) participated. In the studied population, no women experienced postpartum psychosis or depression again.

A fourth reason for the lower relapse rate in this study compared to previous studies could be a selection bias of our study population. Our cohort has a high likelihood of being ethnically Dutch, having postsecondary education, and being married or living with a partner compared to the catchment area. This is alarming because our findings suggest that there is a difference between psychiatric service utilization between native and immigrant residents in the Rotterdam area. For this study, the relatively stable educational, relational, and work situations of our women before postpartum psychosis might have influenced their relapse rate by, for example, increased therapy adherence. In studies on bipolar disorder, the relapse rate is lower in “social stable

patients" [19]. The final difference from previous studies is our low lost-to-follow-up percentage. We have a follow-up percentage of 94%, while other studies have a follow-up percentage that ranges from 78% to 87% [4, 10, 12-15].

Relationship between postpartum psychosis and bipolar disorder clinical aspects

Postpartum psychosis is not distinctly classified in the DSM-IV/V or ICD-10, but it is a phenotypically well-defined disease entity. An important risk factor for developing postpartum psychosis is bipolar disorder, but a large proportion of women with postpartum psychosis have no prior manic or psychotic episodes [20]. In our research, we have particularly focused on this group: women with first-onset postpartum psychosis. Several studies have suggested that postpartum psychosis is frequently the initial presentation of an underlying mood disorder within the bipolar spectrum [10, 11, 14, 15, 21-23]. An important previous study has clearly described the similarities and differences between PP and bipolar disorder [24], but there are to less studies on this topic.

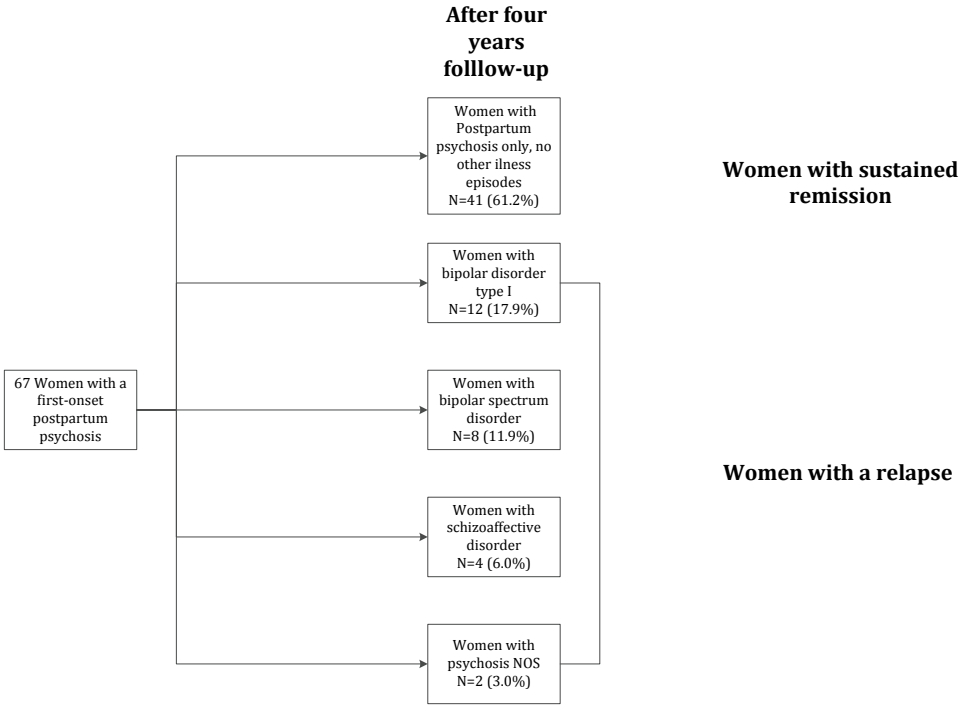

Figure 1. Diagnoses after four-year follow-up after first-onset PP.

Overall studies demonstrate that the prognosis of postpartum psychosis is better during the first four years after a first episode than the prognosis after a first manic episode. We argue that women with a single postpartum psychotic episode (61.2% of our cohort) should not be diagnosed with bipolar disorder instantly because many did not experience further serious psychiatric illness during the four-year follow-up period. In our research population, approximately one third of the women could be diagnosed with bipolar disorder after first-onset postpartum psychosis (12/67, 17.9%), bipolar spectrum disease (8/67, 11.9%), or schizoaffective disorder bipolar type (4/67, 6.0%) after four years follow-up (Figure 1). Women with manic-psychotic relapses should be diagnosed with bipolar disorder. Moreover, women with subsequent depression clearly suffer from a bipolar spectrum disease with a vulnerability to mood disorders.

Immunological parameters in women with postpartum psychosis compared to healthy women (postpartum and non-postpartum)

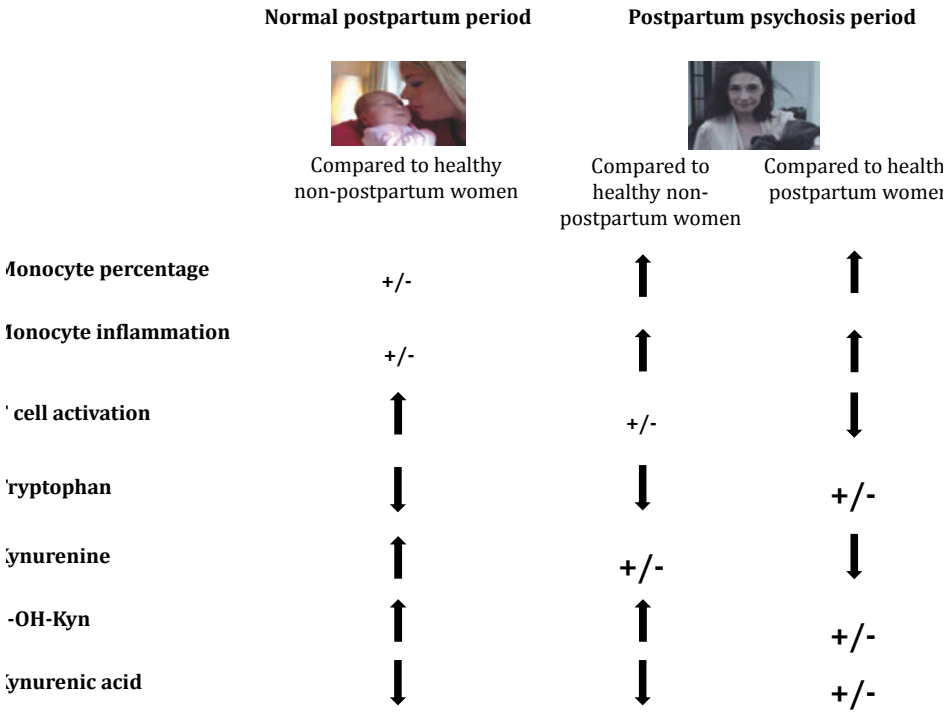

Figure 2. Summary of immune disturbances in postpartum psychosis compared to healthy postpartum and non-postpartum women.

