First-onset Postpartum Psychosis

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Contents

Chapter 1

Introduction

A case report of one of our patients with postpartum psychosis

Mrs. B, a 28-year-old woman with no prior psychiatric history, delivered a healthy daughter after a first, normal pregnancy. During the first two days postpartum, she was breastfeeding her daughter with notably reduced sleep. By the third day postpartum, she became convinced that her husband wanted to kill their newborn. After her mother suggested that she discontinue breastfeeding, she became extremely violent, kicking her mother in the abdomen. Over the next 4 days, the family continued to struggle as Mrs. B became progressively more impulsive, irritable, and disorganized.

One week postpartum, she was admitted 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 were normal. She was treated with haloperidol and lorazepam. One week after admission, she remained actively manic with psychotic features, requiring the addition of lithium. On a combination of haloperidol, lithium, and lorazepam, her manic and psychotic symptoms went into remission over the next 3 weeks. She was discharged home from the hospital seven weeks after delivery, with close outpatient follow-up, lithium monotherapy, and mother-child interaction therapy.

Three months postpartum, she was diagnosed with autoimmune thyroiditis and thyroxine replacement was started. Lithium therapy was discontinued after 9 months. During a follow-up of two years she did not experience major psychiatric symptoms.

During the outpatient follow-up period following discharge from the hospital, the following important questions were raised by the patient, of which the literature provided incomplete answers:

• *"What happened? What triggered this totally unexpected bizarre behavior right after having my baby?"*

• *"I got better with a lot of medication, do I really need all these pills?"*

• *"My thyroid disease, was that coincidental or does it have anything to do with my psychosis?"*

• *"What will happen to me in the future, will I become ill again?"*

• *"What happens if we want to have another baby?"*

Unfortunately however, there was insufficient evidence in the literature to provide Mrs. B with answers to these important questions, many of which are necessary to optimally guide her clinical care. Therefore, in 2005 we designed a postpartum psychosis study to examine both clinical as well as pathophysiological questions: the OPPER study

(Onderzoeksprogramma Postpartum Psychose Erasmus MC Rotterdam). Among the many reasons for the limited evidence base in the literature regarding postpartum psychosis is the relatively low incidence. Encouraging of the research potential, we treat postpartum psychosis on a relatively large scale because our psychiatric ward at the Erasmus Medical Center has the ability to admit postpartum patients together with their baby. Accordingly, over the past 7 years, the OPPER study has evolved into the largest prospective cohort in the world of patients with first-onset postpartum psychosis. We have defined several risk factors, aspects of phenomenology, neurobiology and longitudinal follow-up of patients with postpartum psychosis and no prior episode of mania or psychosis. In this thesis, we present the foundational results of our study, describing postpartum psychosis from both clinical (part I) and pathophysiological perspectives (part II).

In **Part I – Clinical perspective** we try to answer the following research questions:
- Is postpartum psychosis a distinct disease entity?
- What are risk factors?
- What is the most favourable treatment?
- What is the prognosis, how can we prevent further episodes?

Chapter 2 starts with a clinical review of postpartum psychosis. We describe diagnosis, history, phenomenology and the relation with bipolar disorder. At the end of chapter 2, our treatment algorithms for both postpartum psychosis and postpartum depression with psychotic features are introduced.

The objective of Chapter 3 is to assess obstetric, neonatal, and lactational risk factors for postpartum psychosis in women with first-onset postpartum psychosis compared to a population-based cohort. We also describe phenomenological characteristics of our patients and treatment response.

In Chapter 4, we have investigated prevention of postpartum psychosis and mania in patients at high risk: Patients with bipolar disorder and patients with a history of postpartum psychosis but no manic or psychotic symptoms outside the postpartum period.

Part II aims to identify aspects of the biological **pathophysiology of postpartum psychosis:**
- Does the rapid onset, proximity to childbirth, and dissociability from social factors give us a clue about aetiology?
- Is there an immune related trigger underlying postpartum psychosis?

In Chapter 5, we discuss the current prevailing hypotheses regarding the aetiology of postpartum psychosis and we comprehensively summarize previous neurobiological studies.

In Chapter 6, we have introduced a novel "immune theory of postpartum psychosis", which led to the research described in Chapter 7 and 8.

The aim of Chapter 7 is to determine the prevalence of autoimmune thyroid dysfunction in a consecutive series of primiparous women with postpartum psychosis, compared to healthy postpartum women.

In Chapter 8, we have investigated monocyte gene expression and T-cell activation in women with postpartum psychosis. Patients were matched to postpartum and non-postpartum healthy controls.

Part I

Clinical perspective

Chapter 2

A clinical review of postpartum psychosis

Epidemiology, phenomenology and diagnosis

After childbirth, women are vulnerable to the onset of serious psychiatric symptomatology. Women are approximately 22 times more likely to experience the onset of a manic or psychotic episode in the first month postpartum than at any other time in their lives. Postpartum psychosis is the most severe form of childbirth related psychiatric illness. The prevalence of postpartum psychosis in the general population is estimated as 1-2 per 1000 childbirths (1-3).

In the majority of cases, the onset is rapid and within 2 weeks postpartum (4, 5). The early symptoms include insomnia, mood fluctuation, and sometimes obsessive concerns regarding the newborn, followed by more severe symptoms such as delusions, hallucinations, disorganized behavior, and serious mood symptoms (6, 7). The occurrence of these severe mood symptoms such as mania, depression, or a mixed state is very prominent in postpartum psychosis. Affective phenomenology seems to be a hallmark of the disease and is more prevalent in postpartum psychosis compared to non-postpartum psychosis (8). Apart from its prominent affective symptoms, postpartum psychosis is also famous for its curious delirium-like appearance. Women with postpartum psychosis sometimes exhibit atypical cognitive symptoms such as disorientation, confusion, perplexity, misrecognition of people, derealisation, and depersonalization (4, 8-10). Of note, there is a relatively low incidence of schizophrenia-like symptoms, such as "Schneiderian first-rank symptoms" (7-10). Together, given that postpartum psychosis is generally considered a mood disorder and not a primary psychotic disorder, the term postpartum *psychosis* is therefore somewhat misleading.

By far, the most important risk factors of postpartum psychosis are a history of bipolar disorder or a previous episode of postpartum psychosis. In either case, the risk of postpartum psychosis is estimated as 25-50% following every (subsequent) delivery. A family history of postpartum psychosis or bipolar disorder is also a well-known risk factor. Several family studies have consistently reported familial aggregation of psychiatric (particularly affective) disorders for first degree relatives of women with postpartum psychosis (11). Previous studies have suggested a number of demographic and clinical variables that may be associated with postpartum psychosis, such as primiparity and complications during delivery (12). Indeed, primiparity has been repeatedly observed as a significant covariate in modeling the risk factors for postpartum psychosis. However, a recent large population-based study in primiparous mothers without previous psychiatric hospitalization found no significant influence of delivery complications on the risk of postpartum psychosis (13). Furthermore, no significant evidence has ever implicated psychosocial factors.

Postpartum psychosis must be clearly differentiated from postpartum depression (Table 1). In particular, postpartum depression refers to a non-psychotic depressive episode that affects approximately 10% of mothers after childbirth. Women with postpartum depression experience symptoms of misery, apathy, irritability, social isolation, anxiety, failure to cope and guilt, which are likely to have an impact on a mother's relationship with her child. Like non-puerperal depression, this disease entity is highly heterogeneous: psychosocial risk factors, such as a poor social background, lack of support, and stressful life events, factor prominently in the risk and clinical manifestations. Postpartum depression has a markedly different onset from postpartum psychosis. The onset of postpartum depression is highly variable: often with symptoms during pregnancy (in almost half of the cases), as well as episodes of depression with their onset throughout the entire first year postpartum (14-16).

Table 1 Mood Symptoms and Syndromes during the Postpartum Period

	Estimated incidence	Onset	Frequent symptoms	Management
Maternity "blues"	50 %	3-5 days postpartum	Emotional lability, moodswings, anxiety	Self-limited, emotional support
Postpartum depression	10 %	Variable window: during pregnancy up to one year postpartum	Low mood, feelings of guilt, impaired feelings of bonding with the child	Psychotherapy, antidepressant medication, mother-baby therapy
Postpartum psychosis*	0.1-0.2%	Within 4 weeks postpartum (usually within 2 weeks)	Agitation, irritablility, euphoric mood, depression, delusions, hallucinations, confusion, cognitive symptoms	Hospitalization, medical workup, lithium, antipsychotics, ECT

including postpartum mania and postpartum depression with psychotic features

Although an early postpartum onset is typical for postpartum psychosis, prodromal symptoms of postpartum psychosis are sometimes difficult to distinguish from the normal, physiological maternity blues. About half of recently delivered mothers experience the maternity blues between day 3 and 5 postpartum. This term refers to the brief occurrence of dysphoria, irritability and mood swings. In contrast to postpartum psychosis, the duration of maternity blues ranges from a few hours to a few days, and for which the more severe symptoms that define postpartum psychosis are entirely absent (Table 1) (6).

Understandably, most studies and scientific reviews have focused on postpartum blues and depression. The relatively low incidence, the clinical severity, and diagnostic uncertainty regarding the proper classification of postpartum psychosis have all contributed to the paucity of research. In moving forward with a comprehensive research program, the history of postpartum psychosis and changes in its definition over time are illustrative.

Diagnostic classification of postpartum psychosis: a brief history

One of the initial case reports of postpartum psychosis arose from the autobiographical work of Margery Kempe who delivered her first baby in the United Kingdom in 1393 (17). In brief, she described that she became gravely ill after delivery and called for a priest. The priest was not a very sensitive person as he began to censure her before she could divulge her sins, and then left. Fearing eternal damnation, she fell into a delusional state, where she described seeing devils around her. Because she tried to throw herself out of the window and tried to bite through the veins in her wrist, her husband John chained her in a storeroom. After six months, she saw Jesus sitting at her bed side; the effect was miraculous as she was suddenly sane. She went into a domestic brewing business and after two years she became the biggest beer-maker in town.

Later case reports from Germany, France and the United Kingdom describe similar cases: women with an acute onset of severe affective psychosis immediately postpartum. Importantly, some of these case reports described women with multiple postpartum episodes but none outside the postpartum period, which suggested the existence of a specific postpartum disease. Over time, several names have been given to this postpartum disease, such as: "mania lacteal", "amentia", "puerperal insanity", "puerperal psychosis", "puerperal mania", "dreamlike delirium", and finally "postpartum psychosis". Since the 18th century, postpartum psychosis has been widely appreciated as a severe disease, requiring acute intervention (16, 18).

The first treatments described were cutting of hair, applying ice packs to the head, and/or application of leeches. In the 19th century, physicians focused on the control of excitement, guarding against suicide, and supportive management pending an expected spontaneous remission (16, 19). Remarkably, current treatments of postpartum psychosis do not have a substantially improved empirical basis than the treatments over the last centuries (20). Furthermore, in the second half of the 20th century, the diagnostic category of "postpartum psychosis" was abolished: the prevailing view from experts in the field has been that postpartum psychoses are not specific and fall mainly within the bipolar spectrum.

Childbirth is considered a general stressor, which can trigger an attack of any kind of psychiatric illness. Accordingly, the widely used American psychiatric classification system (DSM-IV: Diagnostic Statistic Manual of Disease) does not have a specific category for postpartum psychosis. Further, in this regard the outcome of the upcoming fifth edition of the DSM is reported to be highly similar to the current edition, i.e. without a separate disease category for postpartum psychosis (personal communication, perinatal congress, Pittsburgh 2010).

Meanwhile in the United Kingdom, the British psychiatric classification system ICD-10 (International Classification of Disease) contains a specific section entitled "mental and

behavioral disorders associated with the puerperium". Notably, however, the addendum to this section encourages a very cautious use of this category:

"Most experts in this field are of the opinion that a clinical picture of puerperal psychosis is so rarely (if ever) reliably distinguishable from affective disorder or schizophrenia that a special category is not justified. Any psychiatrist who is of the minority opinion that special postpartum psychoses do indeed exist may use this category, but should be aware of its real purpose".

Despite these serious warnings, and while the term "postpartum psychosis" is officially excommunicated, there is an undiminished interest from researchers to understand this phenomenon. In particular, over the last decades clinical research has focused intensely on the strong link with bipolar disorder.

Postpartum psychosis and bipolar disorder

Women with a diagnosed bipolar disorder are at very high risk (25-50%) for affective psychosis in the weeks following delivery (21). Importantly, however, the majority of women presenting with postpartum psychosis do not have a history of bipolar disorder.

In patients with first-onset postpartum psychosis, researchers have widely hypothesized a link between postpartum psychosis and bipolar disorder (for review see Chaudron and Pies (22)). Cross sectional symptomatology, family history data, and the longitudinal illness course all support the notion of a strong link to bipolar disorder. First, most studies have shown a preponderance of manic symptoms in postpartum psychosis. Further, family studies of patients with postpartum psychosis have consistently found the risk for bipolar disorder to be higher than the risk within the general population. Lastly, a widely-held estimate is that after an incipient postpartum affective psychosis, a woman has between 40-80 % chance of developing an bipolar disorder (22).

Treatment

Postpartum psychosis is a psychiatric emergency that requires immediate medical attention and psychiatric referral. Inpatient psychiatric treatment is essential to ensure the safety of mother and baby. Within the UK, national guidelines (NICE) recommend that all women requiring postpartum admission are admitted with their infants to specialist Mother and Baby Units (MBU). There is some evidence that admission to a MBU is associated with improved satisfaction with care and reduced time to recovery. In the Netherlands, few psychiatric or general hospitals have an MBU: combined mother-baby admission is only possible within the Netherlands at Erasmus MC Rotterdam, RPC Woerden, and RGC Apeldoorn.

The initial clinical evaluation for postpartum psychosis requires a thorough history, physical and neurological examination and laboratory analysis to exclude known organic causes for acute psychosis. There are case reports on misdiagnosis of postpartum psychosis revealing a late-onset urea cycle disorder (23), paraneoplastic encephalitis (24), citrullinemia type I (25), and primary hypoparathyroidism (26). Differential diagnosis should further include infectious diseases, eclampsia, autoimmune diseases, metabolic diseases, vitamin deficiencies, stroke and drug-induced psychosis (27). Therefore, tests should include a complete blood count, electrolytes, blood urea nitrogen, creatinine, calcium, liver function tests, glucose and thyroid function. With proper indication, head CT or MRI scan, vitamins B1, B12 and folate, urinalysis and urine drug screen should also be performed.

For any mother who presents with a postpartum mood disorder, the clinician must inquire about thoughts of harming herself or the infant. Delusional thoughts about harm to the infant or herself in postpartum psychosis are ego-syntonic and associated with psychotic belief. The urge to act on psychotic beliefs, combined with loss of reality testing, can quickly and easily lead to dangerous life-threatening situations.

Pharmacotherapy

Little is known about what interventions are most effective for patients with postpartum psychosis, as research has been very limited and no randomized trials have been performed. In total, only 17 treatment studies of postpartum psychosis can be found in the recent literature (20). Sample sizes are very small: 9 are case reports describing a single patient and only 2 studies included more than 10 patients. These studies exclusively used a retrospective design and a wide variety of diagnostic criteria to determine study inclusion and intervention efficacy. Only one previous treatment study reported using standardized diagnostic criteria.

The effects of lithium, antipsychotics, ECT, hormones and propranolol were examined. Lithium and antipsychotic medication are commonly used in the treatment of postpartum psychosis, however the evidence to support these treatment options is scarce. Lithium was found to be effective in one case study where it was used as monotherapy (28), and in two studies where it was used as adjunctive therapy (29, 30). The effects of antipsychotics have been described in four case reports, for which treatment was reportedly successful on chlorpromazine, clozapine and pimozide (20).

Three studies have explored the influence of ECT in the treatment of PP. In one case study, treatment with chlorpromazine was ineffective, while ECT treatment led to remission (31). Similarly, a case series of 5 women with treatment refractory PP described positive treatment outcomes with ECT (32). Furthermore, a retrospective study compared the clinical responses to ECT of women with postpartum psychosis to outcomes following ECT in women with non-postpartum psychosis. Notably, the postpartum group was found to have greater clinical improvement following ECT compared to the non-postpartum group

(33). Three studies conducted by the same group have found beneficial effects of estrogen (34-36). The potential beneficial use of progesterone and hormonal replacement therapy have been described through case reports (37). Other case reports have provided support for propranolol (a beta-adrenergic blocker used to treat hypertension) as a treatment option for postpartum psychosis (38).

In the Erasmus MC, treatment of postpartum psychosis is administered using the clinical guidelines for the treatment of mania in bipolar I disorder (39). This algorithm is based on our clinical experience, guided by the larger literature for treatment of bipolar patients. Specifically, all patients are initially treated with benzodiazepines. For those patients without a marked improvement on benzodiazepine monotherapy, antipsychotic medication is initiated within the first week of admission. After 2 weeks of combination antipsychotic/benzodiazepine treatment, adjunctive lithium is initiated in those patients without a significant clinical response.

Unfortunately, few treatment recommendations are available in the literature regarding the treatment of postpartum depression with psychotic features. According to DSM-IV criteria, postpartum depression with psychotic features does not constitute a bipolar depression. However based on our clinical experience, we have followed the view that early-onset postpartum depression is likely to have a bipolar diathesis, particularly if psychotic features are present. Therefore, we followed the guidelines for treatment of bipolar II depression in patients with the acute onset of depression with psychotic features during the postpartum period, even in the absence of hypomanic symptoms immediately postpartum or of a history of hypomania (40).

Of our patients (n=7) diagnosed with a major depressive episode with psychotic features and an onset of symptoms within 4 weeks of the postpartum period, six women were treated with lithium and antipsychotics and one woman refused treatment. For all except one woman, the depression went into complete remission. The one patient who did not respond to treatment with lithium and antipsychotics received ECT, and her depression subsequently remitted (40).

We do not know what would have happened if we had treated these seven women with antidepressants, but in our opinion antidepressant treatment could have put these patients at an unacceptable risk for exacerbation of symptoms. Similar to Sharma et al. (41, 42), we also have the clinical experience that antidepressants should be used cautiously in the postpartum period. Over the last 4 years, eight postpartum patients were referred to our clinic as a result of a very unstable illness course (manic and psychotic symptoms) after treatment with antidepressants (Table 2). Future studies will need to be performed to define an optimal treatment algorithm for postpartum depression with psychotic features.

Table 2 Clinical and Treatment Characteristics of Women with an Unstable Disease Course after Receiving Antidepressants (AD) in the Postpartum Period.

	Psychiatric history	Age Years	Parity	Postpartum diagnosis	Onset post-partum	AD treatment	Adverse effect	treatment
1	Anorexia Nervosa	37	P3	Postpartum anxiety	30 days	citalopram	psychosis	Stop AD
2	Postpartum depression	32	P3	Postpartum depression	2 days	paroxetine	mania	Stop AD, Lithium
3	None	29	P2	Postpartum anxiety	7 days	sertraline	anxiety and hallucinations	Stop AD
4	Depression Cannabis use	31	P1	Postpartum depression	7 days	citalopram	psychosis	Stop AD, lithium, haloperidol
5	Depression	29	P1	Postpartum depression	7 days	clomipramine	mania	Stop AD, lithium
6	None	32	P1	Postpartum depression	18 days	citalopram	psychosis	Stop AD, lithium
7	Psychosis NOS	31	P1	Postpartum depression	6 days	sertraline	psychosis	Stop AD, lithium, olanzapine
8	None	27	P2	Postpartum depression	10 days	citalopram	mixed episode	Stop AD, lithium, olanzapine

AD= antidepressant

Mother infant bonding

Interrupted development of a secure mother–infant bond can lead to long-term problems in a child's emotional, cognitive and behavioral development (43). Importantly, severe postpartum psychiatric disorders, such as postpartum psychosis, represent a major challenge to maintaining the integrity of mother–infant bonding while symptoms persist. Two small studies have confirmed a deleterious influence of postpartum psychosis on mother–child bonding during the acute phase of the illness (44, 45). Remarkably however, a recent study from our group demonstrated that women with a postpartum psychosis, in contrast to postpartum depression, experience hardly any difficulties establishing a bond with their child after discharge from the hospital (46). Therefore, a more comprehensive series of studies is required to define optimal treatment algorithms for specific postpartum psychiatric disorders based upon empirical evidence and long-term outcomes.

Prevention of subsequent episodes

The strongest predictors for postpartum psychosis are a history of bipolar disorder and/or postpartum psychosis (3, 20, 22). Consequently, guiding women at high-risk for psychosis through pregnancy and the postpartum period is a major challenge for mental health practitioners and obstetricians (47-49), for which safe and effective relapse prevention would be the optimal strategy.

Six studies have assessed the efficacy of various prophylactic treatments for prevention of postpartum psychosis in bipolar patients: lithium (3 studies) (50-52), estrogen, valproate and olanzapine (53-55). In all 3 studies using lithium, bipolar women receiving prophylactic treatment had significantly lower rates of postpartum psychosis. In contrast, both estrogen and valproate failed to demonstrate significant prophylactic benefits. Olanzapine prophylaxis was equivocal and therefore warrants further investigation. Notably, a major limitation of these studies was that they included both women who initiated prophylaxis during pregnancy and postpartum, without differentiating between these groups. However, the timing of onset for pharmacological prophylaxis is of paramount clinical importance given that the benefits of prophylaxis during pregnancy need to be carefully weighed against the risks for the fetus (56).

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Chapter 3

First-onset psychosis occurring in the postpartum period: a prospective cohort study

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Abstract

Objective: To prospectively characterize a cohort of patients for whom their first lifetime episode of psychosis occurs in the postpartum period.

Methods: Included in the study were 51 women admitted for postpartum psychosis and a population-based control group (n=6969). All patients received naturalistic treatment using the sequential addition of benzodiazepines, antipsychotics, and lithium. A clinician-administered questionnaire and parallel history provided information about obstetric history, pregnancy, delivery, breastfeeding, neonatal outcomes, and onset of the disease. Clinical remission was defined as the absence of psychotic, manic and depressive symptoms for at least 1 week. The study was conducted from 2005 to 2009.

Results: Compared to the general population sample, women with postpartum psychosis had a significantly higher incidence of primiparity, but had no significant differences in delivery-related, lactational, or neonatal-related risk factors. The median onset of psychiatric symptoms occurred at 8 days postpartum (IQR 5-14) and median duration of episode was 40 days (IQR 23-69). Patients with prominent depressive symptoms had a significantly later onset (p=.01) of psychosis and a longer duration of episode (p<.01) than patients without depressive symptoms. Psychotic symptoms were mood-incongruent in 64.7% of patients.

Conclusion: In contrast other findings related to postpartum psychosis in bipolar patients, no delivery-related, neonatal-related, or lactational risk factors could be identified. Further, our findings of a delayed onset and mood-incongruence of postpartum psychotic symptoms markedly contrasts with that of patients with a previous history of bipolar disorder. These results suggest that women with psychosis limited to the postpartum period might have a distinct risk profile and phenomenology.