Our immunological results compared with previous studies

Table 3 summarizes the immunological parameters that are discussed in the introduction and throughout this thesis in patients with postpartum psychosis, bipolar disorder, depression, and schizophrenia.

Table 3. Immunological differences and similarities between postpartum psychosis, the normal postpartum period, bipolar disorder, depression, and schizophrenia (references in the introduction).

	Normal postpartum period	Postpartum Psychosis	Bipolar disorder	Depression	Schizophrenia
Monocyte counts	Normal	Increased	Normal	Normal	Increased
Monocyte gene expression	Hardly changes	Activation cluster 1 and 2	Activation cluster 1 and 2	Activation cluster 1	Activation cluster 1
Cytokines	Increased IL-1β	Increased CCL2	Increased Il-6, TNF- α, IL1-R, TNFR-1, CCL2	Increased TNF-α, IL-6, Il-2, CRP, IL-1β, IFN-ɣ Decreased IL-4, IL-10	Increased IL1-R, sIL-2R, IL-6, IL-12, IFN-γ, TNF-α Decreased IL-2
Microglia	X	X	Activated microglia in the right hippocampus	Contradictory results: no change or increased activity	Activated microglia in hippocampus (acute psychosis) or global brain (recovered patients).
T-cells	Higher percentage T-cells, higher Th1, Th17, and Treg	Normal numbers,	Higher number and percentage of (in patients <40 years) Treg, normal percentage of Th1, Th2, and Th17	Normal numbers, but lower percentage of Treg, Th1, and Th17	Reduced numbers overall, but higher percentage of TH1, TH17, and Treg
Tryptophan metabolites	Decreased tryptophan, Increased kynurenine, decreased kynurenic acid, and increased 3-HK	Decreased tryptophan, Normal kynurenine. decreased kynurenic acid, and increased 3-HK	Normal serum kynurenic acid level, lower plasma tryptophan, increased kynurenine and kynurenine/ tryptophan ratio	Decreased tryptophan level and kynurenic acid	Increased kynurenic acid

This table does not provide a complete overview of all research results on immunological parameters. Instead information reported in this table is mostly based upon previous research done in our study consortium (Moodinflame) and laboratories.

If we compare our results to the previous literature, it is surprising that women with postpartum psychosis do not show all of the previously found immune disturbances. The monocyte numbers in postpartum psychosis are elevated, and this is also found in patients with schizophrenia. Furthermore, women with postpartum psychosis show an up-regulated gene expression profile in monocytes compared to controls; this is previously described for bipolar disorder and schizophrenia [28]. We found a higher serum level of CCL2, and in bipolar patients CCL2 and other cytokines are found to be elevated [29, 30].

Many postpartum immune syndromes (e.g. postpartum thyroiditis) [31] and psychiatric disorders show an activated T-cell system [32-35]. In addition, healthy postpartum women show an increase in T-cells. Unexpectedly, we did not find T-cell activation in women with postpartum psychosis. The percentages of circulating T-cells were significantly decreased compared to women in the normal postpartum period. Remarkably, lower T-helper cell numbers were previously found in patients with major depression and in patients with schizophrenia and acute psychosis [36, 37].

Future research

Fortunately for women and unfortunately for researchers, the prevalence of postpartum psychosis is low. Thus, a long duration of research is required to provide a large research cohort. This study started 10 years ago and is currently continuing. It includes, as far as we know, the largest cohort of women with first-onset postpartum psychosis worldwide. In this study, we collected a unique group of women who wanted to participate in our research and it would be ideal to follow them for a longer period. Some previous studies found another critical period in vulnerable women during menopause [39], and it would be interesting to investigate this in our research cohort. Unfortunately, we did not investigate personality traits during the follow-up period. Previous research on postpartum psychosis has hypothesized that the premorbid personality of women who experienced a classical puerperal psychosis is characterized by “psychasthenic features” as described by Janet [40, 41]. Psychasthenia is an old psychiatric term that refers to a personality trait that is characterized by excessive anxiety, phobias, obsessions, and compulsions [42]. The term is no longer in psychiatric diagnostic use, although it still forms one of the ten clinical subscales of the popular self-report personality inventories, MMPI and MMPI-2. Investigating personality traits could be done in retrospect by sending a SCID 2 to the women in our research group.

A topic of future interest could be an investigation into how many women have postpartum psychosis but are not admitted. We are planning to use the data of the

'acute dienst' to compare how many postpartum psychoses are measured and how many women with postpartum psychosis we see in our outpatient or more frequently, our inpatient clinic. This could be interesting because of the characteristics we found in the women from our cohort, which are different than one would expect in a large city such as Rotterdam. We may miss women with postpartum psychosis, and this would be interesting to investigate. In addition, the clinical characteristics and relapse could be related to the status of admission, which is either voluntary or involuntary [43].

Immunology and psychiatry are increasingly related, and research that links both of these fields is growing; this generates new research ideas. It would be ideal to search for antibodies or HLA determination in postpartum psychosis. It is also interesting to investigate family members of women with postpartum psychosis. Questions that can be addressed include: How many women have relatives with severe psychiatric illnesses, especially affective disorders? And, do women with postpartum psychosis have more family members with auto-immune diseases, such as thyroid diseases?

It is also interesting to study the CRP, creatinine kinase (CK), leucocyte count, rheumatoid factor, anti-CCP, and ANA in postpartum psychosis. Previous studies found disturbances in these immunological/infection parameters in depression and bipolar disorder [44, 45]. Table 3 shows that research on microglia in postpartum psychosis is missing; it would be interesting to perform imaging studies in this unique research group. Another immunological parameter that would be interesting to study in the future is cortisol in hair. Life-events induce stress and generate effects through cortisol. Stress negatively influences the disease course in patients with bipolar disorder and potentially in women with postpartum psychosis. Cortisol in the scalp and hair can be used to study long-term cortisol levels and to study the relationship between life events, hair cortisol, and the clinical course of the disease. In a study with patients who have bipolar disorder and who had experienced recent negative life events, increased hair cortisol levels were found [46].