Introduction

Postpartum psychosis is a rare but severe disorder. The incidence has been estimated as 1 or 2 of 1000 deliveries (1). Phenomenologically, postpartum psychosis has been described as having the abrupt onset of manic or psychotic symptoms within 4 weeks of delivery. In addition, patients frequently experience insomnia, restlessness, irritability, and affective instability (2). Importantly, clinical symptoms vary widely and can often be overlooked in the early postpartum period. However, given the severity of the disorder with very high risks for suicide and infanticide, early recognition is of great importance.

By far, the most important risk factor for postpartum psychosis is a history for bipolar disorder (3). In women with bipolar disorder, the first symptoms of postpartum psychosis are often reported within 1 or 2 days following delivery (4, 5). Indeed for women with bipolar disorder, careful monitoring during the postpartum period, prophylactic treatment, and prevention of sleep loss have been well-documented to improve clinical outcome (6).

Although bipolar disorder is an important risk factor for postpartum psychosis, the majority of patients admitted with postpartum psychosis have no prior diagnosis of a psychiatric disorder (7). Therefore, the etiology of postpartum psychosis in patients with no prior psychiatric history remains unclear. Further, the most commonly reported hypothesis is that their manifestation of postpartum psychosis results from an underlying bipolar diathesis (8-10). Therefore, investigators have now begun to focus studies specifically on this distinct population: those patients with psychotic episodes limited to the postpartum period (11, 12).

Accordingly, the present study was designed to examine prospectively the risk factors, phenomenology, mode of onset, and clinical course in women with psychosis exclusively limited to the postpartum period.

Methods

Participants
This study was approved by the medical ethical committee of the Erasmus MC Rotterdam. All subjects provided written informed consent.

The study was performed at the Mother-Baby Inpatient Unit of the Department of Psychiatry of the Erasmus Medical Centre (Rotterdam, the Netherlands). This 5-bed inpatient unit treats female patients with severe psychopathology in the postpartum period (0-6 months). Patients are given the option for admission together with their baby, in a fully staffed nursery adjoining the unit.

Every patient admitted to the Mother-Baby Inpatient Unit between August 2005 and December 2009 was screened for study inclusion (n = 157), and diagnosed using the Structured Clinical Interview for DSM-IV axis I Disorders, Patient edition (SCID – 1/P) (13). Previous hypomanic and manic episodes were registered using the Mood Disorder Questionnaire (14).

Patients aged 18-45 years with a diagnosis of 'postpartum psychosis' were included into the study cohort. As 'postpartum psychosis' is not described as a distinct disease entity in DSM-IV-TR, we defined subjects as those patients in which the SCID interview generated any of the following DSM-IV-TR diagnoses, and required the specifier "onset postpartum": depressive disorder with psychotic features, mania with psychotic features, mixed episode with psychotic features, psychotic disorder not otherwise specified (NOS), or brief psychotic disorder. Importantly, the specifier *onset postpartum* requires that the onset of symptoms must occur within 4 weeks postpartum. Consequently, patients with a chronic psychotic disorder or psychosis with onset during pregnancy were excluded.

Sixty-six patients fulfilled the criteria for postpartum psychosis. We excluded 15 patients because of a history of psychosis and/or mania occurring outside the postpartum period: 8 patients had a history of bipolar I disorder, 5 patients had psychotic disorder NOS, 1 patient had schizoaffective disorder, and 1 patient had cannabis dependence. Fifty-one patients had psychosis limited to the postpartum period, of which 45 patients were experiencing their first psychotic episode while 6 patients each had a single previous episode of postpartum psychosis. Of these 51 women with psychosis limited to the postpartum period, 9 women reported depressive and anxiety symptoms in history, 6 women had previously seen a psychologist, and 1 woman had been treated with venlafaxine. None fulfilled criteria for a DSM-IV axis II personality disorder.

Since postpartum psychosis is widely considered as a bipolar-spectrum disease, treatment was administered using the clinical guidelines for bipolar I disorder (15). Specifically, all patients were initially treated with benzodiazepines. For those patients without a marked improvement on benzodiazepine monotherapy, antipsychotic medication was initiated within the first week of admission. After 2 weeks of combination antipsychotic/ benzodiazepine treatment, adjunctive lithium was initiated in those patients without a significant clinical response.

The control group was included through the Generation R study, a population-based study conducted in the same catchment area, with delivery dates from April 2002 until January 2006 (16). This study is designed to identify early environmental and genetic determinants of growth, development, and health from fetal life until young adulthood. Study inclusion occurred during pregnancy for n=6969 women, with a follow-up of at least two months in the postnatal phase.

Risk Factors and Precipitating Factors

All participants and their relatives were interviewed by a psychiatrist. A clinician-administered questionnaire provided information about obstetric history, pregnancy, delivery, breastfeeding, and neonatal outcomes.

Phenomenology was quantified using the Bipolar Affective Disorder Dimension Scale (BADDS) (17). The BADDS is a dimensional rating scale intended for use in clinical samples

with a high incidence of bipolar spectrum illness. There are four identified dimensions, which measure the key domains of lifetime psychopathology: mania, depression, psychosis, and mood incongruence. The presence of psychotic symptoms (percentage of time) was defined based upon the comprehensive psychiatric team evaluations throughout the admission course.

Onset of Symptoms and Clinical Course

We defined the onset of psychiatric symptoms as the first date of having any of the following symptoms: delusions, hallucinations, euphoric mood, increased libido, obsessive thoughts, panic attacks, suicidal thoughts, anhedonia, or disorientation. Further, the onset of prodromal symptoms was defined as the time point at which the patient, her partner, or family initially reported becoming concerned about the patient's mental health, but prior to contacting a mental health provider or having a sufficient symptom burden to fulfill the diagnostic criteria for postpartum psychosis.

Clinical evaluation of treatment was performed weekly using the Clinical Global Impressions-Severity Scale (CGI-S), the Young Mania Rating Scale (YMRS) (18), and the Edinburgh Postnatal Depression Scale (EPDS) (19). Clinical remission was defined as the absence of psychotic, manic and depressed symptoms for at least 1 week (including CGI-S score ≤ 3, YMRS score ≤ 8, and EPDS score ≤ 10) (20). Duration of episode was defined as the number of days, from the initial onset of psychiatric symptoms until remission.

Statistical analysis

All analyses were performed using SAS, version 9 (SAS Institute, Inc., Cary, NC). Categorical outcomes were examined using odds ratios (ORs) with corresponding 95% Confidence Intervals (CIs). Continuous variables were evaluated using using a 2-sample t-test. Control cases were matched for ethnic group and parity, drawn randomly from the Generation R population using the sample function in SPSS. Postpartum onset of symptoms was evaluated using Kaplan-Meier methodology and the log-rank test. All hypotheses were tested with an alpha of 0.05 (2-sided).

Results

Demographics and obstetric outcomes

Table 1 shows the demographic, obstetric, and child outcome measures for the enrolled cohorts. Overall, compared to the unmatched general population sample, women with postpartum psychosis were more frequently of Dutch origin (OR 6.68, 95% CI: 2.85-15.67), with post-secondary education (OR 2.37, 95% CI: 1.36-15.67), and living with a partner (OR 0.27, 95% CI: 0.07-1.13). Further, women with postpartum psychosis had a higher incidence of primiparity (OR 2.90, 95% CI: 1.49-5.67) and primigravity (OR 2.74, 95% CI: 1.51-4.96).

Table 1. Demographic Information, Obstetric variables, and Neonatal Outcomes in Women with Postpartum Psychosis

	Postpartum Psychosis (N = 51)[a]	General Population (N = 6969)[a]	OR (95% CI)	General Population (matched for ethnicity and parity) (n = 2847)[a]	OR (95% CI)
General demographics					
Dutch ethnicity	88.2	52.9	6.68 (2.85-15.67)	88.2	1.00 (0.42-2.37)
Postsecondary education	52.9	32.2	2.37 (1.36-4.12)	40.5	1.65 (0.95-2.88)
Marital status	96.1	87.0	0.27 (0.07-1.13)	90.8	2.23 (0.54-9.21)
Primiparity	78.4	55.6	2.90 (1.49-5.67)	78.3	1.01 (0.52-1.98)
Primigravidity	68.6	44.4	2.74 (1.51-4.96)	65.0	1.18 (0.65- 2.14)
Age, Mean (SD)	31.9 (4.5)	30.2 (5.1)	NS	30.7 (4.5)	NS
History of depressive symptoms	17.6	16.2	1.11 (0.54-2.28)	17.0	1.05 (0.51-2.16)
Pregnancy					
Unplanned pregnancy	9.8	27.1	0.29 (0.12-0.74)	19.8	0.44 (0.17-1.11)
Continual smoking	9.8	10.8	0.90 (0.36-2.27)	10.6	0.92 (0.36-2.32)
Continual alcohol use	25.5	17.9	1.57 (0.83-2.96)	22.1	1.21 (0.64-2.28)
Blood loss	3.9	1.0	4.02 (0.96-16.87)	0.8	5.01 (1.15-21.85)
Growth retardation	2.0	1.6	1.22 (0.17-8.94)	1.6	1.25 (0.17-9.21)
Hypertension	3.9	3.6	1.09 (0.26-4.51)	4.7	0.83 (0.20-3.43)
(Pre)eclampsia	5.9	1.9	3.24 (0.97-10.53)	1.9	3.23 (0.98-10.70)
Diabetes gravidarum	0	0.7	NA[b]	0.7	NA[b]
Delivery					
Home delivery	13.7	14.1	0.97 (0.44-2.16)	16.8	0.79 (0.35-1.76)
Fetal distress	7.8	15.4	0.47 (0.17-1.30)	10.3	0.74 (0.27-2.07)
Failure to progress/descend	11.8	16.3	0.69 (0.29-1.60)	21.3	0.51 (0.22-1.21)
Fluxus	3.9	5.4	0.72 (0.17-2.96)	6.4	0.59 (0.14-246)
Prolonged rupture of membranes	2.0	6.0	0.31 (0.04-2.28)	6.6	0.28 (0.04-2.07)
(sub)total rupture	7.8	5.5	1.46 (0.53-4.08)	4.6	1.76 (0.63-4.97)
Elective Caeserean	2.0	4.7	0.40 (0.06-2.93)	5.5	0.34 (0.05-2.50)
Emergency Caeserean	7.8	7.5	1.05 (0.38-2.91)	8.8	0.89 (0.32-2.48)
Vacuum	9.8	13.6	0.69 (0.27-1.74)	17.5	0.51 (0.20-1.29)
Breastfeeding	88.2	87.8	1.04 (0.44-2.45)	87.0	1.12 (0.48-2.66)
Child					
Premature birth < 37 weeks	7.8	5.6	1.44 (0.52-4.00)	6.4	1.23 (0.44-3.46)
Neonatal ward	19.6	16.7	1.22 (0.61-2.44)	18.9	1.04 (0.52-2.10)
Birth Weight mean (SD),g	3391 (818)	3412 (566)	NS	3420 (569)	NS

[a] Values shown are percentages unless otherwise stated
[b] Odds ratio cannot be computed given the absence of diabetes gravidarum in postpartum psychosis
Abbreviations: NA= not applicable, NS=nonsignificant

Of note, 11 of 51 patients had a previous delivery, prior to study enrollment. Six of these multiparous women had previous postpartum psychosis. In contrast, the other 5 patients had no significant psychiatric symptoms following their previous deliveries. Therefore, of the 45 patients with only one episode of postpartum psychosis, 40 (88.9%) were primiparous.

No differences were found in the rates of complications during delivery, nor in the frequency of Caesarean section, compared to controls. Children from mothers with postpartum psychosis had the same mean gestational age, birth weight and no difference in neonatal admission in the first week postpartum was observed. There was no difference in the prevalence of breastfeeding in women with postpartum psychosis compared to controls.

Given the demographic differences between the patients and the control sample, we subsequently matched the cohorts for ethnicity and primiparity, as these demographic factors might influence the development of postpartum symptoms (Table 1). After matching for ethnicity and primiparity, there was a significant difference in blood loss during pregnancy (OR 5.01, CI 1.15-21.85), despite the low absolute incidence of blood loss during pregnancy in all groups. Further, the incidence of (pre)-eclampsia in 3/51 women with postpartum psychosis remained elevated and nearly reached statistical significance (OR 3.23, CI 0.98-10.70). However, there remained no significant differences in any other demographic, obstetric, or child outcome measures.

Phenomenology

Table 2 shows the phenomenological characteristics of the presenting episode of postpartum psychosis. Fifty-one women experienced a postpartum psychosis, of which 36 were without depressive symptoms. Of these women, 32 of 36 had a combination of manic and psychotic features, while 4 of 36 had predominance of psychotic symptoms without a clear evidence of mania.

Fifteen women had a postpartum psychosis with prominent depressive symptoms. Among these 15 women with a postpartum psychosis and prominent depressive symptoms, 7 patients had mood symptoms restricted to depression, while 8 patients fulfilled criteria for a mixed episode involving both manic and depressive symptoms.

Regarding psychotic symptoms, the majority of patients had a mood-incongruent psychosis (33/51, 64.7%). Of these patients with mood-incongruent psychotic symptoms, 25 presented with manic features, 4 with mixed features and 4 with depressive features. Further, 4 of these 33 patients showed Schneiderian first-rank symptoms, of which all four patients presented with manic features.

**Table 2. Phenomenology of Patients with Postpartum Psychosis**

Variable	Postpartum Psychosis N=51	
	n	%
Phenomenology		
Postpartum Psychosis		
With manic psychotic features	32	62.7
With only psychotic features	4	7.8
With depressed psychotic features	7	13.7
With mixed (manic and depressed) features	8	15.7
Relation between mood symptoms and psychotic symptoms		
Only mood-congruent psychotic symptoms	18	35.3
Presence if mood-incongruent psychotic symptoms	33	64.7
Balance between mood-congruent/mood-incongruent	14	27.5
Mood-incongruent psychotic symptoms	15	29.4
Presence of first rank symptoms *	4	7.8
Presence of psychotic symptoms % of time		
Up to 25 % of episode	8	15.7
50 % of episode	11	21.6
75 % of episode	9	17.6
100 % of episode	23	45.1

* 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

Onset of Symptoms

The median onset of the initial psychiatric symptoms occurred at 8 days postpartum (Interquartile range [IQR] 5-14). There was no difference in symptom onset between the 45 women with first-onset postpartum psychosis and the 6 women with a second episode of postpartum psychosis. In contrast, there were significant differences in onset stratified by phenomenological characteristics. Patients without depression had a significantly earlier onset of psychosis (median=7 days, IQR 4-10) than patient with prominent depressive symptoms (median=18 days, IQR 7-21) (Figure 1; log-rank P = 0.01).

Figure 1. Survival curve of Time from Delivery to the initial Onset of Prominent Psychiatric Symptoms in Patients with Postpartum Psychosis
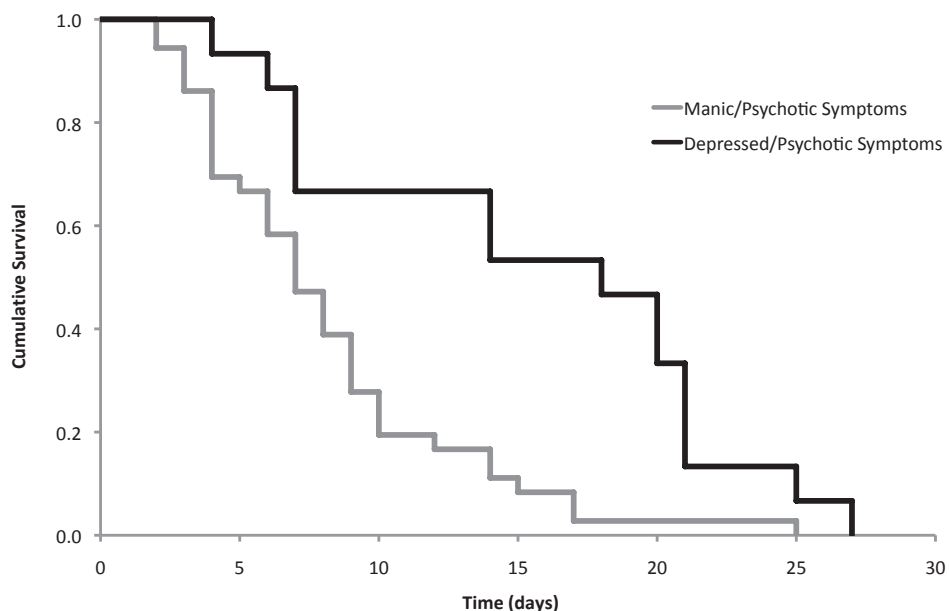

The majority of women reported a history of prodromal symptoms, prior to the overt onset of postpartum psychosis (n=37, 72.5%). Of these 37 women, only 4 reported an onset of prodromal symptoms during pregnancy. In contrast, 33 women had a postpartum onset of symptoms, for which the prodromal phase lasted a median of 5 days (IQR 2-7), while the onset of postpartum psychosis occurred at a median 9.5 day postpartum (IQR 7-17). No prodromal phase was evident prior to the onset of postpartum psychosis in the remaining 14 women (27.5 %), for which the median onset of their acute psychosis was at day 6 (IQR 4-9).

No difference in the incidence of prodromal symptoms was found between patients with a first versus second episode of postpartum psychosis. Similarly, the presence or absence of depressive symptoms was not significantly related to the incidence of prodromal symptoms.

Duration of episode

In our cohort, 47 of 51 patients (92.2%) achieved full remission prior to discharge (Figure 2). The majority of patients (n=34, 66.7%) achieved remission using the combination of lithium, antipsychotics, and benzodiazepines. Nine patients (17.6%) remitted with the combination of antipsychotic medication and benzodiazepines, whereas 3 patients (5.9%) achieved remission with benzodiazepines only. One patient ultimately required ECT treatment to achieve full remission.

Figure 2. Treatment of Patients with Postpartum Psychosis
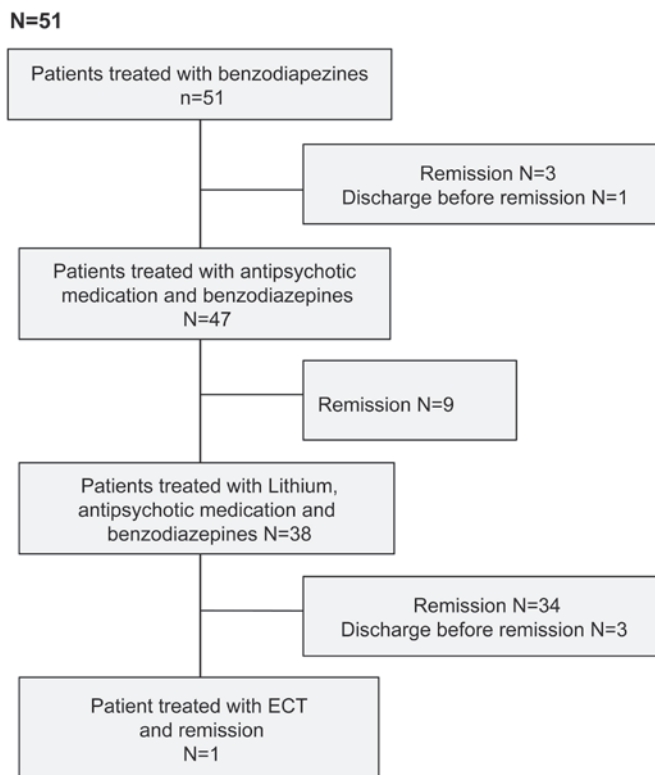
Four patients requested voluntary discharge from the hospital before achieving full remission, at a median 7 weeks after admission. These four patients showed a clear response to treatment, for which both manic and psychotic symptoms were absent for more than one week (1 patient used benzodiazepines and 3 patients used the combination of lithium, antipsychotics, and benzodiazepines). However, they did not fulfill criteria for complete remission at discharge because they still suffered from depressive symptoms or irritability.

In the 47 patients (92.2%) who achieved full remission during their inpatient hospitalization, the median duration of episode was 40 days (IQR 23-69). Further, the duration of episode in patients with first-onset postpartum psychosis was similar to those experiencing a second episode of postpartum psychosis (p=0.81, Mann-Whitney test).

There were significant differences in duration of episode based on the current phenomenology. The clinical course of patients with manic/psychotic features compared to patients with depressed/psychotic features is shown in Figure 3.

Figure 3. Duration of Disease Episode in Patients with Manic/Psychotic Features Compared to Patients with Depressed/Psychotic features
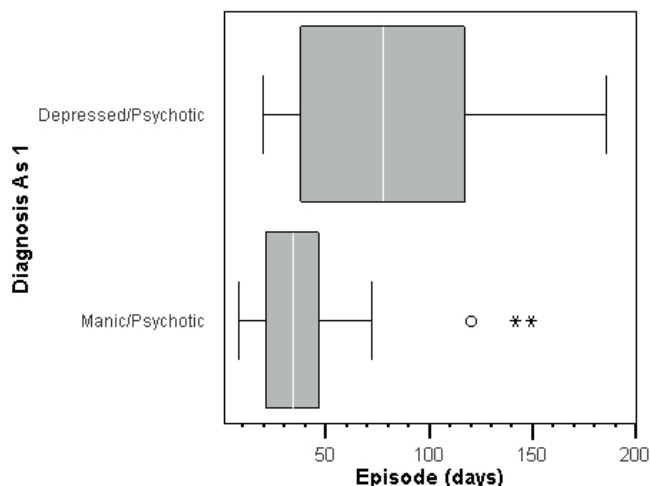
In the 35 women with a predominance of manic/psychotic symptoms, the median duration of episode was 34 days (IQR 19-48). In contrast, the 12 women with postpartum psychosis and depressive symptoms had a significantly longer median duration of episode (77.5 days [IQR 31-117]; p<0.01, Mann-Whitney test). This difference was particularly influenced by the median duration of episode in 6 women with psychotic depression (115 days), compared to 6 patients with a mixed episode (54 days).

Discussion

In this prospective study, we examined risk factors, phenomenology, mode of onset, and clinical course in women with psychosis exclusively limited to the postpartum period.

Primiparity is a highly predictive covariate for postpartum psychosis
Primiparity has been previously observed as a significant covariate, predictive of postpartum psychosis (6). Indeed, our data strongly confirm this finding. Specifically, we find that the initial episode of postpartum psychosis occurs predominantly following a primiparous delivery. Together, these data support a model whereby delivery represents a 'neurobiological stress test', for which a primiparous delivery without psychiatric sequelae is highly predictive of subsequent deliveries. Accordingly, if a woman's initial delivery does not trigger a postpartum psychosis, then the likelihood becomes substantially lower that a subsequent delivery will cause a postpartum psychosis.

Bloodloss and Pre-eclampsia as Riskfactors for Postpartum Psychosis?
Even after correction for ethnicity and parity, we found a higher incidence of blood loss and pre-ecclampsia during pregnancy in women who later developed postpartum psychosis. Accordingly, further research in larger naturalistic cohorts should be used to confirm these findings and to investigate their pathophysiological underpinnings. Importantly however, the low absolute incidence of blood loss or pre-ecclampsia in the PP cohort precludes that either of these factors has a major influence on the general population rates of postpartum psychosis.

No Identified Delivery-related , Neonatal -related, or Lactational Risk Factors
Previous studies in bipolar patients have identified complications during delivery that were associated with postpartum psychosis (6). However, in contrast to these findings with bipolar patients, a recent population-based Swedish study in primiparous mothers with no previous psychiatric hospitalization found no significant influence of delivery complications, such as perinatal death, congenital malformations, preterm birth, or caesarean delivery (12). Similarly, our prospective cohort in non-bipolar patients with no previous psychiatric history also identified no obstetrical or neonatal-related risk factors that were predictive of postpartum psychosis.

   To the best of our knowledge this is the first study of postpartum psychosis to evaluate the influence of lactation. In theory, the dramatic postpartum changes in the hormonal environment, followed by the cyclical neuroendocrine responses governing lactation, could be associated with the abrupt onset of postpartum psychosis. The principle hormones involved in lactation, prolactin and oxytocin, have each been independently associated with disturbances in mental state (21) (22). Importantly in our cohort, the rate of breastfeeding was equivalent in patients and controls. Based on these data we find no evidence of an association between breastfeeding and postpartum psychosis, though prolactin and oxytocin cannot be ruled out as possible factors in the aetiology of postpartum psychosis.

Demographic Characteristics
The patient cohort had a higher likelihood of being ethnically Dutch, having post-secondary education, and being married or living with a partner. Notably however, no significant demographic differences remained after matching for ethnicity. The higher frequency of ethnically Dutch patients could be due to the widely observed difference in psychiatric services utilization between native and immigrant residents (23). Consequently, some immigrant women and their relatives may not have contacted primary care services for serious mental health problems in the postpartum period. Accordingly, substantial efforts in the Netherlands have been increasingly focused on effective solutions for improving ethnic disparities in mental health services utilization (24).

Phenomenology and Family History in Accordance With the Literature

The majority of women suffered from mania (n=32). Less frequently, we observed mixed-episode symptoms (n=8), depression with psychotic features (n=7), or psychosis in the absence of discernible affective symptoms (n=4). As extensively described in the literature, we indeed find that the majority of patients have bipolar symptoms. By the specific DSM-IV criteria, postpartum depression with psychotic features does not constitute a bipolar depression. However, several investigators have more recently advanced the perspective that early-onset postpartum depression is likely to have a bipolar diathesis, especially if psychotic features are present (25).

Importantly, the increased prevalence of mood-incongruent psychosis is similar to that reported in previous studies. In addition, the low incidence of Schneiderian first-rank symptoms has also been described previously (26-29).

One limitation of the current study is the absence of formal cognitive testing. Previous studies of postpartum psychosis have included a detailed description of cognitive symptoms, which include disorientation, confusion, perplexity, misrecognition of people, derealisation, and depersonalization (26, 28-30).

Delayed Onset of Psychiatric Symptoms in the Postpartum Period

The median onset of postpartum psychosis in our study was at 8 days following delivery. Indeed, multiple studies examining naturalistic cohorts of postpartum psychosis, including both bipolar and first-onset patients, have documented the predominant time of symptom onset between 3-10 days postpartum (27, 31). However, these findings of a delayed onset of overt psychotic symptoms contrasts with that of bipolar women for whom the onset of acute psychosis is often immediately postpartum (4, 5). Furthermore, an important confounding factor may be the relative preparedness of women with no prior psychiatric history versus those with bipolar disorder to recognize the emerging symptoms of postpartum psychosis. Additionally from a neurobiological perspective, the threshold for manifesting clinical symptoms of postpartum psychosis might be substantially reduced in bipolar patients as a consequence of previous mood episodes, a phenomenon termed the "kindling hypothesis of mood disorders"(32).

Duration of Episode Appears Similar to Those Observed for Bipolar Disorder

In this study, we report on the duration of episode while patients received naturalistic treatment using the sequential addition of benzodiazepines, antipsychotics, and finally lithium. Our treatment algorithm was based on our clinical experience, guided by the larger literature for treatment of bipolar patients. Importantly, this treatment algorithm also included patients with postpartum psychotic depression based upon the findings of Sharma and colleagues (33, 34) .

Indeed, few treatment recommendations are available in the literature documenting the duration of episode or response to treatment in non-bipolar patients with postpartum psychosis. Accordingly, future studies will need to be performed to define the optimal treatment algorithm for new-onset postpartum psychosis.

Of note, the median duration of episode appears similar in patients with postpartum psychosis and predominantly manic features (5 weeks) compared to the duration of manic episodes previously reported for bipolar patients (7 weeks) (35). Furthermore, we observed a significantly longer duration of episode in patients with postpartum psychosis and depressive features (11 weeks), analogous to the longer median duration of episode in bipolar depression (15 weeks) (35). As expected, patients with a mixed episode exhibiting both manic and depressed features showed a median duration of episode intermediate between the manic and depressed groups (8 weeks).

Psychosis Limited to the Postpartum Period: a Distinct Disease Entity?
Previous studies have clearly described the unusual symptom presentation of patients with postpartum psychosis (26, 28-30) (36). Our data confirm that women with psychosis limited to the postpartum period have a unique risk profile and phenomenology. In particular, and in addition to the clear absence of any manic or psychotic symptoms outside the postpartum period, these patients demonstrate a significantly delayed postpartum onset, the absence of obstetric complications as a significant risk factor, and a prominence of mood-incongruent psychosis, compared to bipolar patients with postpartum psychosis.

Most longitudinal studies have suggested that PP is frequently the initial presentation of an underlying mood disorder within the bipolar spectrum (10, 27, 37-42). Accordingly, the first episode of postpartum psychosis may in retrospect be appreciated as the incipient clinical presentation of bipolar disorder. Further, previous studies have suggested that long-term outcomes are more favorable when bipolar disorder has a postpartum onset (37, 43, 44). Indeed, for some women the occurrence of a postpartum episode of affective psychosis will remain exclusively limited to the postpartum period (10, 27, 37-42). Therefore, an independent status for psychosis limited to the postpartum period might be justified. Further research efforts to distinguish these populations at the time of their first-onset of psychosis will greatly enhance clinical prognosis and treatment.

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Chapter 4

Prevention of postpartum psychosis and mania in women at high risk

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Abstract

Objective: Women with a history of bipolar disorder or postpartum psychosis are at extremely high risk of relapse postpartum. Although lithium prophylaxis has demonstrated efficacy in reducing postpartum relapse, the timing of prophylaxis remains controversial given the balance of risks and benefits for the mother and fetus. The authors compared lithium use during pregnancy compared to its initiation postpartum in women at high risk for postpartum psychosis.

Method: Between 2003 and 2010, 70 pregnant women at high risk for postpartum psychosis were referred to the authors'psychiatric outpatient clinic. Women who were initially medication-free were advised to start lithium prophylaxis immediately postpartum. Women already taking maintenance lithium during pregnancy were advised to continue treatment.

Results: All women with a history of psychosis limited to the postpartum period (n=29) remained stable throughout pregnancy despite being medication-free. Of the women with bipolar disorder (n=41) 24.4 % relapsed during pregnancy, despite prophylaxis use by the majority throughout pregnancy. The postpartum relapse rate was highest in women with bipolar disorder who experienced mood episodes during pregnancy (60.0 %). In contrast, none of the 20 women with postpartum psychosis using postpartum prophylaxis relapsed, compared to 44.4% of postpartum psychosis patients who declined prophylaxis.

Conclusions: The authors recommend initiating prophylactic treatment immediately postpartum in women with a history of psychosis limited to the postpartum period, to avoid in utero fetal exposure to prophylactic medication. Patients with bipolar disorder require continuous prophylaxis throughout pregnancy and the postpartum period to reduce peripartum relapse risk.

Introduction

Psychotic episodes during the postpartum period are life-threatening psychiatric emergencies, occurring after nearly 0.1% of all deliveries. The strongest predictor for postpartum psychosis is a history of bipolar disorder and/or postpartum psychosis (1-3). Consequently, guiding women at high-risk for psychosis through pregnancy and the postpartum period is a major challenge for mental health practitioners and obstetricians (4-6). Although immediate treatment of affective instability or psychosis is clearly warranted, relapse prevention is widely viewed as the most desirable strategy. Indeed, previous studies in high-risk women provide strong support for the benefits of lithium prophylaxis during pregnancy and the postpartum period (7-12). However, the benefits of medication for relapse prevention need to be carefully weighed against risks for the fetus during pregnancy, neonatal complications following delivery, and for breastfeeding in the postpartum period (13).

Previous studies of peripartum relapse have largely focused upon women with a history of bipolar disorder. Viguera et al. provided clear evidence that discontinuation of medication leads to very high rates of relapse in bipolar women during pregnancy (7, 8). Further, four studies with smaller study groups have shown that prophylaxis with lithium is protective for relapse postpartum (9-12). In all four studies, lithium was continued during pregnancy, started in the last trimester of pregnancy, or started immediately postpartum.

While lithium has been demonstrated to be effective in substantially reducing the risk of peripartum relapse, the precise timing of when to initiate lithium prophylaxis, during pregnancy or immediately postpartum, remains unclear. An urgent need exists for clinical data that can be used to adequately weigh the risks and benefits of prophylaxis throughout the entire peripartum period.

Accordingly, we now describe the clinical outcomes of a Peripartum Prevention Program, designed to reduce the incidence and severity of peripartum relapse in women with a history of bipolar disorder, postpartum psychosis, or both. Pregnant women already on maintenance regimen of lithium were advised to continue this prophylactic treatment during pregnancy and the postpartum period. High-risk women who were clinically stable and medication-free at the time of evaluation were advised to start lithium prophylaxis immediately postpartum. These standardized clinical guidelines provided us the opportunity to examine the benefit of lithium prophylaxis during pregnancy compared to immediately postpartum, in women at high-risk for perinatal psychosis. It is important to note that although postpartum psychosis is widely considered as a new episode of bipolar disorder, some studies have indicated that postpartum psychosis is distinct from bipolar disorder (3, 14-17). Therefore, we investigated the clinical outcomes of women with a history of psychosis limited to the postpartum period and of those with a history of bipolar disorder.

Method

Participants

Between January 2003 and December 2010, a total of 618 referrals to the outpatient clinic of the Peripartum Prevention Program at the Department of Psychiatry, Erasmus Medical Center (Rotterdam, the Netherlands), were evaluated. Requests for evaluation and clinical management during pregnancy and the postpartum period were made by obstetricians, psychiatrists, and general practitioners. This study was approved by the Institutional Review Board of the Erasmus Medical Center.

Psychiatric diagnosis was obtained through semistructured interviews by a psychiatrist and review of clinical records. We included women with bipolar I disorder and bipolar II disorder with only non-puerperal episodes and those with both puerperal and non-puerperal episodes. Further, we also included women with a history of postpartum psychosis but without any manic or psychotic symptoms outside the postpartum period. Since 'postpartum psychosis' is not described as a separate disease entity in DSM-IV, we defined 'postpartum psychosis' as a history of any of the following DSM-IV diagnoses: psychotic disorder not otherwise specified, brief psychotic disorder, or mood disorder (manic, mixed, or major depressive episode) with psychotic features, all requiring the specifier "with postpartum onset" ($\leq$ 4 weeks after delivery). Women with chronic psychotic disorders such as schizophrenia or schizoaffective disorder were excluded.

In total, 75 pregnant women fulfilled the inclusion criteria. Five women were lost to follow-up during pregnancy (Figure 1). Therefore, in total we included 70 pregnant women at high risk for postpartum psychosis. Of this number, 29 women had a history of postpartum psychosis but without any manic or psychotic symptoms outside the postpartum period. Conversely, we included 41 women with a diagnosis of bipolar disorder, based on a history of non-puerperal episodes with or without puerperal episodes. For women who had more than one delivery during the study inclusion period, we included only the most recent pregnancy in the main analysis.

Peripartum Prevention Program

The Peripartum Prevention Program at the Erasmus MC was designed to provide standardized evidence-based clinical care for women at high-risk for peripartum relapse (18). Women enrolled in the program received their full obstetric care through the department of Obstetrics and Gynaecology, and peripartum psychiatric care through the department of Psychiatry.

Figure 1. Flowchart of inclusion for women at high risk for postpartum psychosis.
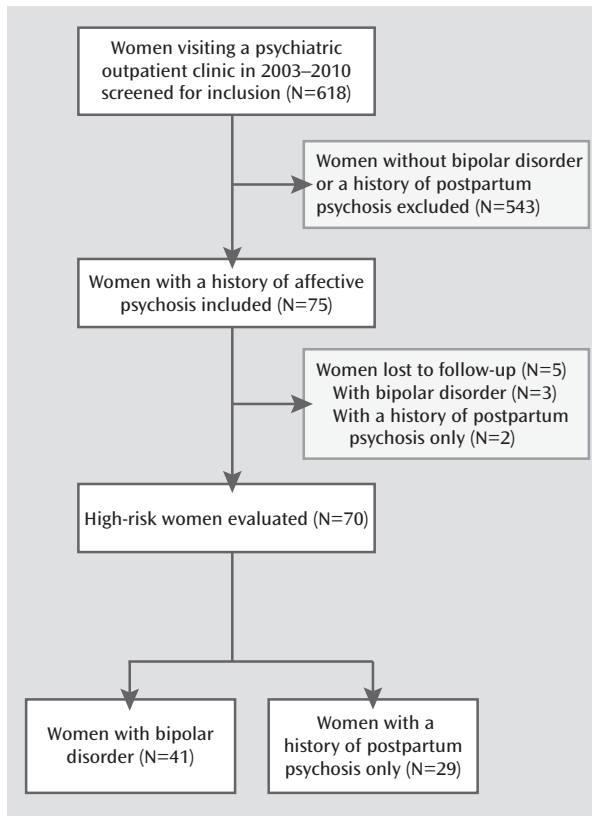
We advised women who were using a mood stabilizer at the time of evaluation to continue pharmacologic treatment during pregnancy. Given that lithium monotherapy has the largest evidence base in the peripartum period as an effective mood stabilizer, this was our primary pharmacological recommendation (2, 19). We also informed women about teratogenic risks of lithium during early pregnancy and the elevated rate of neonatal complications of lithium (20, 21).

We attempted to reduce the incidence of polypharmacy by recommending mood stabilization with a single medication. Further, we advised against the use of valproate during the peripartum period because of high teratogenic risks during pregnancy and the lack of efficacy for postpartum prophylaxis shown in a single study (22, 23). However given the potential risks of switching medications, our treatment plan discussion always included carbamazepine, lamotrigine, and antipsychotics as important considerations, if patients were clinically stable on these medications with manageable side effects, or if they had

a history of a favorable_response to these medications. It is important to note that the final decision regarding prophylaxis during pregnancy was always made by the patient, following a collaborative discussion to consider the risks and benefits of each pharmacologic treatment option, including the potential for teratogenicity and the risk of relapse.

In those women receiving maintenance lithium treatment, we prescribed doses three times a day during pregnancy to avoid peak lithium levels. After delivery, we reduced the numbers of doses to once a day (with a target minimum plasma level postpartum of 0.8 mmol/L). High-risk women who were medication-free at the time of evaluation were advised to start lithium prophylaxis immediately postpartum. For these women, lithium was started the first evening after delivery and given once daily according to the plasma level (target minimum, 0.8 mmol/L). Plasma lithium levels were monitored twice weekly during the first week postpartum, once per week during weeks 2-3, and thereafter as clinically indicated. Lithium levels were individualized based upon clinical symptoms and side effects, incorporating preferences of each patient and their previous history, if any, of lithium therapy.

We particularly emphasized the importance of sufficient sleep during the peripartum period, as sleep loss has been demonstrated to be a modifiable risk factor in bipolar disorder and postpartum psychosis (24-26). Accordingly, all women were advised to spend the first week postpartum in a private room on the inpatient obstetric ward, where nurses performed the overnight newborn feedings to provide mothers with the opportunity to sleep throughout the night. In addition we recommended standardized treatment with benzodiazepines (lorazepam 1 mg at bedtime), during the first week postpartum, during which subjective self-reports of sleep quality were evaluated daily through clinical interviews. Further, women were advised against breastfeeding given the current uncertainty regarding breastfeeding during maternal lithium treatment (21, 27).

In summary, a comprehensive individualized perinatal treatment plan was defined based on the choices of each woman in collaboration with her clinician regarding the risks and benefits of each treatment option, including prophylaxis, breastfeeding, sleep hygiene, and postpartum inpatient obstetric care. All women received follow-up evaluations every 4-6 weeks throughout the peripartum period. We defined the postpartum period according to the DSM-IV definition of the first four weeks postpartum. Therefore, we followed all women for a minimum of four weeks postpartum. The mean period of follow-up was 12.6 weeks postpartum (range=4-52 weeks).

Each patients and her partner were encouraged to immediately contact their psychiatrist in case of affective instability, psychotic symptoms, or refractory insomnia. We defined relapse as the occurrence of any psychiatric episode fulfilling DSM-IV criteria, including hypomanic episodes. During the first week postpartum, all patients were screened daily for prodromal symptoms by a perinatal psychiatric nurse (J.V.) in order to provide the earliest possible intervention.

Table 1. Demographic and Clinical Characteristics of Pregnant Women with Bipolar Disorder or a History of Postpartum Psychosis Only.

Characteristic	Bipolar Disorder N=41		Postpartum Psychosis Only N=29		Difference Between groups
Demographic variables					
	Mean	SD	Mean	SD	Two-Sample t Test (p)
Age (years)	33.6	3.8	32.7	5.2	0.40
	N	%	N	%	Fisher's Exact Test (p)
Caucasian	36	87.8	23	79.3	0.50
High educational level	12	29.3	11	37.9	0.61
Living with father child	38	92.7	29	100	0.26
Childbearing					
Previous pregnancy	30	73.2	29	100 [a]	< 0.01
Previous delivery	24	58.5	29	100 [a]	< 0.01
Unplanned pregnancy	14	34.1	4	13.8	0.09
Smoking during pregnancy	5	12.2	4	13.8	1
Elective caesarean section	2	4.8	3	10.3	0.64
Emergency caesarean section	7	17.1	3	10.3	0.51
Bipolar characteristics					
Bipolar type I	27	65.8			
Number of nonpuerperal episodes					
< 5	21	51.2			
5-10	13	31.7			
> 10	7	17.1			
Previous puerperal episodes	8	19.5			
Treatment					
Prophylaxis during pregnancy	31	75.6			
Lithium prophylaxis	30	96.8 [b]			

[a] All of these women had at least one previous delivery, as required by the study's inclusion criteria.
[b] Based on the 31 receiving prophylactic treatment during pregnancy

Statistical Analysis

All analyses were performed using SAS, version 9 (SAS Institute, Cary, NC). For characteristics of the study group, categorical data were evaluated by means of Fisher's exact test and continuous variables were examined with two-sample t-tests. Categorical outcomes of relapse risks were examined using both Fisher's exact test and odds ratios with corresponding 95% Confidence Intervals (CIs). All hypotheses were tested with an alpha of 0.05 (two-sided).

Results

Table 1 shows demographic, obstetric, and psychiatric characteristics for the enrolled patients. No significant differences were found in age, education, marital status, unplanned pregnancy, smoking during pregnancy, or the frequency of Caesarean section.

Table 2. Characteristics of Women With Bipolar Disorder or a History of Postpartum Psychosis Only Who Had a Relapse During Pregnancy or the Postpartum Period

Patient	Age (years)	Parity	Pregnancy			Postpartum		
			Prophylaxis	Time of Relapse (weeks)	Morbidity	Prophylaxis	Time of Relapse (days)	Morbidity
Bipolar disorder								
1	35	0	Lithium	6	Mania[a]	Lithium	8	Mania[a]
2	28	0	Lithium	6	Mania[a]	Lithium		
3	29	0		11	Hypomania	Lithium		
4[b]	34	1	Lithium	19	Mania[a]	Lithium plus antipsychotic	0[c]	Hypomania
5[d]	32	4		22	Mixed[a]	Lithium plus antipsychotic plus antidepressant		
6[b]	28	2	Lithium	23	Mania[a]	Lithium	4	Depression[a]
7	21	0	Lithium	23	Mania[a]	Lithium	0[c]	Hypomania
8	40	0		23	Depression	Lithium		
9	32	2		29	Depression	Carbamazepine plus antidepressant	0[c]	Depression
10	29	0	Lithium	39	Mixed[a]	Lithium	24	Mixed[a]
11	33	3				Lithium	4	Depression[a]
12[b]	30	1	Lithium			Lithium	7	Mania[a]
13	33	1				Valproate	16	Mania[a]
Postpartum psychosis								
1	37	1					7	Depression[a]
2	20	1					8	Mania[a]
3	34	1					12	Mixed
4	24	3					23	Psychosis[a]

[a] Required inpatient psychiatric admission.
[b] Patient's history included an additional diagnosis of postpartum psychosis.
[c] During pregnancy.
[d] Patient's history included an additional diagnosis of postpartum depression.

Peripartum Relapse in Bipolar Disorder and Postpartum Psychosis Only

The timing of relapse was substantially different between the women with bipolar disorder and those with postpartum psychosis (Figure 2). Remarkably, despite being medication-free throughout the entire pregnancy, none of the 29 women with postpartum psychosis relapsed during pregnancy. Postpartum, four of the 29 (13.7%) relapsed (Table 2). Of these four women with previous postpartum psychosis, the current relapse was manifested as mania for one woman, psychosis for one, a mixed episode for one and depression for one. Three of these four women required postpartum inpatient admission.

Figure 2. Cumulative Incidence of Relapse During Pregnancy and the Postpartum Period in Women with Bipolar Disorder or a history of Postpartum Psychosis Only
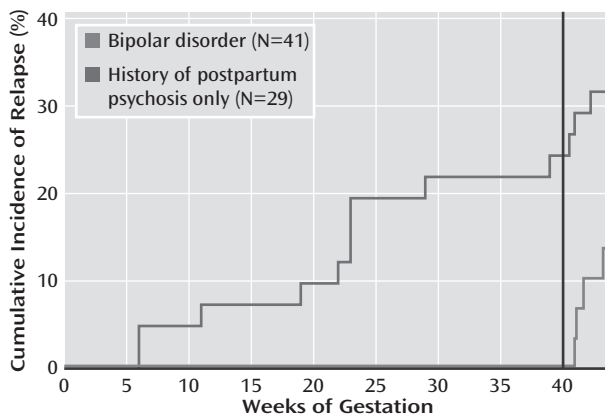
In contrast to the women with a history of postpartum psychosis only, none of whom had a relapse during pregnancy, 24.4% of women with bipolar disorder (10 of 41) relapsed during pregnancy (p<0.01, Fisher's exact test) (Table 2). Of these 10 women, five had a manic episode, two women had a mixed episode, two had a major depressive episode, and one developed hypomania. Those with a manic or mixed episode all required hospitalisation. Relapse postpartum occurred in 22.0% of the women with bipolar disorder (nine of 41), the majority of whom (six of nine) had also previously relapsed during pregnancy. Three out of these six women achieved full remission after the relapse in pregnancy, but relapsed again postpartum. The other three women experienced a postpartum worsening of an episode beginning in pregnancy (Table 2). Consequently, relapse during pregnancy was a significant risk factor for relapse postpartum (P<0.01, Fisher exacts test, odds ratio=14.0, 95% CI= 2.5-80.0). Of all nine women with bipolar disorder and postpartum relapse, three had a manic episode, one had a mixed episode, three had depression, and two had hypomania. Overall, six bipolar women required postpartum inpatient admission (Table 2).