The last topic that is interesting to investigate is the prevalence of autoimmune diseases and severe infections in women with postpartum psychosis. Previous studies found a relationship between these diseases and infections and mood disorders [47]. We can potentially correlate the clinical picture of postpartum psychosis and relapse to the results of these infection/immunological parameters.

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Appendices

Summary

In **Chapter 2** we evaluate the treatment of first-onset postpartum psychosis that is provided at ErasmusMC. We start directly after admission with clinical evaluation, requiring a thorough history, physical, and neurological examination and laboratory analysis to exclude known organic causes of acute psychosis. The pharmacological treatment of patients at ErasmusMC with postpartum psychosis is administered using a standardized treatment algorithm, based on our clinical experience and guided by the larger literature for treatment of bipolar patients. The treatment algorithm consists of four steps: Step 1: All patients were initially treated with lorazepam at bedtime for three days to attempt to restore sleeping. Step 2: When manic and/or psychotic symptoms persisted, antipsychotic medication was recommended, beginning on day 4. Step 3: After two weeks of combination antipsychotic/benzodiazepine treatment, adjunctive lithium was recommended for patients without a significant clinical response. Step 4: Finally, in patients without a response after 12 weeks on the combination of antipsychotic, lithium, and benzodiazepine pharmacotherapy, ECT was recommended. After discharge, women who remitted on antipsychotic monotherapy were advised to continue this treatment as maintenance therapy, while women who required both antipsychotics and lithium to achieve remission were maintained on lithium monotherapy. In Chapter 2, we investigated treatment response and remission outcomes at nine months postpartum using our 4-step treatment algorithm in 64 patients with first-onset postpartum psychosis. All but one of the patients achieved complete remission within the first three steps of the treatment algorithm. None of the patients required ECT treatment. At nine months postpartum, sustained remission was observed in almost 80% of the patients. Patients who were treated with antipsychotic monotherapy had a significantly higher risk of relapse compared to those who received adjunctive lithium. Multiparity and non-affective psychosis were identified as risk factors for relapse.

In **Chapter 3** we studied psychosocial functioning in 78 women nine months after postpartum psychosis. Suffering from postpartum psychosis is a stressful life event and symptoms remain long after the initial illness episode and discharge. Previous studies with small groups of women describe that women experience psychosocial problems; depressive episodes; and milder periods of mood swings, anxiety, and feelings of guilt after the initial illness episode. We found that experiencing a relapse negatively affects functioning. Overall, women were functioning quite well after postpartum psychosis, but they showed more depression and anxiety complaints than a reference population. The majority of these women were working again and

most of the women were satisfied with their lives regarding relationships, work, and other disciplines.
Women with first-onset postpartum psychosis are at a high risk of developing subsequent mood episodes. Unfortunately, studies do not provide evidence based risk estimates, in **Chapter 4** we provide these estimates. Previous studies are scarce and data is usually obtained through retrospective methods, and some studies were conducted a long time ago using diagnostic criteria from a DSM-V that is now outdated. We followed 67 women with postpartum psychosis over four years to describe the disease course, relapse rate, and clinical predictors of relapse; the follow-up rate is 96%. The majority of patients (61.2%) were in sustained remission, and about one-third (38.8%) experienced a relapse: twelve women had depression, eight had a manic episode, and six had non-affective psychosis. Almost all relapses (23/26) occurred during the first 18 months after remission. The majority of the relapses were related to tapering off of medication. No influence of general demographics, psychiatric history, phenomenology, or the presence of life-events on relapse was found.

In **Chapter 5**, we examined immune activation in patients with first-onset postpartum psychosis at the level of monocytes, T-cells, and serum cytokines/chemokines. In previous work by our group, changes were detected in patients with bipolar disorder, depression, and schizophrenia. Because of the hypothesis that postpartum psychosis is the first manifestation of bipolar diathesis, we were curious to search for immunological changes in the group of women with postpartum psychosis. We included 64 women who were consecutively admitted with first-onset postpartum psychosis and matched them with 56 postpartum and 59 non-postpartum healthy controls. We found that monocytes of women with postpartum psychosis have a gene profile that shows more robust immune activation than that which is normally present in the postpartum period, including genes that are not typically elevated in the normal postpartum period.
Furthermore, the GR-β/α gene expression ratio was increased in monocytes of patients with postpartum psychosis, suggesting that steroid resistance is part of this monocyte immune activation state. Surprisingly however, we observed that most T-cell subsets were low in women with postpartum psychosis compared to the levels found in the normal postpartum period.

Chapter 6 describes the tryptophan pathway in the normal postpartum period and in women with a postpartum psychosis or postpartum depression. Tryptophan breakdown is increased as a physiological phenomenon of the postpartum period and might lead to vulnerability to affective psychosis and severe depression. In this study

we investigated alterations in tryptophan breakdown in the physiological postpartum period compared to patients with severe postpartum mood disorders. We found that the high kynurenine levels and increased tryptophan breakdown that is associated with the physiological postpartum period, was not present in patients with severe postpartum mood disorders. No differences were observed in the levels of the 'neurotoxic' 3-OH-kynurenine and 'neuroprotective' kynurenic acid arms between patients and healthy postpartum women.

Appendices

Nederlandse samenvatting

Stemmingsstoornissen in de postpartum periode zijn ernstige aandoeningen die een negatieve invloed kunnen hebben op vrouwen uit verschillende culturen. Er komen drie stemmingsstoornissen in de postpartum periode voor: postpartum blues, postpartum depressie en postpartum psychose. Postpartum blues begint rond dag 3 tot 5 postpartum en heeft een geschatte prevalentie van 40 tot 60%. De postpartum blues wordt omschreven als het kortdurend ontstaan van dysforie, stemmingswisselingen en prikkelbaarheid. De duur van de postpartum blues varieert van uren tot dagen.
Postpartum depressie treft ongeveer 10% van de recent bevallen vrouwen. Veel voorkomende symptomen zijn somberheid, prikkelbaarheid, angst, apathie, schuldgevoelens en het gevoel te falen. Psychosociale factoren kunnen het risico op een postpartum depressie en haar beloop beïnvloeden. Het begin van de postpartum depressie wisselt sterk; het kan voorkomen tijdens de zwangerschap tot aan een jaar postpartum.
Postpartum psychose is de ernstigste en zeldzaamste vorm van de postpartum stemmingsstoornissen; de geschatte incidentie is 1 per 1000 bevallingen. Postpartum psychose wordt omschreven als het plots ontstaan van manische of psychotische symptomen, gemiddeld 8 dagen postpartum en met een gelimiteerde ziekteduur (weken tot maanden). De symptomatologie is uitgebreid en omvat onder andere slapeloosheid, stemmingswisselingen, desorganisatie, rusteloosheid, prikkelbaarheid, wanen en hallucinaties. Het risico op suïcide en infanticide is verhoogd, derhalve is tijdige herkenning en opname van groot belang..
In het Erasmus MC is al meer dan 25 jaar een moeder-baby unit (MBU) aanwezig waar gestandaardiseerde behandeling en niet-farmacologische interventies worden toegepast.