Relapse in the bipolar women, both during pregnancy and postpartum, was especially common in women with a history of puerperal episodes (Table 2). Eight women with bipolar disorder reported a history of both puerperal and nonpuerperal episodes, of whom 50.0% (four of eight) had a peripartum relapse. In contrast, the peripartum relapse rate was 27.3% in the women with bipolar disorder with a history of only nonpuerperal episodes (nine of 33).

Table 3. Relation of Peripartum Prophylaxis to Relapse in Women With Bipolar Disorder or a History of Postpartum Psychosis Only

	Bipolar disorder (N=41)				Postpartum psychosis Only (N=29)			
	Total		Relapse		Total		Relapse	
Time Period and Group	N	%	N	%	N	%	N	%
Pregnancy								
Prophylaxis	31	75.6	6	19.4	0	0.0		
No prophylaxis	10	24.4	4	40	29	100.0	0	0.0
Postpartum								
Prophylaxis								
Stable pregnancy	26	63.4	2	7.7	20	69.0	0	0.0
Unstable pregnancy	10	24.4	6	60.0	0	0.0		
No prophylaxis	5	12.2	1 [a]	20.0	9	31.0	4	44.4

a This patient used valproate , which has a demonstrated lack of efficacy, as shown by Wisner et al. (23)

Influence of Prophylactic Medication in Women with Postpartum Psychosis Only

All 29 women with postpartum psychosis only were medication free during pregnancy. During this time, none of these women had symptoms of relapse, including any manic, psychotic, or depressive episodes (Table 3).

Of the 29 patients with a history of postpartum psychosis only, 20 began prophylactic treatment within 24 hours of delivery. Of these 20, 17 used lithium and three used antipsychotics. Notably, there were no cases of relapse among the women with postpartum psychosis who initiated postpartum prophylaxis upon delivery. Nine of the 29 patients decided against prophylactic medication, with the majority citing their intention to breast-feed. The relapse rate in the women without postpartum prophylaxis and a history of postpartum psychosis was 44.4% (four of nine). The difference in relapse rates between the patients with and without prophylaxis was significant (p<0.01, Fisher's exact test). No differences were found in demographic variables between these two groups. One woman had two deliveries during the study inclusion period. She was medication free throughout the first of these pregnancies, used lithium for postpartum prophylaxis, and remained

clinically stable throughout the entire peripartum period. During the second pregnancy, she was medication free and clinically stable throughout pregnancy. Unfortunately, however, she relapsed without postpartum prophylaxis.

Influence of Prophylactic Medication in Women with Bipolar Disorder

Of the 41 women with bipolar disorder, 31 (75.6%) received maintenance prophylaxis during pregnancy: 27 women used lithium monotherapy for mood stabilization, two women used lithium plus an antidepressant, one woman used lithium plus an antipsychotic, and one woman used haloperidol monotherapy as prophylaxis. Ten (24.4%) of the 41 bipolar women did not use prophylaxis continuously throughout pregnancy: three discontinued prophylaxis during the first trimester and seven were without prophylaxis during the entire pregnancy. No significant differences in demographic or baseline clinical characteristics were observed between the women with bipolar disorder who received prophylaxis and those who did not. The relapse rate during the pregnancies of the women with bipolar disorder who used prophylaxis was 19.4% (six of 31), compared to 40.0% (four of 10) in women without prophylaxis. Relapse during pregnancy was treated as clinically necessary, after which mood stabilization was continued throughout pregnancy and the postpartum period. However, despite maintenance mood stabilization, 60.0% (six of 10) of the women who relapsed during pregnancy also experienced a postpartum relapse ($p<0.01$, Fisher's exact test; odds ratio=14.0, 95% CI=2.5–80.0).

Among women with bipolar disorder who remained stable throughout pregnancy, 83.9% (26 of 31) used prophylaxis postpartum. Of these women, only 7.7% (two of 26) relapsed postpartum. Further, five of the 31 women who were stable throughout pregnancy declined prophylaxis postpartum, of whom one woman (20.0%) relapsed. Five bipolar women had two deliveries each during the study inclusion period. Three women declined prophylaxis during both of their pregnancies: two of them were stable during both pregnancies, while the third woman relapsed during both pregnancies. Two women used lithium prophylaxis and were stable during both pregnancies: one woman used lithium continuously during both pregnancies, whereas the other woman used lithium prophylaxis postpartum after her first pregnancy and continuous prophylaxis during her second pregnancy.

Discussion

A major goal of peripartum psychiatric care is the development of an effective prophylaxis algorithm that optimally balances the risks and benefits for the mother and fetus (28-30). With this goal in mind, we designed a peripartum prevention program using the best available evidence for pregnant women with the two strongest risk factors for postpartum psychosis: a previous postpartum psychosis and/or a history of bipolar disorder. Overall, we

confirmed that lithium is highly efficacious for peripartum prophylaxis. However, women with a history of postpartum psychosis only, compared to those with bipolar disorder, had substantial differences in their clinical outcomes and prophylaxis requirements.

First, all women with a history of psychosis limited to the postpartum period were stable throughout their entire pregnancy, despite using no prophylactic medication. In contrast, women with bipolar disorder had high rates of relapse during pregnancy. Second, initiation of prophylaxis with either lithium or an antipsychotic immediately postpartum in women with a history of postpartum psychosis was highly effective for preventing postpartum relapse. In contrast, the efficacy of postpartum prophylaxis in women with bipolar disorder was much lower. Together, our findings suggest that postpartum prophylaxis is highly efficacious in women at high risk for postpartum psychosis who do not have a diagnosis of bipolar disorder. Moreover, these findings suggest that in striking contrast to women with bipolar disorder, women with a history of postpartum psychosis but without manic or psychotic symptoms outside the postpartum period may not require prophylaxis during pregnancy, thereby offering a substantial risk reduction by entirely avoiding fetal exposure to medications.

Our findings support a wide literature demonstrating that women with bipolar disorder have a substantial risk of relapse during pregnancy as well as in the postpartum period (31-33). In contrast, women with a history of only postpartum psychosis have a vulnerability for mania or psychosis that is restricted to the postpartum period. Therefore, our data contribute to the emerging consensus that women with a history of psychosis limited to the postpartum period might have a distinct variant of bipolar disorder. Accordingly, we have described elsewhere the postpartum-onset psychosis and distinctive phenomenology in this group (34). Therefore, it will be interesting to explore the neurobiological mechanisms that are most highly sensitized in the postpartum period and responsible for this restricted window of vulnerability to psychosis. It is important to note that the bipolar women who were unstable during pregnancy showed the highest rates of postpartum relapse. In particular, we observed that prophylaxis during pregnancy in bipolar women is important not only to maintain mood stability during pregnancy but also to prevent episodes postpartum. However, the benefits of continuous lithium use for affective stability in the mother, both during pregnancy and postpartum, must be carefully weighed against the teratogenic effects of lithium during early pregnancy and the elevated rate of neonatal complications (4, 20, 21). Further, the benefits of postpartum prophylactic treatment with lithium must be considered in light of the relative risk to infants of breastfeeding exposure versus the loss of the benefits of breastfeeding.

This study has some limitations. We have likely missed symptoms associated with transient instability as our study was principally designed to detect mood episodes fulfilling DSM-IV criteria. Further, our study was naturalistic, leaving open the possibility that some

of the outcomes were influenced by patients' preferences. Conversely, a naturalistic study design more likely reflects the scenarios confronting women and their perinatal healthcare providers.

Our primary pharmacologic treatment recommendation for high-risk women was lithium, based on the literature. In contrast, studies using other prophylactic postpartum treatment strategies in bipolar women either failed to show efficacy, as in the case of estrogen administration (35, 36) and valproate (23), or were inconclusive as in the case of olanzapine (37). Notably, the relapse rates in bipolar women on lithium prophylaxis in our study were consistent with previous reports (9-12). To our knowledge, no previous prophylaxis studies have independently examined women with postpartum psychosis limited to the postpartum period. Clearly, more studies are required to compare the efficacy of other potential prophylactic treatment options (e.g. antipsychotics, carbamazepine) with that of lithium, as well as their relative efficacy for prophylaxis in bipolar women and those with a history of psychosis limited to the postpartum period.

In conclusion, our study demonstrates a strong overall benefit of prophylaxis for the prevention of postpartum psychosis in high-risk women. Further, we have identified a clinically relevant algorithm that may prove useful in determining prophylaxis requirements. In bipolar women, prophylaxis during pregnancy appears critically important for maintaining mood stability during pregnancy and for minimizing the high risk of postpartum relapse. In contrast, our findings suggest that women with a history of psychosis limited to the postpartum period should initiate prophylaxis immediately postpartum but remain medication free throughout pregnancy. Accordingly, this treatment algorithm may help reduce the fetal risk that can accompany in utero exposure to medications without compromising the efficacy of postpartum prophylaxis.

Chapter 4

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Chapter 4

Part II

Pathophysiology of postpartum psychosis

Chapter 5

A review of neurobiological studies in postpartum psychosis

Introduction

Postpartum psychosis is a severe mood disorder with an acute onset of severe mood and psychotic symptoms within four weeks after delivery (1). Importantly, and in contrast to postpartum depression, life events and social stress are not implicated in the etiology of postpartum psychosis (2, 3). Consequently, many researchers have argued that neurobiological changes after delivery play a major role in the acute occurrence of affective psychosis immediately postpartum (4). Unfortunately, systematic investigations into the pathogenesis of postpartum psychosis have been hindered by the rare and unpredictable incidence of the disease.

One of the most consistent findings in neurobiological research in postpartum psychosis over the last decades is the vulnerability for postpartum psychosis in women with bipolar disorder. Women with previously diagnosed bipolar disorder are at high risk for affective psychosis in the weeks following delivery (5, 6). In a major step toward causative etiological factors, Jones and Craddock identified the enrichment of specific genetic variants of the serotonin transporter gene (5HTT) and a genome-wide significant linkage signal at the 5HTT locus (chromosome 16p13) in bipolar patients with a history of postpartum psychosis (7, 8).

Interestingly, the majority of women presenting with postpartum psychosis do not have a previous history of bipolar disorder. However following an episode of postpartum psychosis, some women will then begin to experience non-puerperal bipolar episodes, for which the postpartum psychosis could be considered as the first-onset of a bipolar mood disorder. The general assumption is that after an initial postpartum affective psychosis, a woman has between a 40-80% chance of developing a non-puerperal bipolar mood disorder (9). Accordingly, it is of major clinical interest to determine the risk factors for conversion to bipolar disorder after a first episode of affective psychosis in the postpartum period. Therefore, understanding the etiologic pathophysiology of postpartum psychosis will provide a more comprehensive understanding, and will likely provide novel clinical insights into the risk factors governing both an initial postpartum psychosis and the subsequent risk for bipolar disorder. In this chapter, we review previous neurobiological studies of postpartum psychosis, summarizing neuroendocrine hypotheses and the influence of sleep loss.

The sex-steroid withdrawal theory of postpartum psychosis
In the last few decades, neurobiological research in postpartum mood disorders has been most intensely focused on neurosteroid pathways because of the clear changes occurring in hormone levels following delivery. After removal of the placenta following delivery, hCG, estrogen and progesterone levels drop dramatically during the first two weeks, which is the typical time-course for the onset of postpartum psychosis.

Chapter 5

In particular, the rapid fall in estrogen has been widely hypothesized to be a major trigger in postpartum psychosis. The "estrogen withdrawal-associated psychosis theory" can be found in several case reports, describing women within and outside the puerperium, with psychosis possibly related to estrogen withdrawal (10). Wieck et al hypothesized that the fall in estradiol could trigger increased dopamine receptor sensitivity leading to a postpartum psychotic episode in bipolar women (11). Indeed, the onset of affective psychosis after childbirth was associated with increased sensitivity of dopamine receptors in 15 high-risk women. However, Meakin et al could not replicate these findings (12). If estrogen depletion is indeed the culprit trigger for postpartum psychosis, prophylactic administration of estrogens should prevent this psychosis. However, Kumar et al. showed in a study with a group of 28 women that the prophylactic administration of an estrogen could not prevent relapse in subjects at risk for postpartum affective psychosis (13). In addition, an association could not be identified between polymorphisms in estrogen receptor genes and the prevalence of postpartum psychosis (14, 15).

Rapidly declining progesterone levels have also been hypothesized as one of the possible causes of postpartum mood disorders. Unfortunately however, studies of progesterone have only been performed in postpartum depression, but not in postpartum psychosis (16). Higher progesterone levels were observed in postpartum depressed mothers compared to healthy controls (17, 18), however other studies could not confirm these findings (19-21). Thus far, the drop in hCG postpartum has not been linked to the onset of postpartum mood disorders, although data are lacking to make any definitive conclusions.

Together, clear evidence is very limited for a well-defined influence of pregnancy hormones (estradiol, progesterone and hCG) in the aetiology of postpartum psychosis. Furthermore, the pathophysiological background is undoubtedly complex, for which at-risk women might have differential sensitivity to the increase and/or withdrawal of these hormones rather than harboring significantly altered levels of the hormones themselves (22-24). Further research into the influence of pregnancy hormones should be focussed not only on sex-steroid receptor candidate genes but also on a more comprehensive biochemical pathway analysis including sex-steroid receptor co-regulators and their enzymatic metabolism (25).

Other endocrine dysregulation in women with postpartum psychosis

Postpartum dysregulation of non-steroid hormone systems has also been associated with the sudden onset of affective psychosis in the postpartum period. Therefore, we briefly discuss the potential influences of the hypothalamic-pituitary-adrenocortical (HPA) axis, the hypothalamic-pituitary-thyroid (HPT) axis, prolactin and oxytocin, on the development of postpartum psychosis.

The hypothalamic-pituitary-adrenocortical (HPA) axis

Dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis is one of the most consistent biological findings in mood disorders. The HPA axis robustly changes the first weeks after delivery. Immediately postpartum, corticotrophin releasing hormone (CRH) receptors in the hypothalamus are down regulated, leading to a decreased adrenocorticotrophic hormone (ACTH) response and decreased cortisol release. This blunted stress response is restored to normal non-pregnant levels only after 6 weeks postpartum (26).

Remarkably, no alterations in the stress system have ever been conclusively reported for postpartum psychosis. Two studies in small samples reported similar non-suppression in the dexamethasone suppression test in patients with postpartum psychosis compared to healthy controls postpartum (27, 28). Furthermore, no evidence was observed for the enrichment of glucocorticoid receptor (GR) gene polymorphisms in bipolar patients with or without postpartum psychosis (29).

In postpartum depression, findings are inconsistent. Hyperactivity of the HPA axis has been reported in some studies (20, 30), although others have failed to replicate these findings (22, 31). Remarkably, other studies reported exactly the opposite: lower cortisol levels and excessive HPA axis suppression (32, 33). Together, findings in HPA axis abnormalities in both postpartum psychosis and depression have been inconclusive.

The hypothalamic-pituitary-thyroid axis

Considerable alterations to the hypothalamic-pituitary-thyroid axis are also observed in the normal postpartum period. Notably, some women experience thyroid dysfunction, predominantly postpartum thyroiditis, in the initial few months following delivery. Case reports have suggested a significant co-morbidity of postpartum autoimmune thyroiditis and postpartum psychosis (34). One study in puerperal psychotic inpatients with late onset showed no significant differences in thyroid function and thyroperoxidase antibodies (35). In contrast, our recent study found autoimmune thyroid dysfunction more prevalent in patients with early-onset postpartum psychosis (36). This finding is consistent with several studies in postpartum depression reporting a small but statistically significant association between depressive symptomatology postpartum and thyroperoxidase antibody positivity (37-40). Clearly, replication studies investigating thyroid function in postpartum psychosis are warranted.

Lactational hormones: Prolactin and oxytocin

The principle hormones involved in lactation, prolactin and oxytocin have not been measured in patients with postpartum psychosis, except for one case report of a women with postpartum mania and high levels of degraded products of oxytocin (41). In our recent clinical study, we reported a similar prevalence of breastfeeding in women with postpartum

Chapter 5

psychosis compared to controls. However, this similar prevalence of breastfeeding does not preclude an influence of lactation on postpartum psychosis, as both prolactin and oxytocin have each been independently associated with disturbances in mental state.

Some studies have shown that anxiety and depressive symptoms in the postpartum period are correlated with low prolactin levels (18, 22, 32, 42, 43), although other studies could not find such a correlation (44-46). The release of oxytocin during suckling is associated with feelings of well-being, relaxation and a lower responsiveness to stressors, providing a potential substrate protective for the occurrence of mood disorders (47, 48). Clearly endocrine lactational studies investigating these hormones and their receptors in women with postpartum psychosis are warranted.

Sleep loss as a culprit trigger

In clinical practice, sleep loss is a prominent symptom of postpartum psychosis. Sharma et al. described in a small chart review that insomnia is in fact the most common symptom in postpartum psychosis, which invariably preceeds the onset of the mood and psychotic symptoms (49). In this study, women in the postpartum psychosis group had a longer duration of labour and were more likely to have a night-time delivery (50). As expected, in a case series of 3 women with postpartum psychoses, sleep deprivation therapy worsened their psychosis, and all 3 patients improved after recovery sleep (51). Although these small studies suggest causality, sleep impairment could also be seen as one of the first symptoms of an impending postpartum psychosis instead of a causal factor. Indeed, a recent study could not find a difference in sleep/wake activity in women with a history of postpartum psychosis (52). Circadian genes are known to have a regulatory impact in mood disorders (53). In this respect, it would be very interesting to investigate whether circadian gene polymorphisms moderate the relationship between sleep-wake cycle disturbances and the incidence of postpartum psychosis.

Conclusion

The fundamental molecular and cellular mechanisms underlying postpartum psychosis remain elusive. Unfortunately, neurobiological studies in patients with postpartum psychosis are scarce, probably due to the low incidence of the disorder (1 - 2/1000) combined with the acute severity, making it difficult to collect large enough cohorts for a meaningful biological or clinical study. Thus far, research focused on endocrine systems has not led to clear etiological clues. In contrast to postpartum psychosis, neurobiological research of postpartum depression has been extensive, for which several biological mechanisms have been carefully explored. Unfortunately, research in this area has also been inconclusive, likely due to the heterogeneity of the disease, and complex physiology in the normal postpartum

period (54, 55). We believe that neurobiological research in more severe postpartum mood disorders, such as postpartum psychosis, has strong potential for future success guided by standardized and larger-scale designs. In the next chapters, we propose a novel hypothesis to view postpartum psychosis as an immune-related disorder. This perspective has led to the studies described in chapter 7 and 8.

Chapter 5

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Chapter 5

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Chapter 6

An immune hypothesis of postpartum psychosis

Introduction

Women are at high risk for severe psychiatric episodes, such as postpartum psychosis, in the immediate postpartum period (1). For some women, this psychosis remains entirely limited to the postpartum period. Unfortunately however for many women (40-80%), postpartum psychosis is the incipient onset of a bipolar mood disorder (2). Genetic studies have confirmed the strong etiological link between severe postpartum episodes and vulnerability for bipolar disorder (3). This relationship is further evidenced by high relapse rates immediately postpartum in women for whom a diagnosis of bipolar disorder was made already prior to pregnancy (1, 4). Therefore, it is intriguing but unknown *why* bipolar disorder frequently has its onset (or an exacerbation) specifically in the early postpartum period. Furthermore, it is also unknown why some women exhibit only severe affective psychosis in the postpartum period without any non-puerperal episodes.

Bipolar disorder has a lifetime prevalence of 2% and is characterized by episodic pathological disturbances in mood ranging from extreme elation (mania) to severe depression. Based on the most current studies, the heritability for bipolar disorder is estimated up to 80% (5). Although the genetics of bipolar disorder is far from unravelled, the current findings support a concept of Immune-Brain Interaction in its pathogenesis (6, 7). We and others have reported immune dysfunction in patients with bipolar disorder. Immune activation in bipolar disorder encompasses an elevation of serum cytokines and chemokines (8-13), a higher prevalence of organ-specific auto-antibodies (14-16), T-cell activation (17, 18) and inflammatory monocyte gene expression (7, 19). A recent Danish register study described a high co-occurrence of autoimmune diseases in patients with bipolar disorder. They conclude: "... the results suggest the possibility that the onset of psychosis - including bipolar disorder - in some cases arises in connection with a contemporary inflammatory process associated with these autoimmune diseases" (20).

Here, we hypothesize that the frequent onset (or exacerbation) of bipolar disorder in the postpartum period is associated with immune activation postpartum. To further elaborate this hypothesis, we will review some of the existing data on immune dysfunction in bipolar mood disorder, after a general introduction regarding the normal functions of the immune system.

Chapter 6

The normal functions of the immune system.

Among the most fundamental challenges for the immune system is to provide defence against pathogens, by distinguishing pathogenic (foreign) antigens from physiological auto-antigens. The immune system is broadly defined by two distinct components: innate and adaptive responses, each of which utilizes cellular and humoral mechanisms.

The innate immune system represents the evolutionarily more ancient component of the immune system, designed to mount an immediate, antigen-non-specific response following exposure to an invading microorganism. Innate defence mechanisms are mostly represented by the phagocytosis and destruction of microorganisms. The innate immune system prominently includes phagocytic cells of the Mononuclear Phagocyte System (see explanation below), natural killer cells and humoral proteins, such as complement and acute phase proteins (Figure 1).

The adaptive immune response refers to antigen-specific defence mechanisms that require several days to become protective, as they are designed for the targeted clearance of identified antigens. It involves a remarkably specific process of antigen recognition mediated by high affinity receptors localized on T and B-cells. B-cells are responsible for the production of antibodies, which neutralize extracellular bacteria, viruses and toxins. T-cells are responsible for the cell-mediated immunity (see below and Figure 1).

Mononuclear Phagocyte system (MPS)
The cells of the MPS form a system of travelling surveillance cells, of which the monocyte is the representative in blood. These circulating monocytes are capable of infiltrating target tissues, where they differentiate into macrophages or dendritic cells. The classical function of MPS cells is to provide defence against foreign intruders via the recognition, uptake and full degradation of microorganisms in a process called phagocytosis (an "innate" immune process). Importantly, cells of the MPS not only fully degrade foreign intruders but also degrade these to an array of antigenic peptides, which are subsequently presented to T and B-cells. In this process, T-cells and B-cells are triggered and capable of mounting an antigen-specific immune response. While macrophages are examples of these antigen-presenting cells, the most specialized antigen-presenting cells are dendritic cells. Aptly, the entire process of antigen presentation by dendritic cells, followed by stimulation of T and B-cells is called "immunization".

Dendritic cells are not only capable of stimulating antigen-specific T and B-cells to proliferate, but also capable of acting as the conductors of the T and B-cells. Under conditions of "danger" (e.g., foreign intruders, damaged tissues), a molecular program

is engaged within the dendritic cell, leading to proliferative expansion of dendritic cells, and followed by a cytotoxic T and B-cell attack on the intruders. Under "steady-state" (i.e., normal physiologic) conditions, a molecular program exists within dendritic cells to induce T and B-cell tolerance to self-antigens. In autoimmune and allergic conditions, the steady-state molecular program in MPS cells is disrupted by intrinsic abnormalities, driving MPS cells into an abnormally activated "danger" set-point.
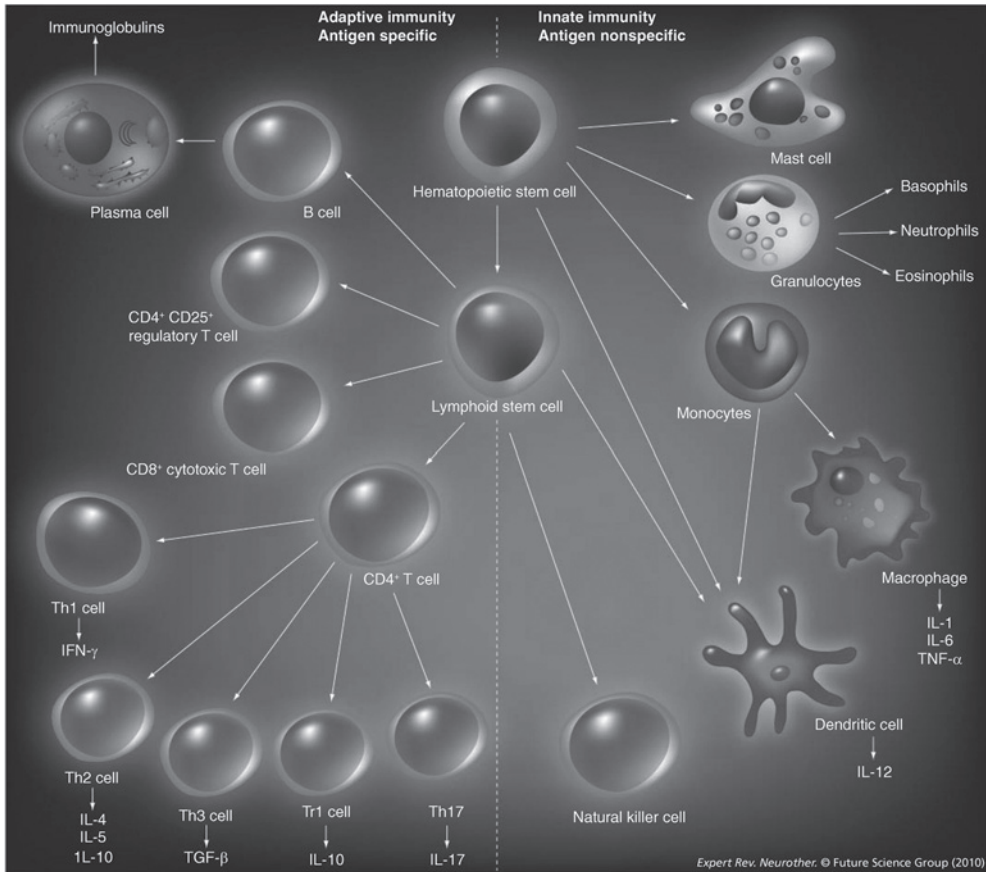
T-cell system

T-cells form a heterogeneous group of cells comprising effector cells, regulatory cells and memory cells. T-cells are typically divided into CD4+ and CD8+ classes. Effector CD8+ cells are cytotoxic and important in killing endogenous cells infected with virus, intracellular bacteria or otherwise dysfunctional (e.g., malignancy). Effector CD4+ cells are important in providing help to other T-cells and are therefore called T-helper cells (Th). Upon stimulation by an antigen-presenting cell, naïve T-helper cells have four distinct potential cell fates of differentiation: Th1, Th2, Th17 and inducible T-regulatory cells. Th1 and Th17 cells are capable of macrophage activation, essential for defence against viruses and intracellular pathogens. Th2 cells play a central role in B cell activation and antibody production.

Reactivity to self is primarily accomplished during fetal development through deletion by the thymus of auto-reactive T-cells, a process called central tolerance. However, this process is not perfect. Occasionally, some low-affinity auto-reactive T-cells escape this mechanism. But, they are prevented from causing autoimmune disease by naturally occurring T-regulatory cells (T-reg) of the thymus (21). These T-reg cells represent 2–5% of all peripheral CD4+ T cells. T-reg cells are believed to be important for immune tolerance via suppression of low-affinity auto-reactive T-cell clones. The best known subtype of the natural T-regulatory cell population is the CD4+CD25+FOXP3+ cell, defined by the high expression of CD25 and FOXP3. Progression towards autoimmune diseases, such as type 1 diabetes (T1D), has been linked to a decline in the capacity of T-reg to maintain functional antigenic tolerance (21).

Immune dysfunction in bipolar disorder

Clinicians have noticed for decades a high prevalence of autoimmune comorbidity in patients with bipolar disorder. In clinical studies, the strongest and most consistent evidence is for high co-occurrence of bipolar disorder with autoimmune thyroiditis and multiple sclerosis (20, 22-24). Accordingly in serum of bipolar patients, there is a higher prevalence of organ-specific auto-antibodies (TPO-, H+/K+ATPase-, GAD65- and antiphospholipid antibodies). Importantly however, the majority of bipolar patients with antibody positivity do not have overt clinical symptoms of an autoimmune disorder (14-16). Rather, these findings are suggestive of an immune system dysregulation in a subgroup of patients with bipolar disorder.

Figure 1. The cells of the immune system

The implication that activation of the immune system is associated with the occurrence of mood symptoms is based on the "Macrophage-T-cell theory of mood disorders", formulated in the 1990s (25). This theory states that chronically activated macrophages (and their counterparts in the brain, i.e. microglia) together with T-cells produce cytokines and inflammatory compounds impacting brain development, thereby exposing the brain to liability for precipitating mood symptoms determined by a given person's genetic and environmental risk factors.

Indeed, numerous studies have reported elevated levels of inflammatory cytokines in the serum, plasma and cerebrospinal fluid of patients with major mood disorders (26). In bipolar disorder, there is evidence for increased cytokine production across all phases of illness, although acute exacerbations appear to be a particularly sensitive period in demonstrating accentuation of this pro-inflammatory state. During mania, there is evidence

for increased CRP, soluble Il-2 receptor, IL-6 and TNFα (27). In contrast, relatively few studies have examined immune markers during bipolar depression, for which the findings have partly overlapped with those observed during mania but with substantial inconsistence across different studies (28). Notably, normalization of the immune activation is observed upon clinical remission of bipolar episodes (29).

How could elevated serum levels of peripheral cytokines influence the brain? Cytokines are relatively large molecules, of which only a subset are capable of readily entering the brain through the blood-brain barrier. However, several routes have been uncovered through which cytokines might enter and act in the brain (30). For example, cytokines can enter the brain through parts where the blood-brain barrier is relatively permeable due to inflammation or acute stress (via the cerebral endothelium). After entering the brain, it has been shown that cytokines bind to their receptors on glial cells and neurons in multiple brain regions, where they can trigger dysregulation of major neurotransmitter systems (31).

Notably, one must take into account that increased levels of pro-inflammatory cytokines are not only found in psychiatric disease, but also in cardiovascular disease, autoimmune disease and cancer. In addition, it is important to consider that cytokine levels in serum or plasma are strongly confounded by age, gender, socioeconomic status, metabolic syndrome, visceral obesity, smoking, exercise, poor-rated self-health and medication. Further complicating research efforts, cytokine measurements are known to be notoriously difficult to analyze in a standardized manner. Accordingly, we have focused our investigations on the cellular producers of cytokines and proinflammatory compounds, namely MPS cells and T-cells (30).

Supporting this approach, our group has identified an elevated number of circulating CD25$^+$T cells in patients with bipolar disorder (17, 18). Further, T-cell activation was particularly evident within the regulatory arm, for which higher numbers of CD25$^+$FOXP3$^+$T$_{regulator}$ cells were present (predominantly in younger patients). T-cell activation was further evidenced by elevated serum levels of IL2-R, a global indicator of T-cell activation. With regard to MPS cells, we also found enhanced expression of immune genes in circulating monocytes. These gene expression studies were carried out on purified monocytes of 56 bipolar patients and matched healthy controls using Affymetrix analyses followed by confirmatory quantitative real-time PCR. In total, aberrant expression of 34 mutually correlated genes was detected (7, 19).

Other groups have found evidence for dysregulated expression of inflammatory related genes in post-mortem brain samples of patients with bipolar disorder. In particular, changes in transcriptome profiles across multiple brain regions (the frontal cortex, the prefrontal cortex and the orbitofrontal cortex) were observed (32, 33). Notably, while genes involved in energy metabolism and mitochondrial function were downregulated, genes involved in immune response and inflammation were found to be significantly upregulated, consistent with our immunological findings (34).

Conclusion

Taken together, there is increasingly solid evidence to implicate a dysregulation in the immune system as a pathophysiological mechanism for bipolar disorder (35). Therefore, we intend to address the following primary research question: Is the frequent onset (or exacerbation) of bipolar disorder in the postpartum period associated with immune activation postpartum?

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Chapter 6

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Chapter 7

Prevalence of autoimmune thyroid dysfunction in postpartum psychosis

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Abstract

Background: Postpartum psychosis is a life-threatening psychiatric emergency, which often occurs without significant premorbid symptoms. Although many studies have hypothesized an involvement of the immune and endocrine systems in the onset of postpartum psychosis, the specific aetiologic factors have remained unknown.

Aims: We examine the hypothesis that autoimmune thyroid dysfunction may be associated with the onset of postpartum psychosis.

Method: Thirty-one consecutive primiparous women with no prior psychiatric history were referred to our inpatient unit for postpartum psychosis (n=31). The control group (n=117) compromised primiparous women with consecutive deliveries at a community practice. Blood samples were obtained from all participants at 4 weeks and 9 months postpartum. Thyroperoxidase antibody levels were quantified as immunological measures of autoimmune thyroid disease (AITD). Thyroid stimulating hormone and free thyroxine levels were measured to assess clinical thyroid dysfunction.

Results: At 4 weeks postpartum and prior to the initiation of mood stabilizers, 19 % of women with postpartum psychosis had AITD compared with 5 % in the control group. Women with both postpartum psychosis and AITD had a dramatically higher risk of progression to clinical thyroid dysfunction (67%) than control subjects with AITD (20%).

Conclusion: Women with postpartum psychosis are at higher risk not only of AITD but also of clinical thyroid failure. These data implicate thyroid function as an important clinical outcome in patients with postpartum psychosis. Further, AITD represents a potentially strong aetiologic factor for the development of postpartum psychosis. Therefore, screening for thyroperoxidase antibodies is warranted in patients with postpartum psychosis.

Introduction

Postpartum psychosis is a severe disorder occurring in 0.1% of childbearing women. The clinical symptoms include fluctuations in mood accompanied by delusions and hallucinations, as well as agitation, insomnia, and cognitive impairment. Patients often require acute hospitalization with thoughts of suicide and infanticide (1-4). Although there are no current treatment guidelines for postpartum psychosis, both antipsychotics and mood stabilizers are recommended and widely used (4, 5). Women with bipolar disorder are at very high risk of developing postpartum psychosis: up to half of women with bipolar disorder relapse in the early postpartum period, often with psychotic symptoms (6-8). However, most patients with a postpartum psychosis have no history of psychiatric disorder (9). During the past century many possible determinants of postpartum psychosis have been proposed. In particular, many studies have focused on neurosteroid pathways, given the dramatic changes in hormone levels throughout pregnancy and the postpartum period. However, no specific mechanism has been conclusively identified as an aetiological factor in postpartum psychosis.

Postpartum autoimmune thyroid disease (AITD) is defined by autoimmune thyroid inflammation and elevated thyroid antibody titres, occurring within the first year after delivery. With a postpartum prevalence of 5–7% in the general population (10), AITD has been identified as a risk factor for postpartum depression (11-15). In contrast to the emerging consensus regarding the link between AITD and postpartum depression, the lower incidence of postpartum psychosis has thus far precluded analogous studies. Although case reports have documented the co-occurrence of postpartum psychosis and AITD (16, 17), the only previous systematic study found no evidence for an increase of AITD in patients with a late-onset presentation of postpartum psychosis (> 4 weeks after delivery) (18). Importantly however, no prior study has reported prospective AITD screening in patients with classic early-onset postpartum psychosis (≤ 4 weeks after delivery) before the start of medication. Lithium, frequently used in the treatment of postpartum psychosis, has several deleterious effects on thyroid function (19). Our study was therefore designed to document the prevalence of serological and clinical evidence for autoimmune thyroid dysfunction in patients with early-onset postpartum psychosis during the initial 9 months following delivery.

Method

The study protocol was approved by the institutional review board of the Erasmus University Medical Centre, Rotterdam, The Netherlands. After receiving a complete description of the study, all patients and their authorised legal representatives provided written informed consent before participation. Between August 2005 and November 2008 we examined all

patients referred to the mother and baby in-patient unit of the department of psychiatry at the Erasmus Medical Centre for evidence of postpartum psychosis, using the Structural Clinical Interview for DSM–IV (SCID)(20). The catchment area for this unit includes the provinces of South Holland, Zeeland and North Brabant. Since 'postpartum psychosis' is not described as a separate disease entity in DSM–IV, we selected patients for whom the SCID interview generated the following DSM–IV diagnoses: psychotic disorder not otherwise specified, brief psychotic disorder or mood disorder (manic, mixed or major depressive episode) with psychotic features, all requiring the specifier 'with postpartum onset' (44 weeks after delivery). Of the 123 patients examined, 55 fulfilled the criteria of postpartum psychosis. Twenty-one patients were excluded because of their psychiatric history (eight patients with bipolar disorder, five patients with psychosis not otherwise specified, five patients with a previous postpartum episode, two patients with schizoaffective disorder and one patient with chronic cannabis misuse). Thirty-four patients reported no previous psychiatric history. A parallel history was obtained to confirm the time course of symptoms for all patients examined. One patient declined to participate. All patients except two were primiparous. As parity is a potential risk factor for thyroid autoimmunity (21), data-analysis was restricted to the 31 primiparous women.

Patients were referred by acute psychiatric services and the majority had been briefly treated with benzodiazepines (lorazepam, temazepam or oxazepam: 23 patients with a treatment duration of 3.5 days, s.d.= 0.6) and/or antipsychotics (haloperidol or olanzapine: 19 patients, treatment duration 4.5 days, s.d.= 1.1). Of the 31 primiparous women with postpartum psychosis, 23 had a presentation of manic psychosis, 5 had a mixed episode and 3 presented with psychotic depression. During admission all 31 patients were treated with benzodiazepine anxiolytic medication and 29 patients required clinical treatment with an antipsychotic. In 25 of these 29 patients a trial of antipsychotic monotherapy provided suboptimal efficacy, with addition of lithium for improved mood stabilisation. Lithium dose was determined by plasma level (0.6–1.0 mmol/l). Importantly, no patient received lithium prior to the plasma sampling at admission.

The control group was established by screening 291 women consecutively evaluated during pregnancy between 1994 and 1996 in the North Brabant province. Selection was based exclusively on primiparity, regardless of medical or psychiatric history. Each control group participant (n = 117) was followed during pregnancy and the first year after delivery to determine the incidence of postpartum thyroid dysfunction and postpartum depression. Laboratory thyroid function assays in both the postpartum psychosis and control groups were performed using the same immune assays in the same laboratory (Laboratory of Autoimmune Diseases, Department of Immunology, Erasmus Medical Centre, Rotterdam).

Laboratory assessments

Blood samples were obtained from all participants 4 weeks and 9 months after delivery. In addition, patients with postpartum psychosis had blood samples taken at various times over the 9-month study period, as clinically indicated. Thyroperoxidase antibodies were measured using the Immulite human immunoassay (Siemens, Los Angeles, California, USA); values greater than 35 IU/ml were regarded as positive serological evidence of autoimmune thyroid disease. Thyroid-stimulating hormone and free thyroxine levels were measured in the clinical laboratory of the Erasmus Medical Centre using reference ranges (thyroidstimulating hormone 0.4–4.0mIU/l; free thyroxine 10–24 pmol/l) defined by the Centre's validated standards. Clinical thyroid dysfunction was defined as the coexistence of abnormal levels of the two hormones.

Statistical analysis

All analyses were performed using SAS version 9 for Windows. 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. Categorical outcomes were examined using odds ratios with corresponding 95% confidence intervals. Time to clinical thyroid dysfunction was evaluated using Kaplan–Meier methodology and the log-rank test. All hypotheses were tested with an alpha of 0.05 (two-sided).

Table 1. Sample characteristics of women with postpartum psychosis and a general population postpartum control group

	Postpartum psychosis Group (n=31)		Postpartum control group (n=117)		P
Ethnicity, white, n (%)	29	(94)	117	(100)	
Never smoked, n (%)	20	(65)	91	(78)	
Smoked in pregnancy, n (%)	1	(3)	26	(22)	< 0.05 [a]
Primigravida, n (%)	27	(87)	105	(90)	
Caesarean section, n (%)	4	(13)	10	(9)	
Preterm birth, n (%)	1	(3)	7	(6)	
History of thyroid disease, n (%)	0	(0)	0	(0)	
History of other autoimmune disease, n (%)	0	(0)	0	(0)	
Age, years: mean (s.d)	31.2	3.8	28.0	3.3	< 0.0001 [b]
Birth weight of child, g: mean	3340		3314		

[a] Fisher's exact test
[b] Two-sided t-test

Results

Participants with postpartum psychosis were 3.2 years older than the general population cohort (Table 1). Although a similar percentage of patients and controls had ever smoked in the past, a significantly higher percentage of the control group smoked during pregnancy (22%) compared with the patient cohort (3%). No difference was found in the frequency of Caesarean section, rate of primigravidity, birth weight of the child or incidence of preterm birth. None of the patients or controls had a history of thyroid or autoimmune disease.

Prevalence of AITD in the early postpartum period
At 4 weeks postpartum, 5% of the control group had AITD, with no case of clinical thyroid dysfunction. In contrast, 19% of the patients with postpartum psychosis met criteria for AITD on admission to the hospital, before the start of antipsychotic or lithium pharmacotherapy (OR = 4.44, 95% CI 1.32–14.92; Table 2). Further, half of the patients with postpartum psychosis and AITD also demonstrated clinical thyroid dysfunction at the time of admission to the hospital.

Table 2. Prevalence of autoimmune thyroid disease and clinical thyroid dysfunction

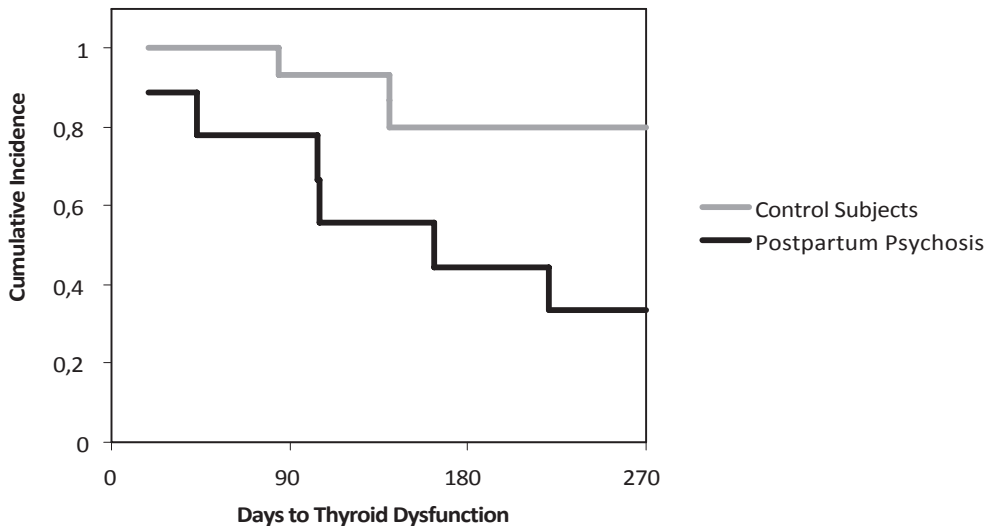|	Postpartum psychosis group (n=31) % (n/N)		Postpartum control group (N=117) % (n/N)		Odds ratio (95% CI)	
4 weeks postpartum (prior to treatment)						
Autoimmune thyroid disease (AITD)	19	(6/31)	5	(6/117)	4.44	(1.32-14.92)
Clinical thyroid dysfunction	10	(3/31)	0	(0/117)	NC [a]	
Clinical thyroid dysfunction per AITD	50	(3/6)	0	(0/6)	NC [a]	
9-months postpartum						
Autoimmune thyroid disease (AITD)	29	(9/31)	13	(15/117)	2.78	(1.08-7.17)
Clinical thyroid dysfunction	19	(6/31)	3	(3/117)	9.12	(2.14-38.96)
Clinical thyroid dysfunction per AITD	67	(6/9)	20	(3/15)	8.00	(1.23-52.25)

AITD, autoimmune thyroid disease; NC, not computed
[a] Odds ratio cannot be computed given the absence of clinical thyroid dysfunction in controls at 4 weeks postpartum

Follow-up

The 9-month prevalence of AITD was significantly higher in women with postpartum psychosis (29%) compared with controls (13%; OR= 2.78, 95% CI 1.08–7.17; Table 2). Further, clinical thyroid dysfunction occurred in 19% of patients compared with only 3% of controls (OR = 9.12, 95% CI 2.14–38.96). Patients with postpartum psychosis showed a significantly higher rate of progression from subclinical AITD to clinical thyroid dysfunction (log-rank P = 0.017; Fig. 1). Specifically, of the patients with AITD at the 9-month follow-up, 67% had overt thyroid dysfunction compared with only 20% of the control group (OR = 8.00, 95% CI 1.23–52.25). Importantly, as shown in both Fig. 1 and Table 2, the increased rate of clinical thyroid dysfunction in patients with postpartum psychosis was already evident at the time of hospital admission, prior to the administration of antipsychotic or lithium treatment. At 9 months, 23 patients remained on lithium monotherapy, 2 patients were taking antipsychotics and 2 patients required initiation of antidepressant medication (sertraline and citalopram). Notably, the 3 patients who developed AITD and clinical thyroid dysfunction during treatment with mood stabilisers were all taking lithium. In contrast, none of the 18 lithium-treated patients without AITD developed clinical thyroid dysfunction.

Figure 1. Survival curve of thyroid function during the 9 month study period in patients and controls with autoimmune thyroid disorder.

Discussion

To the best of our knowledge, this is the first observational study of primiparous women with first-onset postpartum psychosis and no previous psychiatric history. Our data show that autoimmune thyroid disease is much more prevalent in women with first-onset postpartum psychosis than in postpartum women from the general population. Further, clinical thyroid failure occurs significantly faster and in a greater percentage of patients with postpartum psychosis. Importantly, these differences appear to be independent of antipsychotic or lithium treatment in the early postpartum period. Taken together, the high prevalence of clinical thyroid dysfunction in patients with postpartum psychosis is an important consideration for both clinical management and pathophysiological understanding.