Vrouwen die toestemming gaven voor studiedeelname worden binnen de OPPER-studie prospectief gevolgd sinds 2005; zowel tijdens opname (hoofdstuk 2, 5 en 6) als 9 maanden (hoofdstuk 2 en 3) en 4 jaar postpartum (hoofdstuk 4). De meeste onderzoeken die zijn beschreven in dit proefschrift zijn uitgevoerd binnen deze groep van vrouwen met een postpartum psychose zonder psychiatrische voorgeschiedenis, wij noemen dit een een first-onset postpartum psychose.
Behoudens primipariteit zijn er weinig risicofactoren bekend voor first-onset postpartum psychose. De meest gangbare hypothese is dat een postpartum psychose een presentatie is van een onderliggende stemmingsstoornis, in de meeste gevallen binnen het bipolaire spectrum. Vrouwen met een voorgeschiedenis van bipolaire

stoornis of met een eerder doorgemaakte postpartum psychose hebben een hoog risico van het ontwikkelen van een (recidief) postpartum psychose. Een recente studie vond een algemeen terugval risico van 31%. Hoewel postpartum psychose een ernstig ziektebeeld is, is er weinig bekend over welke interventies het effectiefst. In de afgelopen 25 jaar zijn er 19 studies over de behandeling van postpartum psychose te vinden. Deze studies hebben echter aanzienlijke beperkingen; de onderzoeks aantallen zijn klein en de onderzoeksmethode is retrospectief. Daarnaast zijn de diagnostische criteria niet eenduidig en is de uitkomst van de verschillende behandelmethoden (hormoontherapie, ECT, propanolol, lithium en antipsychotica) op andere manieren gemeten.

In **hoofdstuk 2** evalueren we ons behandelalgoritme voor first-onset postpartum psychose dat wij geven in het Erasmus MC. Deze behandeling wordt voorafgegaan aan grondige diagnostiek bestaande een uitgebreide anamnese, lichamelijk en neurologisch onderzoek en laboratoriumonderzoek. De farmacologische behandeling van patiënten met een postpartum psychose in het Erasmus MC wordt gegeven met behulp van een gestandaardiseerd behandel algoritme. Dit behandelalgoritme is gebaseerd onze klinische ervaring en op de literatuur over de behandeling van patiënten met een bipolaire stoornis en bevat de volgende vier stappen. Stap 1 : Alle vrouwen worden initieel behandeld een benzodiazepine voor de nacht gedurende 3 dagen, met als doel een normaal slaapritme te induceren. Stap 2: Bij persisterende manische en/of psychotische symptomen wordt op dag 4 begonnen met een antipsychoticum. Stap 3: Na 2 weken behandeling met de combinatie van een antipsychoticum en een benzodiazepine wordt lithium toegevoegd bij patiënten zonder een significante klinische respons. Stap 4: Tenslotte wordt bij de vrouwen met een postpartum psychose die na 12 weken nog geen respons lieten zien met de gecombineerde behandeling van benzodiazepines, antipsychotica en lithium, ECT aanbevolen. Als de symptomen in remissie zijn, werd aan de vrouwen die antipsychoticum monotherapie gebruikten, geadviseerd dit als onderhoudsbehandeling te continueren. Aan de vrouwen die een antipsychoticum en lithium gebruikten, werd geadviseerd om alleen lithium te continueren, beiden gedurende een half jaar na ontslag.
In hoofdstuk 2 beschrijven wij een prospectieve naturalistische studie, negen maanden na de bevalling, naar de behandelrespons en terugval bij 64 vrouwen die een postpartum psychose gehad hebben. Op één na bereikten alle vrouwen volledige remissie met de eerste drie stappen van ons behandelalgoritme. Geen enkele patiënt had ECT-behandeling nodig. Negen maanden postpartum, was bijna 80% van de vrouwen nog steeds in remissie. Patiënten die werden behandelend met alleen een antipsychoticum hadden een significant hoger risico op een recidief in vergelijking

met vrouwen die ook met lithium behandeld waren. Als risicofactoren voor terugval identificeerden wij het doormaken van een niet-affectieve psychose en multipariteit.

In **hoofdstuk 3** hebben we het psychosociaal functioneren onderzocht bij 78 vrouwen na een postpartum psychose. Twee eerdere studies bij kleine groepen vrouwen beschrijven dat vrouwen na het doormaken van een postpartum psychose nog geruime tijd problemen ondervinden, zoals stemmings- en angstklachten, en schuldgevoelens. Wij vonden dat het doormaken van een terugval grote invloed heeft op het psychosociaal functioneren 9 maanden postpartum. Over het algemeen kan je concluderen dat vrouwen na een postpartum psychose vrij goed functioneren, alhoewel zij wel wat meer angst en depressie klachten ervaren dan een referentiepopulatie. Wel is de meerderheid van de vrouwen alweer aan het werk en is een groot deel van de vrouwen erg tevreden met hun relatie, vrienden en werkhervatting.

Het is bekend dat vrouwen met een first-onset postpartum psychose een verhoogd risico hebben op het ontwikkelen van latere stemmingsstoornissen, meestal van het bipolaire soort. Helaas zijn er weinig studies die een duidelijke inschatting maken van dit risico. Wij hebben dit in **hoofdstuk 4** geprobeerd te doen. Eerdere studies gebruiken meestal een retrospectief design, zijn lange tijd geleden uitgevoerd en gebruiken andere diagnostische criteria dan wij nu doen op basis van de DSM-IV/V. Wij vervolgden vier jaar lang een 67 vrouwen die bij ons opgenomen waren (vanaf 2005) met een first-onset postpartum psychose om het beloop en terugval te kunnen beschrijven. Alle patiënten werden behandeld volgens het in hoofdstuk 2 beschreven behandelalgoritme, bestaande uit de sequentiële toediening van benzodiazepinen, antipsychotica en lithium. Het follow-up percentage na vier jaar is 96%. De meerderheid van de patiënten (61.2%) was in persisterende remissie, zij hebben dus geen terugval gehad gedurende de vier jaar na de postpartum psychose. Iets meer dan een derde (38.8%) van de vrouwen kreeg wel een terugval; twaalf vrouwen hadden een depressie, acht een manische episode en zes vrouwen kregen een niet-affectieve psychose. Bijna alle recidieven deden zich voor in de eerste 18 maanden na remmissie. De meerderheid van de terugvallen was gerelateerd aan het afbouwen van medicatie. Wij konden geen invloed van demografische gegevens, psychiatrische voorgeschiedenis of fenomenologie op het risico op terugval vinden.