Although one limitation of the current study is that the control group was not drawn from the identical population within The Netherlands, the 5% point prevalence of AITD in our control group at 4 weeks postpartum closely matches the mean prevalence of 5–7% determined from a review of over 20 studies on women from the general population (10, 22, 23). Further, our findings in patients with postpartum psychosis are similar to the increased prevalence of AITD in women with bipolar disorder (24). In addition, a twin study of people with bipolar disorder showed that AITD was not only related to the disorder itself but also to the genetic vulnerability to development of the disorder (25).

During pregnancy, changes in the maternal immune system are necessary to induce tolerance of the mother towards genetically different fetal tissue. From a clinical point of view, this state of tolerance is reflected by a substantial amelioration of symptoms in patients suffering from certain autoimmune diseases, such as rheumatoid arthritis or autoimmune thyroiditis (26). Consistent with this model, substantial decreases of the relevant serum autoantibody concentrations are frequently observed during pregnancy (12). After delivery, the immunosuppressive state of pregnancy is not only restored but shoots into overreaction (the "rebound phenomenon"). In some women this results in exacerbation of pre-existing autoimmune disease or a first manifestation of an episode of autoimmune disease, reflected by increases in autoantibody concentrations (27). Postpartum immune activation is postulated to produce the clinical manifestations of both thyroid dysfunction and psychiatric illness (Figure 2). In one scenario, the postpartum psychotic condition *per se* may exacerbate an underlying postpartum thyroiditis. Conversely, in some cases postpartum thyroiditis may serve as an important aetiological factor, leading to either depression or mania, depending upon the patient's neurobiological vulnerability.

Figure 2. Pathophysiological model for a shared vulnerability to autoimmune thyroid dysfunction and postpartum psychosis.
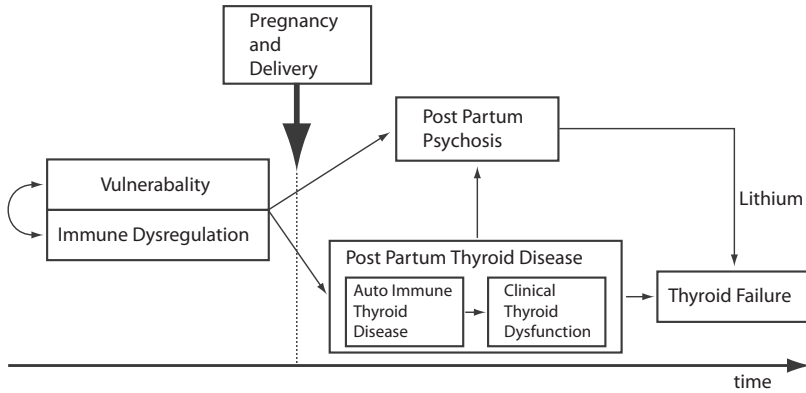
From a clinical point of view, it is evident that postpartum thyroid dysfunction needs to be diagnosed and treated early (22, 23). Given our findings of a dramatically increased rate of autoimmune thyroid dysfunction in women with postpartum psychosis, we strongly suggest that thyroid function and autoantibody titers should be rigorously monitored in all women presenting with postpartum psychosis. Further, we believe that all women at high risk of developing postpartum psychosis should be screened for thyroperoxidase antibodies prior to delivery. Clinically, a previous history of bipolar disorder and/or postpartum psychosis is the only known strong risk factor for developing a subsequent postpartum psychosis. Therefore, we recommend that any woman with a previous history of bipolar disorder and/ or postpartum psychosis should have thyroperoxidase antibody testing. Importantly, for effective perinatal screening of this antibody, we recommend testing in early gestation or preferably before pregnancy because TPO antibody levels decrease significantly during pregnancy. Further, in these high risk groups we recommend testing thyroid function and autoantibody titers at both 4 weeks and 6 months postpartum, given the well-documented postpartum rebound of thyroid autoantibodies.

Several studies have documented that in addition to female gender, elevated thyroperoxidase antibody titre and lithium treatment are both independent risk factors for the development of thyroid dysfunction (24, 28). However, lithium has widespread clinical support as a highly effective mood stabilizer in postpartum psychosis (4, 29). Although our study lacks the statistical power to determine the influence of lithium treatment on thyroid function, the risks and benefits of lithium should be weighed carefully in choosing the most appropriate pharmacologic regimen for treatment of postpartum psychosis, particularly for patients with elevated thyroperoxidase antibody titres.

Chapter 7

Together, these data demonstrate compelling evidence for autoimmune thyroid dysfunction in patients with postpartum psychosis. Further research is needed to confirm our findings and ascertain whether AITD is an aetiological factor in postpartum psychosis.

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Chapter 7

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Chapter 8

Immune system dysregulation in first-onset postpartum psychosis

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Abstract

Background: 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 64 women consecutively admitted with first-onset postpartum psychosis (PP). Control groups included healthy postpartum (n=43) and non-postpartum (n=37) women. A quantitative-PCR monocyte gene expression analysis was performed using 45 genes previously identified as abnormally regulated in non-postpartum mood disorder patients including the isoforms of the glucocorticoid receptor. T-cell percentages were measured by FACS analysis, while serum cytokines/chemokines were determined using a cytometric bead array.

Results: Compared to healthy non-postpartum women, monocyte gene expression and T-cell levels in the postpartum period were significantly elevated. Among the postpartum women, PP patients had a significant up-regulation of monocyte genes not otherwise elevated in the normal postpartum period. Further, the glucocorticoid receptor-β/α gene expression ratio was increased in monocytes of PP patients, strongly correlating with their immune activation. Remarkably however, PP patients had significantly reduced levels of total T-cells and total T helper cells, as well as Th1 and Th17 subsets, compared to healthy postpartum controls.

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 postpartum mood disorder. 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 neuro-steroid 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, as well as through an 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 immune suppressive 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 signalling, to specifically evaluate the hypothesis that postpartum psychosis is the psychopathological endpoint of a deregulated neuro-immuno-endocrine axis (6, 25-27). In addition to monocyte gene expression, we also determined the percentages of circulating lymphocytes, Th1, Th2, Th17, Treg, and of natural killer (NK) cells using detailed FACS analysis. Lastly, we determined the level of monocyte and T-cell related cytokines/chemokines in serum.

Methods and Materials

Participants

This study was approved by the medical ethical committee of the Erasmus MC Rotterdam. All subjects provided written informed consent. Sixty-four (n=64) 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 Center in Rotterdam, the Netherlands between August 2005 and May 2011. 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 enrolment to confirm the absence of infection. All our patients were in an acute disease state at moment of blood withdrawal.

Monocyte gene expression was conducted in 2 distinct cohorts, to allow for independent replications of our analyses. In the first cohort, we used a group of 23 healthy control women, with low levels of depressive symptoms as assessed by the Edinburgh Postnatal Depression Rating Scale (EPDS) score <10 at the time of 4 weeks postpartum blood sampling, collected between 1994-1996 (30) (31). The monocyte gene expression replication cohort, for which all T-cell and cytokine tests were also performed, consisted of 43 healthy postpartum women recruited between 2008-2011 through the Department of Obstetrics & Gynaecology (Erasmus MC, Rotterdam), with an EPDS score <10 at the time of 4 week postpartum blood sampling. Thirty-seven (n=37) healthy age-matched non-postpartum women were recruited from the Rotterdam general population between 2005-2011. Inclusion criteria for both postpartum and non-postpartum controls included the absence of any medical, neurologic, psychiatric, autoimmune disorder or acute infections.

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 (32), 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) (33).

For the initial monocyte gene expression analysis, we included 15 consecutive PP patients, 23 controls postpartum (CP), and 17 healthy controls (HC). We used the BIOMED-1 protocol (15). To obtain cDNA for RT-qPCR, 1 µg RNA was reversed-transcribed using Superscript-II (Invitrogen) and random hexamers (Amersham Biosciences, Roosendaal, The Netherlands) for 50 min at 42 C. RT-qPCR was performed with Taqman Universal PCR Mastermix (Applied Biosystems, Foster City, CA) as previously described (16). RT-qPCR conditions were 2 min at 50 C, 10 min at 95 C, followed by 40 cycles of 15 s at 95 C, and finally 1 min at 60 C. PCR amplification of the reference gene ABL was performed for each sample to allow normalization between the samples. Expression values were calculated using the comparative threshold cycle (CT) method.

For the independent replication sample, we included 23 consecutive PP patients, 17 controls postpartum (CP), and 9 healthy controls (HC), using a more advanced gene expression technique. 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. The next-generation assay for RNA expression analysis (TaqMan Low Density Array, TLDA) used in cohort 2 was extensively validated against the single RT-qPCR method used in cohort 1.

T-cell subsets

Intracellular staining and fluorescence-activated cell sorting (FACS) analysis

We determined the percentages of circulating T-cell subsets in 41 consecutive women with PP, 30 CP, and 31 HC using intracellular staining and fluorescence-activated cell sorting (FACS)

analysis, as described previously (34, 35) and in the legend of Table 3 in detail. Specifically, we determined the percentages of 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 is not a homogeneous group but can be subdivided into three effector and one regulator subgroups. 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. Natural T-regulator cells can be identified by CD25 and FOXP3 expression. Membrane staining of CD3, CD4, and CD25 enabled us to determine the percentages of Th1, Th2, and Th17 cells, respectively, as well as the regulatory T-cell population, in combination with staining of the hallmark intracellular cytokines IFN-γ, IL-4, and IL-17A and transcription factor FoxP3.

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 12 months, 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. The T-cell growth factor receptor sIL-2 levels were measured using a commercially available serum ELISA (DIACLONE Besancon, France).

Statistical Analysis

All analyses were performed using SAS, version 17.0 (SAS Institute, Inc., Cary, NC). 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 (serum cytokines/chemokines and percentages of T-cells). Statistical analysis on the gene expression data in monocytes was performed using DataAssist version 3.0 (Applied Biosystems, Life Technologies Corporation). Correlations were determined via Spearman rank correlation coefficients. All hypotheses were tested with an alpha of 0.05 (two-sided).

Results

Sample Characteristics

There were no significant differences in obstetric characteristics between women with postpartum psychosis (PP) and healthy postpartum women (CP) (Table 1). In the 1st CP cohort women were significantly younger and weighted less compared to patients. There was no difference in age and weight between patients and controls in the 2nd CP cohort. Significantly more CP women in both control cohorts were breastfeeding at the time of blood withdrawal (P < 0.01), given that all women with postpartum psychosis were advised to stop breastfeeding upon admission. 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).

Table 1. General and obstetric characteristics of healthy controls, healthy controls postpartum (2 different cohorts) and patients with first onset postpartum psychosis.

	Healthy Controls N=37	Controls Postpartum-I N=23		Controls postpartum II N=43		Postpartum Psychosis N=64		Difference between groups	
		Mean	S.E.M	Mean	S.E.M	Mean	S.E.M	P ¹	P ²
Age (years)	32.4 (1.1)	28.6	(0.6)	32.7	(0.6)	32.0	(0.6)	< 0.01	0.50
Weight		62.5	(1.2)	71.8	(1.8)	71.6	(1.7)	< 0.01	0.94
bloodwithdrawal, days postpartum		28.0	(0.8)	28.1	(2.0)	33.6	(3.7)	0.36	0.25
		N	%	N	%	N	%		
Primiparity		19/23	82.6	25/43	58.1	41/64	64.0	0.12	0.55
Primigravidity		19/23	82.6	28/43	65.1	51/64	79.6	1.0	0.11
Caeserian section		2/23	8.7	10/43	23.2	9/64	14.0	0.72	0.30
Vacuum extraction		3/23	13.0	4/43	9.3	7/64	10.9	0.72	1.0
Breastfeeding at time of bloodwithdrawal		9/23	39.1	28/43	65.1	2/64	3.1	< 0.01	< 0.01

¹ *Significance versus Controls Postpartum cohort I*
² *Significance versus Controls Postpartum cohort II*

Activation state of monocytes

In a first series of experiments, we determined the gene expression in monocytes in a sample of 15 consecutive first-onset PP patients, 23 CP women, and 17 healthy non-postpartum (HC) women. For this cohort we determined the monocyte expression of 25 genes which had been identified as strongly up regulated in bipolar disorder within 2 highly correlated gene clusters (15). The first cluster of genes predominantly consisted of pro-inflammatory

genes, while the second cluster consisted of adhesion, motility and, chemotactic factors.
A drawback of this series is the prolonged storage of the cells from CP women as compared to the PP and HC women. In order to overcome this drawback, we examined a second independent cohort of patients and controls that were collected in parallel over the same time period (2008-2011) in order to validate and further extend our findings.

We included a new group of 23 consecutive PP women, 17 CP women from the same hospital, and 9 HC women. We determined the monocyte gene expression of 43 genes, including the 25 genes examined in the first cohort, plus an additional set of 5 genes identified as up regulated in schizophrenia (16), 6 genes identified in studies of major depressive disorder (36), 4 interferon-inducible genes (37), 1 gene from studies of autoimmune thyroid disorder (38), as well as the transcripts for both the active and inactive glucocorticoid receptor.

Given the more extensive set of genes analysed in the replication cohort, we performed a new cluster analysis for postpartum psychosis (Figure 1). Two main clusters were identified and these clusters extensively overlapped with the previously identified monocyte gene cluster 1 and 2 from bipolar patients (15, 16).

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 23 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.
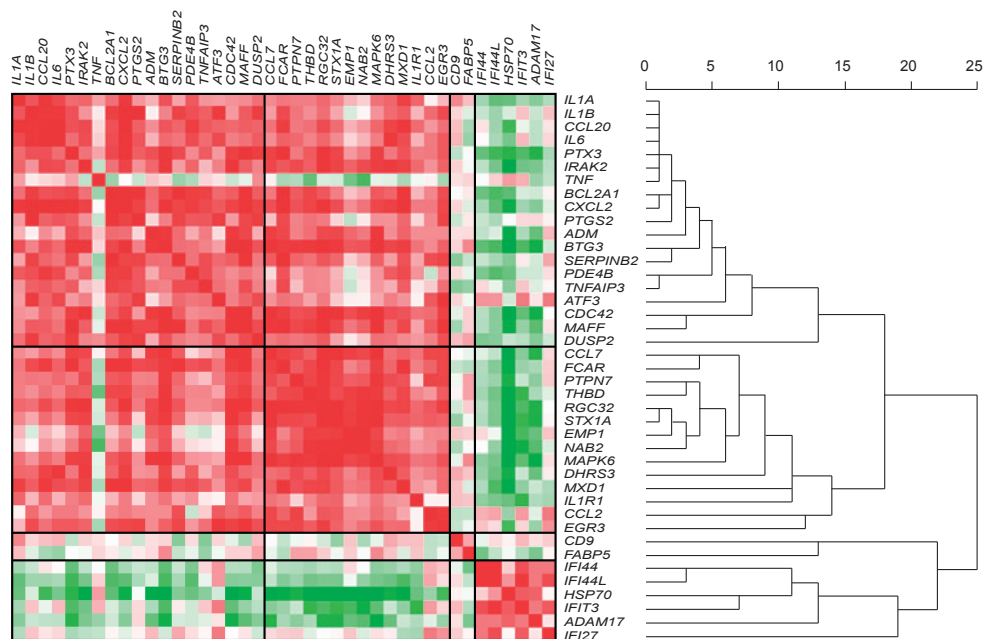
Healthy postpartum women

Monocytes of CP women showed moderate upregulation of cluster 1 genes, compared to HC women (Table 2). In the 1st cohort, 6/13 cluster 1 genes were significantly upregulated; while in the 2nd cohort, expression levels for only 3/19 of the cluster 1 genes were significantly increased. In contrast to the upregulation of cluster 1 genes, the changes in the cluster 2 genes were not consistent between the two study cohorts: in the initial cohort 4/13 were altered; while in the 2nd cohort, significant changes were not observed.

Postpartum psychosis

In women with PP, monocyte gene expression was consistently and more robustly upregulated, compared to both the HC and CP women (Table 2). Compared to HC, all cluster 1 genes upregulated in CP were also upregulated in PP within both the initial and replication cohorts. Of the remaining cluster 1 genes that were unchanged in CP monocytes, PP women showed upregulation of 4/6 genes in the initial cohort and 7/16 genes in the replication cohort as compared to the HC women (Table 2). Further, compared to the expression in the CP cohort, expression levels of 4/13 genes in the 1st cohort and 5/19 genes in the 2nd cohort were significantly increased.

In contrast to the more robust changes in cluster 1 gene expression, changes in cluster 2 were more modest. In the initial cohort, 2/11 cluster 2 genes in PP women had an altered expression level compared to HC, while just 1 gene was significantly different from CP women. In the replication cohort, 7/16 cluster 2 genes were significantly upregulated compared to HC and 3/16 were significantly upregulated compared to CP women.
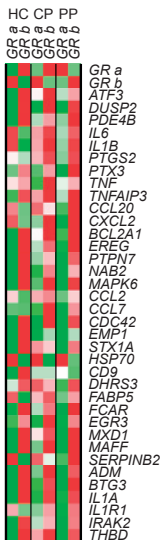
Figure 2. Correlations of all tested genes to GR α and GR β expression in patients with postpartum psychosis (PP), healthy controls postpartum (CP) and healthy controls not postpartum (HC). Significant positive correlations (p < 0.05) are given by the red scale (darkest red are correlations > 0.50), significant negative correlations are given by the green scale.

Chapter 8

Together, all genes showing significant upregulation between postpartum psychosis and postpartum healthy controls were genes not otherwise upregulated in the normal postpartum period.

With regard to the GR expression we found the inactive GR-β up regulated in PP women as compared to HC and CP women, while the active GR-α expression was somewhat reduced. This resulted in a significantly higher GR-β/GR-α ratio in monocytes of women with PP as compared to those of both control groups (P = 0.02, Figure 2). The upregulation of the inactive GR-β correlated positively and significantly to the over expression of many of the monocyte activation genes (Figure 2).

With regard to 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 significant higher expression levels of CCL2 compared to both HC (p= 0.040) and CP (p=0.036).

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).

	Postpartum control group n=23		Postpartum psychosis group n= 15		Postpartum control group n=17		Postpartum psychosis group n=23	
Cluster 1	mean	P-Value	mean	P-Value	mean	P-Value	mean	P-Value
IL1A					0,49	0,54	2,04	0,32
IL1B	**49,47**	0,00	**109,10**	0,00	1,35	0,55	2,24	0,08
CCL20	**192,18**	0,00	**936,13**	0,00	1,18	0,90	**5,59**	0,01
IL6	**557,96**	0,00	**1819,87**	0,00	**4,11**	0,02	**6,89**	0,00
PTX3	3,85	0,11	10,53	0,14	0,93	0,83	1,39	0,18
IRAK2					1,07	0,91	1,53	0,22
TNF	**16,86**	0,00	**11,63**	0,02	0,62	0,38	0,83	0,60
BCL2A1	1,60	0,90	**4,69**	0,06	1,73	0,19	**2,70**	0,00
CXCL2	**7,71**	0,00	**18,03**	0,02	2,46	0,19	**5,41**	0,00
PTGS2	4,10	0,13	**7,56**	0,00	**3,16**	0,02	**5,33**	0,00
ADM					1,10	0,83	**1,92**	0,04
BTG3					1,08	0,83	1,68	0,06
SERPINB2					1,53	0,52	**2,26**	0,02
PDE4B	2,46	0,80	**4,76**	0,03	1,21	0,55	**2,54**	0,00
TNFAIP3	**8,50**	0,00	**8,90**	0,01	1,20	0,68	1,60	0,17
ATF3	1,29	0,49	**3,18**	0,06	**2,59**	0,04	**3,28**	0,00
CDC42	1,31	0,49	1,94	0,91	1,52	0,52	1,85	0,11
MAFF					2,66	0,52	5,22	0,06
DUSP2	3,13	0,40	3,59	0,07	2,05	0,41	**3,27**	0,02

	Postpartum control group n=23		Postpartum psychosis group n= 15		Postpartum control group n=17		Postpartum psychosis group n=23	
Cluster 2	mean	P-Value	mean	P-Value	mean	P-Value	mean	P-Value
CCL7	11,89	0,11	19,46	0,54	0,67	0,83	**9,57**	0,02
FCAR	**0,72**	0,01	1,42	0,59	1,17	0,55	**1,81**	0,00
PTPN7	**0,84**	0,02	**0,73**	0,01	0,91	0,83	1,11	0,64
THBD					1,20	0,52	**1,86**	0,00
RGC32					1,52	0,55	**2,81**	0,02
STX1A	1,61	0,18	1,15	0,22	1,09	0,91	2,29	0,12
EMP1	0,88	0,14	0,80	0,19	1,38	0,52	**2,12**	0,01
NAB2	**0,40**	0,00	**0,55**	0,00	0,83	0,80	1,44	0,27
MAPK6	1,08	0,39	1,50	0,90	0,88	0,55	1,13	0,38
DHRS3	**3,87**	0,00	1,97	0,22	1,26	0,52	1,24	0,34
MXD1					1,22	0,52	**1,97**	0,00
IL1R1					0,96	0,91	1,57	0,08
CCL2	1,82	0,11	3,95	0,52	1,23	0,80	1,93	0,07
EGR3					5,47	0,19	**9,24**	0,02
CD9	2,04	0,51	1,29	0,41	1,57	0,67	1,11	0,86
FABP5	1,61	0,17	1,41	0,94	1,01	0,91	0,98	0,85
IFN related cluster								
IFI44					1,14	0,55	1,31	0,06
IFI44L					1,09	0,83	1,36	0,22
IFIT3					1,26	0,64	1,24	0,52
HSP70	**1,77**	0,00	**1,69**	0,01	1,40	0,52	1,03	0,92
ADAM17					1,13	0,52	1,03	0,85
IFI27					1,01	0,98	1,47	0,27
Glucocorticoid receptor genes								
NR3C1-GR-alpha					0,99	0,93	0,88	0,18
NR3C1-GR-beta					1,04	0,91	1,54	0,06
beta/alpha *1000					1,09	0,67	1,63	0,02

Significant dysregulation compared to healthy controls (p<0.05, see table) is given in bold. Significant dysregulation in patients with postpartum psychosis compared to controls postpartum are highlighted in grey (p<0.05, p values not given). ND= Not Determined; these genes were only determined in cohort 2. 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 ΔΔCT method (2-ΔΔCT, User Bulletin 2, Applied Biosystems, Foster City, California). To correct for inter-assay variance, we set the mean of the studied genes found in the healthy control groups (HC) in the same assay for each gene to 1. The fold change values of the genes in patient monocytes were expressed relative to this set mean of 1.

Lymphocyte subsets

T cell counts and T-cell growth factor sIL2-R were measured in 41 consecutive patients with PP, 30 CP and 31 HC (Table 3).

Healthy postpartum women

Circulating Natural Killer cells were reduced in the postpartum period (P = 0.04), while percentages of circulating T-cells were elevated ($P < 0.01$, Table 3). This rise in T-cells was due to a significant rise in CD4+ T helper cells (P = 0.02). Within the CD4+ helper compartment, not only were the Th1 and Th17 cell percentages increased (P = 0.04 and $P < 0.01$), but also the percentages of T regulatory cells (P = 0.03), suggesting a balance between effector and regulator forces despite T-cell activation. The rise in T-cell numbers was not reflected by a rise in the levels of the sIL2-R in serum.