De etiologie van de meeste psychiatrische ziekten is nog onbekend. In de 20ste eeuw verschenen de eerste studies over de relatie tussen psychiatrische ziekten en immunologie. Deze relatie wordt verondersteld vanwege het gezamenlijk voorkomen van psychiatrische stoornissen, auto-immuunziekten en chronische

inflammatoire aandoeningen, de gelijkenis tussen pathofysiologische mechanismen van psychiatrische ziekten en auto-immuniteit, de gevonden immuundysfunctie bij patiënten met psychiatrische ziekten, de ontdekte immuun-modulerende effecten van antipsychotica en anti-depressiva en de beïnvloeding van de stemming bij behandeling met inflammatoire therapieën.
Het immuunsysteem bestaat een aspecifiek (aangeboren) en een adaptief (verworven) deel. Het aspecifieke immuun systeem genereert een snelle, weinig specifieke reactie met en bestaat uit barrières (slijm, speeksel, tranen en huid), defensie cellen (neutrofiele granulocyten, monocyten, macrofagen, natural killer cellen en mest cellen) en oplosbare factoren (cytokines en chemokines).
Het adaptieve immuunsysteem is antigeen specifiek, bevat een geheugen en wordt een aantal dagen na het aangeboren immuunsystheem geactiveerd. De hoofdrolspelers zijn T-cellen en B-cellen.

In **hoofdstuk 5** hebben we de immuunactivatie bij patiënten met postpartum psychose onderzocht. In eerder werk van onze onderzoeksgroep zijn er verandering gevonden bij patiënten met een bipolaire stoornis, depressie en schizofrenie. Omdat men veronderstelt dat een postpartum psychose een eerste manifestatie is van een gevoeligheid voor bipolaire stoornissen, waren wij benieuwd of dit ook tot immunologische overeenkomsten leidt. Wij hebben gekeken naar monocyten, T-cellen en serum cytokines/chemokines. Wij onderzochten 64 vrouwen met een first-onset postpartum psychose, 56 gezonde vrouwen postpartum en 59 gezonde vrouwen die niet zwanger of recent bevallen waren. bij vrouwen met een postpartum psychose is het immuunsystheem meer geactiveerd op het gebied van de monocyte genexpressie dan bij gezonde vrouwen in de postpartum periode. Verrassend genoeg werd echter waargenomen dat verschillende T-cel soorten verlaagd waren bij vrouwen met een postpartum psychose.

In dit proefschrift zullen wij ons ook op serotonine (5-HT) pathway richten. Serotonine is een invloedrijke factor bij de behandeling van psychiatrische ziekten, vooral depressie. Belangrijke antidepressiva zijn selectieve serotonine heropname remmers (SSRI's), serotonine en noradrenaline heropname remmers (SNRI's), monoamine-oxidase remmers (MOAIs) en de tricyclische antidepressiva (TCA's). Al deze medicijnen beïnvloeden de beschikbaarheid van serotonine middels verschillende mechanismen. Bij verscheidene psychiatrische ziekten, zoals de bipolaire stoornis, schizofrenie en depressie, zijn verstoringen in het serotenerge mechanisme aangetroffen wisselend van een verhoogd tot een verlaagd kynurenine en de andere metabolieten van de pathway.

Gedurende een normale zwangerschap treden er verandering op in het immuunsystheem, o.a. in T-cellen, cytokinen en in het tryptofaan metabolisme. Dit metabolisme onderzochten wij in **hoofdstuk 6.** De afbraak van tryptofaan is verhoogd als een fysiologisch verschijnsel van de postpartum periode en kan leiden tot kwetsbaarheid voor affectieve psychose en ernstige depressie. In deze studie onderzochten wij veranderingen in de afbraak van tryptofaan in 58 vrouwen met ernstige postpartum stemmingsstoornissen (postpartum psychose en postpartum depressie) in vergelijk met 53 gezonde vrouwen postpartum. Wij ontdekten dat de hoge kynurenine spiegels en verhoogde afbraak van tryptofaan als een fenomeen van de fysiologische postpartum periode niet aanwezig was bij patiënten met ernstige postpartum stemmingsstoornissen. Geen verschillen werden waargenomen in de niveaus van de 'neurotoxische' 3-OH-kynurenine en de 'neuroprotectieve' kynurenic zuur tussen vrouwen met een postpartum psychose en gezonde postpartum vrouwen.

In **hoofdstuk 7** bediscussiëren we onze bevindingen. We beschrijven dat de prognose voor first-onset postpartum psychose optimistischer is dan eerder gedacht werd. Er is een groep vrouwen met een kwetsbaarheid voor ernstige stemmingsstoornissen, beperkt tot de postpartum periode. Postpartum psychose moet worden geclassificeerd als een aparte ziekte-entiteit, niet als een primaire psychotische stoornis of direct als bipolaire stoornis in de DSM-VI.
Op immunologisch gebied vonden wij verschillen tussen vrouwen met een postpartum psychose en gezonde postpartum vrouwen. Mogelijk speelt een T-cel defect in de postpartum periode een rol bij het ontstaan van postpartum psychose. Dit zal dan gecompenseerd worden door een verhoogde activiteit van de macrofagen en monocyten. Dit heeft weer invloed op IDO welke een belangrijke speler in de tryptofaan pathway is.
Ook deze studie heeft haar beperkingen, bestaande uit (relatief) kleine patiënten aantallen, het naturalistisch studie design, de mogelijkheid tot vergelijken met een referentie populatie. Daarnaast hebben wij de vrouwen niet kunnen bezoeken op het moment van een terugval, en hebben wij niet het IDO in de monocyt zelf bepaald.
In de toekomst zou het interessant zijn om nog veel meer dingen te onderzoeken in vrouwen met een postpartum psychose zoals de persoonlijkheidstrekken, het aantal vrouwen dat niet wordt opgenomen (of zelfs geen zorg krijgt) en diverse immunologische parameters zoals antilichamen, HLA-bepaling, cortisol in haar en de prevalentie van auto-immuun ziekte bij patiënten (en hun familieleden).