Table 3 Percentage of different T-cell subsets in female healthy controls (HC), healthy controls postpartum (CP) and of patients with first onset postpartum psychosis (PP) using FACS analysis.

	Healthy Controls N=31		Controls Postpartum N=30			Postpartum psychosis N=41			
	Mean	SD	Mean	SD	P [1]	Mean	SD	P [1]	P [2]
NK cells: CD3-CD56+ (%)	14.19	(7.8)	9.93	(3.5)	0.04	11.43	(4.6)	0.31	0.32
T-cells: CD3+ (%)	73.15	(5.8)	79.56	(5.4)	0.00	73.46	(8.0)	0.67	0.01
Cytotoxic T-cells: CD3+/CD4- (%)	17.26	(10.7)	16.81	(7.6)	0.11	20.25	(8.1)	0.09	0.68
T helper cells: CD3+/CD4+(%)	46.11	(9.8)	52.00	(8.5)	0.02	47.49	(8.5)	0.92	0.04
Th1: CD4+IFNγ+ (%)	4,83	(2,4)	6,07	(2,3)	0.04	4,58	(2,5)	0.56	0.01
Th2: CD4+IL-4+ (%)	0,97	(0,4)	1,10	(0,5)	0.22	0,98	(0,4)	0.84	0.26
Th17: CD4+IL17A+ (%)	0,24	(0,2)	0,38	(0,2)	0.00	0,29	(0,2)	0.30	0.02
Treg:CD4+CD25+FoxP3+ (%)	2,10	(0,6)	2,62	(0,8)	0.03	2,18	(0,5)	0.40	0.06
IL-2R+ T-cells : CD25+	14,63	(7,2)	16,32	(7,58)	0.39	16,86	(8,4)	0.29	0.82

[1] *Significance versus Healthy Controls (Mann Whitney U test)*
[2] *Significance versus Controls Postpartum (Mann Whitney U test),*

To obtain detectable cytokine levels within lymphocytes, PBMC samples were suspended in complete culture medium and stimulated with PMA and ionomycin (both from Sigma Aldrich, Missouri, USA) in the presence of transport inhibitor GolgiStop (Becton Dickinson, New Jersey, USA) for 4 hours in 37°C under a 5% CO_2 environment. Cells were harvested and stained extra-cellularly with anti-CD4 APC and anti-CD45RO FITC (DAKO, Glostrup, Denmark). For determination of regulatory T-cells, non-stimulated PBMC samples were stained with anti-CD3 FITC, anti-CD4 PerCP-Cy5.5, anti-CD25 APC and anti-CD56 PE-Cy7. Following extracellular staining, cell samples were fixed and permeabilized using the FoxP3 staining buffer set (eBioscience, California, USA) according to the manufacturer's instructions. Next, stimulated cell samples were stained intra-cellularly with anti-IL-4 PE-Cy7, anti-IFN-γ PerCP-Cy5.5 (both from eBioscience, California, USA) and/or anti-IL-17A PE and non stimulated cell samples with anti-FoxP3 PE. All antibodies were from Becton Dickinson, New Jersey, USA, unless stated otherwise. Stained cells were analyzed on a BD LSR II flow cytometer (BD Biosciences, California, USA) as described previously and analyzed using FlowJo (Tree Star Inc. Ashland, Oregon, USA) research software.

Postpartum psychosis

Women with postpartum psychosis did not show the higher percentages of total T-cells, Th1, Th17 and T regulator cells observed in the healthy postpartum period. Consequently, there were significantly reduced levels of T-cells (P = 0.01), T-helper (P = 0.04), Th1 (P = 0.01), and Th17 (P = 0.02) cells compared to healthy postpartum control women (table 3). T regulatory cells were reduced at a significance level of $P = 0.06$. Serum levels of sIL2-R were in the range of both the healthy postpartum and non-postpartum control group.

Relation of monocyte activation and T cell 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 bloodsampling. Antipsychotic and/or benzodiazepine use did not result in a significant change in gene expression in cohort 1. In the larger patient cohort 2, antipsychotics decreased the expression of 3/43 genes: DUSP2 (r=-0,45, p=0.03), PTX3 (r=-0,58 p=0.03), TNF (r=-0,49, p=0.02), while benzodiazepines decreased expression in 4/43 genes: IL1B (r=-0,43, p=0.04), PTX3 (r=-0,43, p=0.04), PTGS2 (r=-0,52, p=0.01), TNFAIP3 (r=-0,48, p=0.02). Benzodiazepine use was positively correlated with Th2 helper cells (r=0,34, p=0.03). Further, medication use was not related to significant changes in cytokine/chemokine levels.

Patients with symptoms of psychotic depression showed lower gene expression for 3 genes compared to patients with manic psychotic symptoms in cohort 1, but this finding was not replicated in the larger cohort 2 analyses. Further, there were no differences observed in T-cell subsets 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 in healthy controls or patient, in either cohort. However, there was a significant increase of the monocyte/macrophage chemokine CCL2 (r=0.27, p=0.04) in patients with a caesarean section. Further, CP with delivery by caesarean section showed higher percentages of Th1 helper cells (r=0.52, p=0.03). In contrast, there was no significant correlation between the duration of delivery and any of these immune parameters.

Although there was no significant correlation between breastfeeding and inflammatory gene expression in healthy controls from cohort 1, healthy controls from the larger replication cohort who were breastfeeding at time of blood withdrawal had a significant upregulation of FAB5 (r=0.63, P=0.006). Further, we found no effect of breastfeeding on T-cell subsets or cytokine/chemokine levels.

Chapter 8

Discussion

Our study confirms that the normal postpartum period is a time of immune system alteration. Our findings show a modest gene transcription activation of monocytes, an increase in serum IL-1β and circulating T-cell numbers across multiple T-cell subtypes, but a decrease in NK 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 (39). The observation of low NK cell numbers during the normal postpartum period is also consistent with previous reports (40). Therefore, our data support the concept that the immune system reaches a distinct activation set point in the postpartum period of the macrophage-T cell arm. It is therefore not surprising that across the lifespan of women, the risk of immune disease exacerbation is elevated during the postpartum period. (41-43).

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 (34, 44-46). 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 and T cell subsets were even significantly decreased as 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 (47, 48).

With regard to monocyte function we found that monocytes of women with postpartum psychosis show a gene expression profile more robustly up-regulated than normally in the postpartum period. A similar high transcription of immune genes has been described for bipolar disorder and schizophrenia (8).

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 downregulate inflammatory gene expression (49, 50). Indeed, we found a significantly attenuated upregulation for a few genes in patients using medication compared to patients without medication. Therefore, based on these findings, we expect that monocyte immune activation in postpartum psychosis would be even more robust in an entirely medication-free cohort.

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 (51). 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.

The pregnancy and postpartum period are periods in which the HPA-axis undergoes substantial changes. Several reports suggest a causal relation between these HPA-axis disturbances and the occurrence of postpartum mood disorders (26, 52-57). We found that the ratio of the blocking GR-β to stimulating GR-α was not altered in monocytes of healthy postpartum women in comparison to that of non-postpartum women. However, the blocking GR-β to stimulating GR-α ratio was elevated in monocytes of women with postpartum psychosis due to a specific increase in the level of the blocking GR-β. This pattern of GR-β up-regulation and the correlation patterns of GR-β to the expression level of inflammation related genes indicates that steroid resistance – due to a higher production of the inactive GR-β – is part of the monocyte activation state in postpartum psychosis.
Our data thus clearly underscore the close link between a disturbed endocrine and immune system in postpartum psychosis.

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 while infiltrating the tissues and this phenomenon may thus represent an ongoing mild inflammatory monocyte/macrophage response.

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 (58). Further, an activated immune set point of microglia has been detected in acute schizophrenia patients for which animal models have demonstrated robust causal influences of microglial function on psychopathology (59-61). Together, we hypothesize that an altered set point postpartum 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. In support of such a theory, our data showed an abnormal set point of the neuro-immuno-endocrine axis in women with postpartum psychosis, given their elevated macrophage activity and significant reduction of T cell numbers.

Chapter 8

Acknowledgements

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Chapter 8

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Chapter 9

General Discussion

Conclusions

- Our data show that women with psychosis limited to the postpartum period have a unique risk profile and phenomenology, compared to bipolar patients with postpartum psychosis. In particular, these patients demonstrate a significantly delayed postpartum onset and the absence of obstetric complications (Chapter 3).

- We report adverse reactions on antidepressants in patients with postpartum psychosis with depressive features. In contrast, we demonstrate a more favourable treatment response when these patients are treated with lithium and antipsychotics (Chapters 2 and 3).

- We highlight the importance of distinguishing postpartum psychosis from bipolar disorder in the clinical care of women during subsequent pregnancies, as both groups optimally require distinct clinical treatment algorithms. In contrast to bipolar patients, there is no indication for pharmacological prophylaxis during pregnancy in patients with a history of psychosis limited to the postpartum period. Rather, prophylaxis should begin immediately postpartum in order to avoid the fetal risk of *in utero* medication exposure (Chapter 4).

- Thyroid autoimmunity has a significantly elevated incidence during episodes of postpartum psychosis (Chapter 7).

- The normal postpartum period is characterized by both monocyte and T-cell activation. Patients with postpartum psychosis have exaggerated monocyte activation, but lower T cell counts, compared to the normal postpartum period (Chapter 8).

Postpartum psychosis, a separate diagnostic entity?

Postpartum psychosis is a phenotypically well-defined disease entity, even though its nosological status is not distinctly classified in DSM-IV or ICD-10. Previous studies have clearly described the unusual symptom presentation of patients with postpartum psychosis, as well as similarities to bipolar disorder (1, 2). Although bipolar disorder is certainly an important risk factor for postpartum psychosis, a large proportion of postpartum psychosis patients have no history of prior manic or psychotic episodes (3). In our research we have particularly focused on this group: patients with first-onset psychosis postpartum. Together, our data contribute to the emerging consensus that women with a history of psychosis limited to the postpartum period might have a distinct variant of bipolar disorder (4).

For patients, clinicians and researchers, there are many advantages to give postpartum psychosis an official status as a discrete gender-specific diagnostic entity. First, it will aid in reducing stigma as women will not be categorized immediately as bipolar, a life-long

Chapter 9

illness, but instead diagnosed with "a postpartum condition". Women are now forced into current diagnostic criteria because ICD-10 and DSM-IV do not adequately recognize the syndrome. The result of these conceptual problems is an impression of confusion that has hindered research into this specific condition. More research can lead to official treatment algorithms and distinct prevention plans for subsequent pregnancies. Further, it would facilitate long-term prognosis and maintenance recommendations. Perhaps most notably, if not all psychotic episodes postpartum convert to bipolar disorder during lifetime, use of long-term mood stabilizers is not required for all women who experience a postpartum psychosis.

Overall, we strongly believe that a classification of postpartum psychosis as distinct gender-specific diagnostic entity would be very beneficial for our patients. Here we summarize the most prominent arguments in favor of a distinct classification:

1. Postpartum psychosis is the only psychiatric disease with an intrinsically defined onset, namely within 4 weeks postpartum.
2. Clinical features do not fit with the current diagnostic criteria. Women suffering from postpartum psychosis do not always present with features typical of bipolar disorder (manic episode, mixed episode) or a psychotic disorder. Postpartum psychosis patients often show a prominence of mood-incongruent delusions, in the absence of schizophrenia-like criteria. Longitudinal studies have reported that for some women, affective psychosis remains exclusively limited to the postpartum period.
3. First-onset postpartum psychosis has markedly different characteristics compared to postpartum psychosis in bipolar patients. Postpartum psychosis patients demonstrate a significantly delayed postpartum onset compared to postpartum relapses in bipolar patients. Further, and in contrast to bipolar patients, obstetric complications are not a risk factor for patients with psychosis limited to the postpartum period.
4. The overwhelming majority of patients experience a complete symptom remission within 3 months postpartum after treatment.
5. In stark contrast to the high rates of relapse in bipolar disorder, women with psychosis limited to the postpartum period are not at elevated risk of psychiatric episodes during pregnancy.

Immune theory of postpartum psychosis

The pathogenesis of psychosis and mania is considered genetically complex and heterogeneous. Current theories suggest that an interaction between genetic factors and other stressors or external factors determine an individual's risk of psychosis or mania. For example, the effect of cannabis may be stronger in those with a high genetic risk for the development of psychosis (5). In addition to drugs, other common examples of external

factors leading to psychiatric disease in subjects with high genetic susceptibility are trauma, severe stress, infection, brain injury and severe sleep loss. It has been shown that childbirth has the highest relative risk of any factor heretofore identified in psychiatry (6). Several neurobiological pathways are highly sensitized in the immediate postpartum period, and could thus serve as a potential trigger. Thus far, most research in postpartum psychosis has been focused on endocrine pathways because of the dramatic postpartum hormonal changes (7, 8). However despite extensive efforts, no consistent endocrinological aetiology for postpartum psychosis has been demonstrated. We propose an alternative mechanism underlying the sudden onset of psychosis postpartum: an immune related trigger. Moreover, we propose that the sharp increase in the occurrence of psychotic and manic symptoms after delivery could be associated to postpartum immune activation.

Most importantly supporting our immune hypothesis of postpartum psychosis: *Every* other known medical condition with a postpartum flare pattern has been demonstrated as originating from immune system dysfunction (9). Autoimmune diseases such as autoimmune thyroid dysfunction, rheumatoid arthritis, multiple sclerosis, autoimmune hepatitis, and myasthenia gravis classically remit during pregnancy, but have an exacerbation or initial onset during the postpartum period (10-17). Accordingly, there is consensus that immune activation in the peripartum period is a critical physiological trigger for the clinical manifestations of these autoimmune diseases. Intriguingly, the pathogenesis of another postpartum disease, peripartum cardiomyopathy, has only recently been elucidated. Although this is not a classical autoimmune disease, peripartum immune changes appear to function prominently in the disease pathogenesis (18), further supporting the notion that postpartum psychosis may be governed by a similar immunological mechanism.

Here, we provide 4 major lines of evidence in support of an autoimmune pathophysiology for postpartum psychosis:

1. Common characteristics of pregnancy-related autoimmune diseases include familial occurrence, progression from subclinical to clinical disease, a cyclical exacerbation-remission pattern, and a high recurrence risk with subsequent pregnancies. Remarkably, postpartum psychosis has been definitively shown to possess all of these clinical features. Postpartum psychosis is highly familial, frequently exhibits a bipolar-like exacerbation-remission pattern after a first-onset postpartum psychosis, and has recurrence rates of approximately 50% with subsequent pregnancies.

2. The co-occurrence with autoimmune thyroid dysfunction is suggestive of immune relatedness. It is well known that autoimmune diseases show associations with each other. As described in Chapter 7, there is high comorbidity between bipolar disorder and postpartum psychosis with autoimmune thyroid dysfunction (19-21).

Chapter 9

3. There is increasing evidence that immune activation postpartum is related to anxiety and mood symptoms (22). Postpartum depressive symptoms are significantly correlated with the increase of cytokines IL-1b, IL-6 and IL-8, an activation of a pro-inflammatory type-1 T cell response and a deficiency of tryptophan (23-29). Further, differential immune activation was recently demonstrated through investigation of gene expression profiles in blood mononuclear cells of women with postpartum depression (30).

4. There is emerging evidence that dysregulation in the immune system is central to the pathogenesis of bipolar disorder. Several studies have reported elevated serum cytokines and chemokines (31-36), a higher prevalence of organ-specific auto-antibodies (20, 37, 38), T cell activation (39, 40) and inflammatory monocyte gene expression (41, 42) in patients with bipolar disorder. Furthermore, in this thesis, we have reported on alterations of monocyte activation in patients with first onset postpartum psychosis.

Taken together, the robust combination of disease onset, clinical course, familial loading, co-occurrence with AITD, monocyte activation and T-cell dysregulation are highly suggestive of an immunological etiology for postpartum psychosis. Importantly however, it remains a very open question of which immunological mechanism(s) are directly responsible for triggering affective instability and psychosis. Moreover, even for well-defined autoimmune disorders, such as AITD, MS and RA, the postpartum immune trigger is only partially understood (9, 10, 17).

During pregnancy, changes in the immune system are necessary for inducing tolerance of the mother towards the genetically distinct foetus. In general, there is a down-regulation of potentially dangerous T-cell mediated immune responses, in parallel with a coordinated activation of the innate immune system. Further, endocrinological changes lead to a T helper 1 (Th1) suppression and Th2 up-regulation during pregnancy, for which there is a rapid reversal of this balance in the early postpartum period (43). Accordingly, this restoration of the Th1/Th2 balance postpartum has been widely hypothesized to model rheumatoid arthritis (RA) and autoimmune thyroid disease, as Th1-driven diseases often have their initial onset during the postpartum period (44). Importantly however, the precise immunological processes that are most highly influential during normal human pregnancy and the postpartum period remain under intense debate, given that the historical conceptualizations of T helper 1 (Th1) suppression and Th2 up-regulation during pregnancy, with postpartum restoration of this balance postpartum, appears to incompletely capture the full complexity of observed data.

An emerging alternative explanatory model for the high occurrence of autoimmune disorders postpartum regards the influence of T regulatory cells (45). T regulatory cells play a major role in pregnancy by inhibiting T cells. T regulatory cells increase early in

pregnancy, peak in the second trimester and then decline in the postpartum period (46). A decline T regulatory cells function has been linked to progression towards autoimmune diseases outside the postpartum period. Therefore, some investigators have suggested that disordered postpartum T regulatory cell function might lead to maternal autoimmunity (11).

Lastly, there is also reason to believe that several adaptations of the innate immune system during pregnancy and postpartum are highly relevant for autoimmunity in the peripartum period. In general, the innate immune system appears activated during pregnancy, in a "controlled state of inflammation" (47). Enhancement occurs in the numbers and activation state of circulating granulocytes and monocytes, leading to a more aggressive attack on invading bacteria. Besides a prominent function in host defense, monocytes participate in the maintenance of tolerance by displaying tolerogenic signals to T-cells (48). This state of innate immune activation during pregnancy appears to extend into the early post-partum period. During the initial few days postpartum, serum levels of inflammatory cytokines such as IL-6 and IL-1β (23, 24) are typically increased. Unfortunately however, the differential rates of change in various aspects of postpartum innate immune function have hardly been investigated, for which possible links with autoimmunity remain largely unexplored.

Taken together, the mother is protected from infection during pregnancy by an increased innate immunity. Adaptive immunity against fetal tissue is in a tolerogenic mode, likely due to increased T regulatory cells and tolerogenic dendritic cells. Postpartum, there is evidence for both monocyte and T cell activation with altered T regulatory subsets. The postpartum occurrence of autoimmunity might therefore be linked to this monocyte and T cell activation and/or the imbalance in T regulator cells.

A similar mechanism could hold true for the occurrence of mania and psychosis postpartum. We propose that the elevated set point of the monocyte/macrophage/T cell system in the normal postpartum period might critically alter a set point of the immune-endocrine system leading to the onset of bipolar disorder in vulnerable women. This "immune hypothesis of postpartum psychosis" could be seen as complementary to previous endocrine hypotheses. Several studies have shown bidirectional interactions between endocrine systems and the immune system. Accordingly, it is well established that glucocorticoid stress hormones have profound immune modulatory effects, and that sex hormones also modulate immune responses (49). A specific hormone of interest is prolactin, as this hormone is associated with acute disease exacerbations in autoimmune disorders (50, 51).

A combined endocrine-immune trigger postpartum could lead to disease in vulnerable women. An alternative model could be that different subtypes lead to the same phenotypes. Altered signaling mediated by immune molecules possibly underlies the biology of some subtypes of postpartum psychosis, whereas other subtypes might be caused by susceptibility for endocrine changes. Elucidating these immune-endocrine mechanisms might reveal new

Chapter 9

insight into the onset of postpartum psychosis and bipolar disorder. Clearly, more research focused on immune dysfunction in bipolar women during pregnancy and the postpartum period is warranted.

Clinical Recommendations

- Diagnostic efforts to distinguish between women with a first onset postpartum psychosis, versus women with postpartum psychosis and a history of bipolar disorder, will greatly enhance clinical prognosis and treatment.

- We propose a treatment algorithm for postpartum psychosis based on our clinical experience, guided by the larger literature for treatment of bipolar patients. We recommend using the sequential addition of benzodiazepines, antipsychotics, and finally lithium in those patients without a significant clinical response within 2 weeks.

- We recommend following the treatment guidelines for bipolar II depression in patients with acute onset during the postpartum period of depression with psychotic features. This recommendation is valid even in the absence of hypomanic symptoms in history or at the time of evaluation within the first 4 weeks postpartum. Further, we discourage the use of antidepressants (particularly in the absence of appropriate mood stabilization) during the postpartum period in patients with postpartum depression and psychotic features.

- Close monitoring of thyroid function is critically important for optimal clinical management. We suggest measuring TSH, f T4 and thyroperoxidase antibodies at the time of diagnosis and 6 months postpartum.

- We recommend using a postpartum psychosis prevention plan in patients at high risk for postpartum psychosis: women with a history of postpartum psychosis and/or women with bipolar disorder. For specific guidelines, see Addendum 1.

- In bipolar women, prophylaxis during pregnancy appears important for maintaining mood stability during pregnancy and to minimize the high risk of postpartum relapse. Importantly, use of medication during pregnancy should always be weighed against the risks for the fetus.

- In women with a history of psychosis limited to the postpartum period, we recommend initiating prophylactic treatment immediately postpartum, thereby offering an important clinical advantage by avoiding *in utero* foetal exposure to prophylactic medication.

Future research

Replication and enlargement of the cohort

The sample sizes of our studies in patients with postpartum psychosis are relatively small, so our results should be interpreted with caution. Therefore, we will not only try to replicate our findings in our ongoing OPPER study within the Erasmus MC, but we also intend to enlarge the cohort through inclusion of postpartum psychosis patients from other hospitals throughout the Netherlands.

Long-term follow-up studies

We are currently analyzing the nine-month and four-year follow-up data of our first onset postpartum psychosis patients. Through the nine-month postpartum follow-up dataset, we hope to obtain definitive rates of sustained remission. Furthermore, the four-year follow-up data will provide increasing guidance for the necessary duration of treatment following full remission. In particular, we intend to quantify the risk for conversion to bipolar disorder over the four-year period following a first-onset postpartum psychosis. Clearly, it is of major interest to determine predictive characteristics and biological determinants of women who are particularly vulnerable for conversion to bipolar disorder, versus women who are only vulnerable for relapse immediately following delivery.

Prevention of postpartum psychosis

While our recent work is a step forward in establishing standardized clinical guidelines for the prevention of postpartum psychosis, several key questions are outstanding. Specifically, the optimal duration of prophylactic treatment and the efficacy of antipsychotics for prophylaxis remain unclear. Consequently, there is a need for a larger clinical data set that can evaluate the risks and benefits of specific antipsychotic and mood stabilization pharmacotherapies for moderating peripartum relapse risk and neonatal outcomes. Further, advancing the care of pregnant women at high risk for postpartum psychosis will involve the precise identification of the clinical and biological characteristics of women who are at risk for peripartum relapse, to allow individualized and maximally effective prophylaxis regimens while minimizing *in utero* fetal exposure.