Appendices

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Prof. dr. Hengeveld, beste Michiel, dank dat u mij als jonge studente aan Veerle heeft voorgesteld. Ook ben ik erg blij dat u mij als jonge studente heeft aangenomen voor de opleiding tot psychiater. Helaas kan u niet meer in mijn promotiecommissie zitting nemen, maar ik hoop dat ik u in de toekomst nog vaak ergens mag begroeten.

Prof. dr. Van de Broek, beste Walter, u kent mij vanaf mijn 19e en heeft mij van een heel jong studentje op afdeling P2 naar AIOS en nu bijna doctor zien groeien. Ik vond het fijn dat u altijd een luisterend oor kon bieden en dat u mij tijdens de opleiding de ruimte heeft gegeven om mijn promotie-onderzoek af te maken. Tot slot, veel dank voor het plaatsnemen in de leescommissie.

Beste dr. Birkenäger, beste Tom. Dank voor uw hulp als waarnemend opleider en als supervisor op P2, ik heb veel geleerd over het voeren van moeilijke gesprekken met patiënten.

Prof. dr. Hoogendijk, beste Witte, dank voor de interesse in het onderzoek en het mogelijk maken van de groei van ons expertisecentrum "Zwangerschapspsychiatrie". Ik heb als OIO en als AIOS met u samengewerkt en ik vind het mooi om te zien hoe u ook in de kliniek uw kennis van de biologische psychiatrie gebruikt. Dank dat u in de grote commissie wilt plaatsnemen.

Prof. dr. Pop, dank u voor het plaatsnemen in de leescommissie en het kritisch lezen en beoordelen van het manuscript. Ik bewonder uw expertise op het gebied van zwangerschapspsychiatrie en uw kennis over het opzetten van grote onderzoeken.

Dr. Versnel, beste Marjan, hoewel je niet direct bij mijn onderzoek was betrokken voelde ik mij toch altijd erg welkom bij jou. Je bent altijd geïnteresseerd in hoe het met je promovendi gaat en wilt hen graag helpen het beste uit zichzelf te halen. Ook aan jou dank voor het plaatsnemen in de leescommissie.

Verder bedank ik ook graag Prof. dr. Claes, Prof. dr. Feltz-Cornelis en Dr. Hillegers, voor hun bereidheid om plaats te nemen in mijn grote commissie.

Dr. Tulen, beste Joke, wij leerden elkaar kennen toen ik nog een keuze-onderzoek-student (en echt een beginneling in de statistiek) was, maar inmiddels ben ik dan toch bijna gepromoveerd. Altijd was je vol belangstelling en behulpzaam hetgeen ik zeer gewaardeerd heb!

Naast de mensen waarmee ik direct heb samengewerkt zijn er nog heel veel andere collega's die allen op hun eigen manier geholpen hebben om dit promotie onderzoek te volbrengen.

Saskia, Hetty, Astrid, Mayke, Sharon, Deborah, Anchela, Mieke, Marjolein Kasi, Cheyenne, Nienke, John, Paula, Ellen, Ria, Marjolein de Bos, Harriët, Alie en Petra, dank voor de gezelligheid, koekjes en luisterende oren de afgelopen jaren! Ik zal nog vaak blijven langslopen op zoek naar wat (zoete) steun!

Dit onderzoek zou er niet zijn geweest zonder de praktische hulp van de verpleegkundigen van P3. Grote dank, zonder jullie hulp was het mij nooit gelukt om alle patiënten te blijven motiveren voor het invullen van de wekelijkse vragenlijsten en de bloedafname.

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Bij dit rijtje verpleging mag ook de verpleging van P1 niet ontbreken, dank voor de gezelligheid tijdens de diensten en de vele kopjes soep die ik bij jullie mocht halen..

Tom, Marjolein, Climmy, Stefanie, Marieke, Sophie, Marlies, Fatima, Cato en Laurien. Jullie hebben allen meegewerkt aan een deel van het onderzoek. Ik vond het erg leuk jullie te begeleiden en de groei van geneeskundestudent/dokter tot (keuze) onderzoeker mee te beleven.

Marlijn, collega, kamergenoot, onderzoeksmaatje. Dank voor de gezelligheid en steun, ik bewonder jouw Engels taalgebruik en schrijftalent. Wellicht kunnen wij in de toekomst elkaar nog eens aanvullen op onderzoeksgebied, maar nu zijn wij eerst collega's bij PsyQ.

Astrid, van "buurvrouw op de gang" naar zeer gewaardeerde collega. Hartelijk dank voor alle hulp in het voortzetten van mijn project. Ik heb onze samenwerking als heel leerzaam en vaak ook heel smakelijk ervaren en ik hoop dat wij dit in de toekomst kunnen voortzetten.

André, dank voor jouw hulp bij de statistiek, jouw bevlogenheid om de statistische methodes in de wetenschap te verbeteren werkt motiverend.

Richard, ik was al even onderzoeker toen jij begon als tweede promovendus onder de supervisie van Veerle. Dank voor de interesse in mijn onderzoek en de vele praatjes over onderzoek, opleiding en al het andere wat ons bezighoudt op mijn onderzoeksdagen. Heel veel succes met de verdere voortzetting van jouw interessante onderzoek.

Janneke, als nieuwste lid binnen onze onderzoekslijn wil ik je heel veel succes wensen met de voortzetting van ons mooie onderzoek! Ik ben er zeker van dat je er een succesvolle toevoeging aan zal geven.

Sanne, Gabry, Asia, Inge, Vandhana, Eline, Stefanie, Roos, Ernst, Jurate, Yoeri, Babette, Nina en alle andere onderzoekers van de psychiatrie, door jullie was mijn promotietraject niet alleen een leerzame, maar ook een hele gezellige periode. Ik denk bijvoorbeeld aan de jaarlijkse congressen in Maastricht en de gezamenlijke lunches. Het was leuk en leerzaam om met OIO's van zo veel verschillende onderzoeksrichtingen in de psychiatrie te mogen samenwerken.

De Collega AIOSSEN van het ErasmusMC, jullie hebben mij verwelkomt in de opleiding en veel begrip en de interesse getoond tijdens de laatste loodjes van mijn onderzoek. Ik zie ernaar uit de rest van de opleiding met jullie te volbrengen!

Psychiaters van het ErasmusMC. Dank voor jullie steun en belangstelling en bij sommigen ook de betrokkenheid bij mijn onderzoek. Sabine, Kathelijne en Mijke, ik vond het erg leuk om jullie te leren kennen als onderzoeker en later ook als supervisor/psychiater, dank voor de fijne samenwerking. Robert Jan, bij jou begon ik ooit, dank voor de interesse door de jaren heen naar de vooruitgang van mijn onderzoek.

Collega's van PsyQ. Jullie hebben maar een heel klein deel van mijn onderzoekstijd meegemaakt maar ik waardeer de interesse en ik zal jullie nog graag alles vertellen over postpartum psychoses.

Harm, Angelique, Annemarie en Thomas, dank voor het zeer welkome gevoel dat ik altijd kreeg als ik bij jullie op het immunologielab kwam. Ook de eindeloze uitleg over sommige onderwerpen heb ik zeer gewaardeerd. Tevens koester ik warme herinneringen aan onze congressen, lunches, labdagen en andere uitjes samen.

Karin W, Wouter, Noami, Zana en alle andere promovendi van de immunologie. Het was leuk en leerzaam met jullie samen te werken! Ik ben volgens mij de laatste die haar proefschrift afrondt van ons, dus ik heb goed kunnen spieken, veel succes allemaal met de rest van de loopbaan!

Alle Moodinflame collega's wil ik bedanken voor de samenwerking en inspirerende ontmoetingen.Ik voel mij bevoorrecht dat ik al vroeg in mijn onderzoekscarrière de kans kreeg om veel internationale, vooraanstaande collega's te ontmoeten.

Esther Mesman, iets eerder begonnen en iets eerder gepromoveerd... Mijn deelgenoot klinisch werk en immunologie uit Utrecht. Ik vond het heel leuk ervaringen met je te delen, congressen te bezoeken en gewoon contact te hebben, ik hoop dat wij dit in de toekomst zullen voortzetten!

Intervisie clubje NNITV. Dank voor de steun in de laatste fase van het proefschrift, jullie zijn erg dierbare collega's, allen op een eigen manier.

Bavo collega's, bedankt dat ik via jullie de band kon onderhouden met de kliniek naast mijn onderzoek. Ik heb met zeer veel plezier met jullie gewerkt tijdens mijn onderzoeksperiode!

JC Tango, dank voor jullie luisterend oor en vooral afleiding tijdens het schrijven van dit proefschrift. Wij zijn nu al bijna 15 jaar een club en het is verrassend hoe wij zijn veranderd maar tegelijkertijd ook weer helemaal niet in deze periode. Ik hoop nog veel mooie dingen met elkaar mee te maken.

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van mijn leven mijn vriendin en doet compleet ander werk, toch ben je altijd zeer geïnteresseerd en betrokken, dank daarvoor!

Annelien, mijn soos-mama en eeuwige voorloper-in-alles. Nu sta je als paranimf naast mij, ik stond vier jaar geleden al naast jou.. Ik ben net mama, jij hebt al drie kids.. Jij gaat altijd net iets sneller, waardoor ik jou om advies kan vragen, nog steeds dus een beetje mijn soos-mama. Ik ben benieuwd of ik ooit met iets sneller zal zijn.. Dank voor jouw steun en soms ook hulp bij het maken van dit proefschrift, ik vind het bijzonder dat je nu naast mij staat als paranimf maar vooral als trouwe vriendin!

Leontien, inmiddels meer dan 6 jaar geleden startten wij beiden met ons PhD. De eerste tijd leek wel een verlengde studententijd in ons gezellige hok met het tosti ijzer. Inmiddels zijn wij beiden ouder en iets wijzer en niet vaak meer samen in het ErasmusMC. Gelukkig zie ik je nu buiten het werk en samen vakantie vieren of andere leuke dingen doen vind ik nog leuker dan samen werken! Dank voor de gezelligheid en vriendschap, ik hoop dat ik binnenkort ook jouw paranimf kan zijn!

Margot en Fred, Martine, Patrick en de kids, bedankt voor jullie steun bij het schrijven van dit proefschrift! Margot, superlief dat je mij kon helpen door op Amélie te passen zodat ik de laatste loodjes kon volbrengen.

Laura, zelfbenoemd nichtje, dank voor de grote interesse in mijn onderzoek, ik vind het leuk dat jij echt de eerste versie van het hele proefschrift hebt doorgelezen!

Lex en Dorien. Dank voor de onvoorwaardelijke steun, warmte en soms ook praktische hulp die ik van jullie krijg. Ik hoop het binnenkort eindelijk echt minder druk te hebben en meer tijd te hebben voor leuke dingen samen! Ik prijs mezelf gelukkig met zo'n geweldig broer(tje) en schoonzus.

Mama (en papa). Lieve mama, dank dat jij altijd in mij geloofd hebt en mij gesteund hebt op alle mogelijke manieren (o.a. het oppassen op Amélie in de laatste fase van dit proefschrift en het blijven proberen ons huis wat beter te structureren). Jouw kijk op de wereld is voor mij vaak erg relativerend geweest. Helaas maakt papa dit niet mee, maar ik weet zeker dat hij gezegd zou hebben dat hij altijd al wist dat ik het kon en op een wolkje zit te glunderen van trots. Dank dat jullie mij de basis hebben gegeven om keuzes te maken en te durven doen wat soms onmogelijk lijkt! Je bent een supermama en inmiddels superoma!

Jan, mijn grote liefde en steun en toeverlaat! Wij leerden elkaar kennen toen ik nog een co-assistent (en erg studentikoos) was en bijna met mijn promotie-onderzoek ging beginnen. Ik weet zeker dat ik zonder jou het traject niet had kunnen volbrengen. Jij bent zowel een praktische als mentale steun geweest, zo heb jij mij eindeloos geholpen met de eerste presentaties in het Engels, maar heb je mij ook ook de finesses van het Excellen geleerd. Jij wist mij te motiveren om vooral door te gaan met het onderzoek, ook als het soms wat moeilijker verliep. Ik ben benieuwd wat wij verder voor goede teams in de toekomst kunnen gaan vormen! Qua samen klussen, koken en zeilen moeten wij in ieder geval de samenwerking nog wat verder perfectioneren ;). Inmiddels zijn wij samen de ouders van onze kleine Amélie, een echte bekroning op onze relatie en de ideale afleider in de allerlaatste fase van dit proefschrift.

Appendices

PhD Portfolio

Summary of PhD training and teaching

Name PhD student: Karin Burgerhout
Erasmus MC Department: Immunology and psychiatry
Research School: Molmed

PhD period: 01-01-2010 to 01-01-2014
Promotor(s): H.A. Drexhage, S.A. Kushner
Supervisor: Veerle Bergink

1. PhD training		
	Year	**Workload (Hours/ECTS)**
General courses		
- Biomedical English Writing and Communication	2010	4.0 ECTS
- Integrity in medical research	2011	4.0 ECTS
- Statistics (biostatistics for clinicians-NIHES)	2011	4.0 ECTS
- Methodology	2011	0.5 ECTS
- Good clinical practice (BROK)	2011	4.0 ECTS
- Systemic literature retrieval in Pubmed	2012	1.0 ECTS
- Presenting Skills for PhD-Students (Molmed)	2012	3.0 ECTS
- The Photoshop CS3 Workshop for PhD-Students	2012	1.0 ECTS
- Basic Introduction Course on SPSS	2010	1.0 ECTS
Specific courses (e.g. Research school, Medical Training)		
- SCID Course	2010	2.0 ECTS
- NIBI (management for promovendi and postdocs)	2011	1.0 ECTS
- The advanced course “molecular immunology”	2011	2.0 ECTS
- Medical immunology	2013	4.0 ECTS
Seminars and workshops		
- Basiskwalificatie Onderwijs (BKO)	2012-2013	4.0 ECTS
- Teach-the-teacher1 en 2		
- Workshop omgaan met kleine groepen		
- Workshop ICK		
- Workshop Individueel Begeleiden		
- PhD-day	20-03-2010	0.25 ECTS

Presentations		
- NVVP Voorjaarscongres oral presentation	2012, 2013, 2014	
- Marce Society Congres oral presentation	2015	
- Unitmeetings Immunology oral presentations	2012	
- Researchgroup Psychiatry oral presentations	2010-2014	
- Moodinflame poster presentations	2011-201	
(Inter)national conferences		
- Marce Society	2010, 2012	
- Moodinflame Meeting	2009, 2010	
- NVVP Voorjaarscongres	2011	
- LKPZ	2011-2015	
	2010, 2011, 2013	
2. Teaching		
	Year	**Workload**
- ICK Psychiatrie	2011-2013	6.0 ECTS
- VO Tuchtzaak Geneeskunde	2010- 2012	1.0 ECTS
- Immunologie casusonderwijs tweedejaars	2011-2013	7.5 ECTS
Supervising practicals and excursions, Tutoring		
- Second year “keuzeonderwijs” for medical students	2011-2013	4.0 ECTS
Supervising Master’s theses		
- KOZ student Tom Smans 2011	2011	14.0 ECTS
- Master student Climmy Koopal	2011	
- KOZ student Marjolein Vreugdenhil 2011-2012	2011, 2012	
- KOZ student Marieke Koet 2012	2012	
- KOZ student Stephanie van Dijk 2012	2012	
- KOZ student Sophie Koorenhof 2012, 2013	2012	
- KOZ student Marlies Holterhues 2013	2013	
Other		
Organizing “Onderzoeksgroep Psychiatry”	2011-2013	3.0 ECTS
Organizing Women’s Mental Health researchgroup	2012-2013	0.5 ECTS

Appendices

List of publications

- Functioning 9 months after a postpartum psychosis.
  KM Burgerhout, AM Kamperman, SJ Roza, MP. Lambregtse-Van den Berg, KM Koorengevel, WJG Hoogendijk, SA Kushner, V Bergink.
  Accepted by Journal of Clinical Psychiatry.
- Tryptophan pathway alterations in the postpartum period and in acute postpartum psychosis and depression.
  C Veen, AM Myint, KM Burgerhout, MJ Schwarz, G Schütze, SA Kushner, WJ Hoogendijk, HA Drexhage, V Bergink.
  J Affect Disord. 2015 Oct 8;189:298-305.
- Evaluation of a treatment algorithm in 64 patients with first onset postpartum psychosis.
  KM Burgerhout*, V Bergink*, KM Koorengevel, AM Kamperman, WJG Hoogendijk, MP Lambregtse-van den Berg, SA Kushner.
  Am J Psychiatry. 2015 Feb 1;172(2)
- Postpartum psychosis in clinical practice: diagnostic considerations, treatment and prevention.
  R Wesseloo, KM Burgerhout, KM Koorengevel, V Bergink.
  Tijdschr Psychiatr. 2015;57(1):25-33.
- Immune System Dysregulation in First-Onset Postpartum Psychosis.
  V Bergink, KM Burgerhout, K Weigelt, VJ Pop, H de Wit, RC Drexhage, SA Kushner, HA Drexhage.
  Biol Psychiatry. 2013 May 15;73(10):1000-7.
- Down-regulation of inflammation-protective microRNAs 146a and 212 in monocytes of patients with postpartum psychosis.
  K Weigelt, V Bergink, KM Burgerhout, M Pescatori, A Wijkhuijs, HA Drexhage.
  Brain Behav Immun. 2013 Mar;29:147-55.

Appendices

Curriculum vitae

Karin Burgerhout werd geboren op 4 augustus 1984 in Nieuwkoop. Zij groeide op in Waddinxveen en behaalde haar in 2002 haar VWO-diploma. Hetzelfde jaar startte zij met haar studie geneeskunde in Rotterdam. Gedreven door haar interesse in de psychiatrie, ging zij in 2003 aan de slag in het studententeam op de depressie afdeling van het Erasmus MC. Alhier kwam zij tot de conclusie dat zij psychiater wilde worden. Vanaf haar derde studiejaar ondersteunde Karin Dr. R.J. Osse (psychiater in het ErasmusMC) bij zijn onderzoek naar de invloed van een delirium op de cognitie bij ouderen na een thoraxoperatie. Zij sloot haar doctoraal succesvol af met een onderzoek naar de invloed van het doormaken van een delirium op de kwaliteit van leven. Tijdens haar laatste co-schappen (in 2009), startte Karin met haar promotieonderzoek naar de klinische en immunologische follow-up van postpartum psychoses, als onderdeel van het OPPER onderzoek in het ErasmusMC. Naast het promotieonderzoek heeft zij met veel plezier gewerkt als algemeen arts in de avonden, nachten en weekenden in de Bavo-Parnassia Groep in Capelle aan den IJssel. Sinds 2014 is Karin arts in opleiding tot psychiater; zij zal haar opleiding naar verwachting in 2018 afronden.

Karin woont samen met Jan in Rotterdam en samen hebben zij dochter Amélie en hond Guusje. Karin houdt van haar werk maar vindt het ook fijn tijd te besteden aan haar lieve familie en vrienden, en hobby's zoals skiën, zeilen, duiken, krachttrainen, boksen, wandelen, zingen en lezen.