Marker molecules

In this thesis, we have discussed that disease onset, clinical course, familial loading, co-occurrence with AITD and monocyte activation are in combination very suggestive of an immunological aetiology for postpartum psychosis. Therefore, we will not only evaluate clinical characteristics predictive for conversion to bipolar disorder versus a more favorable disease course, but also to search for immune and endocrine serum markers. In particular,

Chapter 9

we are currently in the process of screening the serum of patients with postpartum psychosis for biomarkers of vascular function and angiogenesis, tryptophan metabolites, and auto-antibodies with affinity for endogenous central nervous system (CNS) antigens.

Genetics

Our model of postpartum psychosis hypothesizes that for any given woman in the postpartum period, acute immune-endocrine factors interact with underlying genetic factors to determine the risk of developing postpartum psychosis, with or without an ongoing bipolar disorder. Because our cohort is itself too small for independent genome-wide genetic studies, we plan to collaborate within an (inter)national consortia to identify differential genetic susceptibility for responsiveness to childbirth related neuro-immuno-endocrine triggers. In particular, we have established collaborations with the Danish reproduction and mental health studies (Aarhus), Perinatal Genetic Consortium (PACT, North Carolina), BIG consortium (Bipolar Genetics, Utrecht), PREDESIS (Tilburg), and Moodinflame (Rotterdam). Towards this goal, we have already designed and validated a standardized screening instrument for application in genetic studies, in order to accurately quantify childbirth-associated severe psychiatric symptoms (Addendum 2).

Ideally, our current and future research will ultimately contribute to individualized, highly effective and minimally invasive strategies to prevent the development of chronic mental illness after a first onset postpartum psychosis.

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Chapter 9

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Chapter 9

Addendum 1

Postpartum Psychose Preventie Behandelplan

Naam:

Gravida :   , Para :

À terme datum:

Psychiatrische diagnose:
VOORBEELD: Postpartum psychose in de voorgeschiedenis, bipolaire stoornis.

Psychiatrische voorgeschiedenis:
Vermeld ook of patiënte klachten had tijdens eerdere zwangerschap of na eerdere partus.

Somatische diagnose:

Obstetrische voorgeschiedenis:
Vermeld bijzonderheden eerdere bevallingen.

Huidige zwangerschap:
Medische complicaties en of patiënte stabiel is tijdens deze zwangerschap.

Medicatie:
Huidige medicatie inclusief start datum en spiegels.
VOORBEELD 1: Wij adviseerden medicatie tijdens de zwangerschap te continueren, aangezien uit onderzoek blijkt dat afbouwen van medicatie tijdens de zwangerschap een hoog risico geeft op terugval. Wij informeerden patiënte over het risico op … [vul hier evt. gevolgen voor het (ongeboren) kind in afhankelijk van middel].
VOORBEELD 2: Wij adviseerden medicatie af te bouwen vanwege de mogelijke gevolgen voor het ongeboren kind.
Vermeld ook medicatie die voor de zwangerschap gebruikt werd en de stopdatum.

Bevalling:
Vermeld als er een inleiding gepland is, sectio of pijnstilling en waar de bevalling gaat plaatsvinden. Vermeld ook de naam van de gynaecoloog.

<u>Handelingsplan rondom bevalling:</u>

VOORBEELD:

– Mevrouw is geïndiceerd voor een klinisch kraambed (geplande duur 5 dagen) i.v.m. het risico op postpartum psychose. Wij adviseren opname op een alleenstaande kamer.

– Dagelijks wordt zij bezocht door haar behandelend arts (naam), sociaal psychiatrisch verpleegkundige (naam), of een dienstdoend arts-assistent psychiatrie.

– Mevrouw geeft geen borstvoeding. Lactatieremmers zijn gecontraïndiceerd.

– De eerste avond na de bevalling wordt om 20.00 Lithium verhoogd/gestart in een dosering van 1000 mg . De lithiumspiegel wordt bepaald op dag 2, 5 en 12 post partum. De streefspiegel is tussen 0.8-1.0 mmol/l. Op dag 12 tevens TSH en fT4 en thyroperoxidase antistoffen bepalen.

– Lorazepam 1 mg wordt standaard aangeboden voor de nacht en evt. opgehoogd bij slaapproblemen.

– De baby slaapt 's nachts op de babykamer. Verpleegkundigen nemen de nachtvoeding over. Na ontslag zal partner de eerste maand de nachtvoedingen op zich nemen.

– Indien medicatie gebruikt werd tijdens de zwangerschap gebruik de volgende zin; de baby zal direct na de bevalling door de kinderarts worden onderzocht i.v.m. psychofarmacagebruik en gedurende 48 uur geobserveerd worden op ontwenningsverschijnselen. In navelstrengbloed zal de lithiumspiegel, TSH, fT4, en TSI bepaald worden.

<u>Signaleringsplan:</u>

VOORBEELD:

Eerste symptomen:

· Bij depressie: aanhoudende somberheid en vermoeidheid (enkele dagen), minder slapen en verminderde concentratie.

· Bij (hypo)manie: snel praten, druk gedrag, denken alles aan te kunnen.

Wat kan ik zelf doen:

· Rust, regelmaat en reinheid.

· Met anderen emoties en klachten bespreken en signalen delen.

· Vooraf kraamafdeling zien.

· Vooraf afspraken maken over bezoek en mobiele telefoon.

Wat kan mijn omgeving doen:

· Hulp met huishouden en helpen dagstructuur aanbrengen/vasthouden.

· Vragen naar stemming/gevoel.

· Stimuleren en activeren, bijvoorbeeld samen buiten wandelen bij sombere stemming.

Chapter 9

· Laagdrempelig contact opnemen met de afdeling psychiatrie (telefoon polikliniek: 010-7040139) of huisarts.

Nazorg:

VOORBEELD:

Wij adviseren lithium minimaal 3 maanden postpartum te continueren en vervolgens in overleg zeer geleidelijk af te bouwen.

……………   Mw…………..

Psychiater   (naam patiente, en handtekening)

Kopie:

- Huisarts
- Behandelend gynaecoloog
- Patiënte zelf
- Behandelaren in de GGZ

Addendum 2

Questionnaire Postpartum Mood Disorders (NL)

Patiëntnummer: ………………   Datum invulling: ………………..

Screeningsvraag: Bent u ooit zwanger geweest?
□ Nee   → deze vragenlijst hoeft niet te worden afgenomen
□ Ja   → vervolg deze vragenlijst

1   Heeft u kinderen? Vul de geboortedata van de kinderen in.

2   Heeft u ooit een miskraam/doodgeboren kind gehad? *Vul het jaartal in*.

3   Heeft u ooit een abortus ondergaan? *Vul het jaartal in.*

4   Heeft u na de geboorte van ......of miskraam of abortus een manische, psychotische of depressieve periode doorgemaakt?
   ⇒   *Indien patiënte een manie of een gemengde episode heeft doorgemaakt vul 'M' in;*
   ⇒   *Indien een psychose: vul 'P' in;*
   ⇒   *Indien een depressie vul 'D' in.*
   (psychose én manie en psychose én depressie kunnen beide ingevuld worden)

5   Wanneer is deze postpartum episode begonnen?
   ⇒   *Indien tijdens de zwangerschap al begonnen, vul in 'zw'.*
   ⇒   *Indien begonnen binnen 4 weken postpartum, vul in '< 4 wk'.*
   ⇒   *Indien begonnen tussen 4 en 8 weken postpartum, vul in '4-8 wk'.*
   ⇒   *Indien begonnen tussen 8 weken en 6 maanden postpartum, vul in '2-6mnd'.*

Geboortedata kinderen *dd/mm/yyyy*	Postpartum episode? **Vul in:**	Indien M, P of D: Aanvang episode **Vul in:**
.. ../.. ../..	[ ] neen; [ ] M; [ ] P; [ ] D	[ ] zw; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 mnd
.. ../.. ../..	[ ] neen; [ ] M; [ ] P; [ ] D	[ ] zw; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 mnd
.. ../.. ../..	[ ] neen; [ ] M; [ ] P; [ ] D	[ ] zw; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 mnd
.. ../.. ../..	[ ] neen; [ ] M; [ ] P; [ ] D	[ ] zw; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 mnd
.. ../.. ../..	[ ] neen; [ ] M; [ ] P; [ ] D	[ ] zw; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 mnd
Jaar miskraam *yyyy*		
.. ..	[ ] neen; [ ] M; [ ] P; [ ] D	[ ] zw; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 mnd
.. ..	[ ] neen; [ ] M; [ ] P; [ ] D	[ ] zw; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 mnd
.. ..	[ ] neen; [ ] M; [ ] P; [ ] D	[ ] zw; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 mnd
.. ..	[ ] neen; [ ] M; [ ] P; [ ] D	[ ] zw; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 mnd
Jaar abortus *yyyy*		
.. ..	[ ] neen; [ ] M; [ ] P; [ ] D	[ ] zw; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 mnd
.. ..	[ ] neen; [ ] M; [ ] P; [ ] D	[ ] zw; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 mnd
.. ..	[ ] neen; [ ] M; [ ] P; [ ] D	[ ] zw; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 mnd

⇒ *Indien patiënte een manische, gemengde of psychotische episode postpartum heeft doorgemaakt vul dan sectie D van de MINI voor deze episode in. Indien patiënte meerdere episoden heeft doorgemaakt, neem dan de episode die binnen de kortste tijd na de bevalling begonnen is.*

⇒ *Indien patiënte een depressieve episode heeft doorgemaakt vul dan sectie A van de MINI voor deze episode in. Indien patiënte meerdere postpartum depressies heeft doorgemaakt, neem dan de episode die binnen de kortste tijd na de bevalling begonnen is.*

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Questionnaire Postpartum Mood Disorders

Patient number: ………………   Date: ……………….

Screenings question: Have you ever been pregnant?
□ No   → please don't fill in this questionnaire
□ Yes   → continue this questionnaire

1   Do you have children? Please fill in dates of birth.

2   Did you ever experience a miscarriage or stillbirth? Please fill in the year.

3   Did you ever experience an abortion? Please fill in the year.

4   Did you suffer from a manic, psychotic or depressive episode after birth of …or miscarriage or abortion?
   ⇒   *If patient suffered from a manic or, a mixed episode, please fill in 'M';*
   ⇒   *If patient suffered from a psychotic episode, please fill in 'P';*
   ⇒   *If patient suffered from a depressive episode, please fill in 'D'.*
   (Psychosis ánd mania and psychosis ánd depression can be filled in at the same time)

5   When did this episode start?
   ⇒   *If started during pregnancy, please fill in 'pr'.*
   ⇒   *If started within 4 weeks postpartum, please fill in '< 4 wk'.*
   ⇒   *If started between 4 and 8 weeks postpartum, please fill in '4-8 wk'.*
   ⇒   *If started between 8 weeks and 6 months postpartum, please fill in '2-6 m'.*

Birhtdate Children *dd/mm/yyyy*	Postpartum episode? **Please fill in:**	If M, P or D: Start episode **Please fill in:**
.. ../.. ../..	[ ] no; [ ] M; [ ] P; [ ] D	[ ] pr; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 m
.. ../.. ../..	[ ] no; [ ] M; [ ] P; [ ] D	[ ] pr; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 m
.. ../.. ../..	[ ] no; [ ] M; [ ] P; [ ] D	[ ] pr; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 m
.. ../.. ../..	[ ] no; [ ] M; [ ] P; [ ] D	[ ] pr; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 m
.. ../.. ../..	[ ] no; [ ] M; [ ] P; [ ] D	[ ] pr; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 m
Year miscarriage *yyyy*		
.. ..	[ ] no; [ ] M; [ ] P; [ ] D	[ ] pr; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 m
.. ..	[ ] no; [ ] M; [ ] P; [ ] D	[ ] pr; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 m
.. ..	[ ] no; [ ] M; [ ] P; [ ] D	[ ] pr; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 m
.. ..	[ ] no; [ ] M; [ ] P; [ ] D	[ ] pr; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 m
Year abortion *yyyy*		
.. ..	[ ] no; [ ] M; [ ] P; [ ] D	[ ] pr; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 m
.. ..	[ ] no; [ ] M; [ ] P; [ ] D	[ ] pr; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 m
.. ..	[ ] no; [ ] M; [ ] P; [ ] D	[ ] pr; [ ]<4 wk; [ ] 4-8 wk; [ ] 2-6 m

⇒ *If the patient suffered from a manic, mixed or psychotic episode postpartum, please fill in 'section D from the MINI for this episode. If the patient suffered from more than one episode, please fill in the episode with earliest start postpartum.*

⇒ *If the patient suffered from depressive episode postpartum, please fill in section A from the MINI for this episode. If the patient suffered from more than one episode, please fill in the episode with earliest start postpartum.*

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Summary

Part I Clinical perspective

Chapter 2.

Postpartum psychosis is a severe disorder occurring in 0.1% of childbearing women. The clinical symptoms include fluctuations in mood accompanied by delusions and hallucinations, as well as agitation, insomnia and cognitive impairment. Patients often require urgent hospital admission. At the Erasmus MC, patients can be admitted together with their baby. Although women are severely ill during this episode, the duration of postpartum psychosis is limited (weeks to months) and recovery is complete. At discharge, women experience minimal difficulties in bonding with their child.

At the Erasmus MC, patients are treated using a standardized algorithm consisting of the sequential addition of benzodiazepines, antipsychotics, and finally lithium. Our treatment algorithm was established based largely upon the treatment guidelines for bipolar patients, and guided by our specific clinical experiences in caring for patients with postpartum psychosis. Importantly, this treatment algorithm includes patients with postpartum psychosis in the setting of depressive, manic, or mixed affective features. Over the last 4 years, eight postpartum patients were referred to our clinic as a result of very unstable illness course after treatment with antidepressants. We suspect that antidepressant treatment without adequate mood stabilization places women with postpartum depression and psychotic features at an unacceptable risk for exacerbation of symptoms. Therefore we suggest treating these patients with antipsychotics and lithium.

Although bipolar disorder is certainly an important risk factor for postpartum psychosis, a large proportion of postpartum psychosis patients have no prior history of manic or psychotic episodes. In our research, we have particularly focused on this group: those patients with first-onset psychosis in the postpartum period. We have investigated risk factors for postpartum psychosis, phenomenological characteristics, treatment response and prevention of further episodes. Our studies demonstrate that women with psychosis limited to the postpartum period have distinct characteristics during their first episode (chapter 3), and a unique risk profile during subsequent pregnancy and postpartum period (chapter 4), compared to bipolar patients with postpartum psychosis.

In **chapter 3**, we report the outcome of our prospective cohort study of patients with first-onset postpartum psychosis. We included 51 women with postpartum psychosis and the absence of any previous manic or psychotic symptoms outside the postpartum period. We have investigated obstetric, neonatal, and lactational risk factors in these women, compared to a large population-based cohort. Furthermore, we documented their phenomenological characteristics and response to treatment.

Women with postpartum psychosis had a significantly higher incidence of primiparity, but no significant differences in delivery-related, lactational, or neonatal-related risk factors.

Further, our data show that patients with first-onset psychosis have a significantly delayed postpartum onset (median day 8) compared to bipolar patients, and a prominence of mood-incongruent psychosis. Encouragingly, a beneficial treatment response was observed in nearly all women. The median duration of episode was 40 days; prominent depressive features predicted a significantly longer duration of the postpartum psychosis episode.

In **chapter 4**, we evaluated the outcome of lithium prophylaxis during pregnancy, compared to immediately postpartum, in 70 women at high risk for postpartum psychosis using standardized clinical guidelines. Specifically, we have investigated relapse rates both during pregnancy and in the postpartum period for 41 women with bipolar disorder and 29 women with a history of postpartum psychosis. Women with postpartum psychosis, compared to those with bipolar disorder, had a substantial difference in their clinical outcomes and prophylaxis requirements.

 Notably, all women with a history of psychosis limited to the postpartum period were stable throughout their entire pregnancy despite using no prophylactic medication. In contrast, women with bipolar disorder had high rates of relapse during pregnancy. Furthermore, initiation of prophylaxis immediately postpartum in women with a history of postpartum psychosis with either lithium or antipsychotics was highly effective for preventing postpartum relapse. In contrast, the efficacy of postpartum prophylaxis in women with bipolar disorder was much lower. During the postpartum period, relapse was highest in women with bipolar disorder who experienced mood episodes during pregnancy. Therefore, we have proposed distinct clinical treatment algorithms for women with bipolar disorder versus women with a history of postpartum psychosis. In bipolar women, prophylaxis during pregnancy appears critically important for maintaining mood stability during pregnancy and to minimize the high risk of postpartum relapse. In contrast, we recommend initiating prophylactic treatment immediately postpartum in women with a history of psychosis limited to the postpartum period, offering an important clinical advantage by avoiding *in utero* fetal exposure to prophylactic medication.

II. Pathophysiology of postpartum psychosis

Postpartum psychosis is widely hypothesized to be a disease with a strong neurobiological basis, however studies demonstrating robust biological influences have not yet been realized. Most neurobiological research has focused on endocrine pathways, given the dramatic changes in hormone levels after delivery, as summarised in **chapter 5.**

In **chapter 6,** we propose the novel hypothesis that postpartum immune dysregulation is a critical biological trigger for the onset of postpartum psychosis.

In **chapter 7,** we examine the hypothesis that autoimmune thyroid dysfunction may be associated with the onset of postpartum psychosis. We investigated the prevalence of autoimmune thyroid dysfunction in a consecutive series of 31 primiparous women with postpartum psychosis, compared to postpartum women from the overlapping general population. Thyroperoxidase (TPO) antibody levels, Thyroid stimulating hormone (TSH), and free thyroxine (fT4) levels were measured at four weeks and nine months postpartum.

Our data showed that autoimmune thyroid disease is much more prevalent in women with first-onset postpartum psychosis (19%) than in postpartum women from the general population (5%). Furthermore, clinical thyroid failure occurs significantly faster and in a greater percentage of patients with postpartum psychosis. Importantly, these differences appear to be independent of antipsychotic or lithium treatment in the early postpartum period.

Taken together, the high prevalence of clinical thyroid dysfunction in patients with postpartum psychosis is an important consideration for both clinical management and pathophysiological understanding. Therefore, screening for TPO antibodies is warranted in patients with postpartum psychosis. Of note, in our studies we used lithium as the final treatment option. While lithium has widespread clinical support as a highly effective mood stabilizer, lithium treatment is a risk factor for thyroid dysfunction. Therefore, the risks and benefits of lithium should be weighed carefully in choosing the most appropriate pharmacologic regimen for treatment of postpartum psychosis, particularly for patients with elevated TPO antibody titers.

In **chapter 8** we examined immune activation in patients with first-onset postpartum psychosis at the level of monocytes, T-cells, and serum cytokines/chemokines. We included 64 women consecutively admitted with first-onset postpartum psychosis matched to postpartum and non-postpartum healthy controls, in order to control for confounding factors related to the normal postpartum period. A quantitative-PCR case-control monocyte gene expression analysis was performed using 45 genes previously identified as abnormally regulated in non-postpartum mood disorder patients including the activating and inactivating isoforms of the glucocorticoid receptor (GR–α and β). T-cell percentages were measured by FACS analysis, while serum monocyte and T-cell related cytokines/chemokines were determined using a cytometric bead array.

We found that monocytes of women with postpartum psychosis have a gene profile showing more robust immune activation than 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 decreased

in women with postpartum psychosis in comparison to the levels found in the normal postpartum period.

Taken together, we have demonstrated that postpartum psychosis is characterized by a robust dysregulation of the immuno-neuro-endocrine set point, including prominent monocyte/macrophage activation.

Nederlandse Samenvatting

Casus: een patiënte met postpartum psychose

Een 30 jarige vrouw, met een blanco psychiatrische voorgeschiedenis, bevalt bij een zwangerschapsduur van 39 weken poliklinisch van haar eerste kind: een gezonde dochter. De zwangerschap en de bevalling zijn ongecompliceerd verlopen. Tijdens de kraamtijd is de vrouw bezorgd of haar dochter wel voldoende borstvoeding krijgt. Als de kraamverzorgende weg is, voert zij de frequentie van het aantal voedingen op. Zij raakt gepreoccupeerd met de regel: "rust, reinheid en regelmaat" en drinkt daarom veel water. Daarnaast is zij tot diep in de nacht druk met het huishouden en vergeet zij soms te slapen. Er is sprake van toenemende agitatie, onder andere naar haar partner als hij haar maant rustiger aan te doen. Verder is zij toenemend achterdochtig ten aanzien van haar schoonzus die in huis is gekomen om patiënte na de kraamtijd extra te ondersteunen. Patiënte raakt in wisselende mate verward, heeft het idee dat haar dochter met hagedissenogen naar haar kijkt, herkent soms haar partner of andere familieleden niet, heeft het idee dat er een rollenspel wordt gespeeld en geeft speciale betekenissen aan kleuren die zij om zich heen ziet. Als de situatie uitmondt in een handgemeen, wordt de crisisdienst ingeschakeld en volgt opname.

Het lezen van dit verhaal zal mogelijk een aantal vragen oproepen:
- Hoe kan het zijn dat iemand met een blanco psychiatrische voorgeschiedenis zo ziek wordt vlak na de bevalling?
- Wat is de oorzaak van deze ernstige psychiatrische ziekte?
- Wat voor behandeling heeft deze vrouw nodig?
- Wordt deze vrouw weer helemaal beter?
- Wat gebeurt er na een eventuele volgende zwangerschap?

Deze vragen zijn voor ons in 2005 de reden geweest om te starten met de OPPER studie, Onderzoeksprogramma Postpartum Psychose Erasmus MC Rotterdam. De eerste resultaten van dit onderzoek hebben geleid tot dit proefschrift. In dit proefschrift wordt postpartum psychose vanuit verschillende invalshoeken benaderd. In het **eerste deel** beschrijven we postpartum psychose vanuit een klinisch perspectief. Na een beschrijving van de symptomatologie en de geschiedenis worden risicofactoren en de behandeling onderzocht. Dit klinisch onderzoek richtte zich ook op het voorkómen van een volgende ziekteperiode**.** In het **tweede deel** worden mogelijke pathofysiologische oorzaken besproken. Na een overzicht van het onderzoek tot nu toe komen we tot een nieuwe hypothese: spelen de veranderingen in het immuunsysteem na de bevalling een oorzakelijke rol bij het ontstaan van postpartum psychose? We hebben verschillende immuunparameters onderzocht.

Deel I: Klinisch perspectief

In **hoofdstuk 2** geven we een klinisch overzicht.

In de periode na de bevalling, de postpartum periode, zijn vrouwen kwetsbaar voor het ontwikkelen van een psychiatrische aandoening of het verergeren van een al bestaande psychiatrische stoornis. Ook is bekend dat opname in de psychiatrie bij vrouwen vaker in de postpartum periode voorkomt dan op enig ander moment in hun leven.

Postpartum psychose (kraambedpsychose) komt na 1 à 2 per 1000 bevallingen voor. Vaak zijn de eerste symptomen van een postpartum psychose al in de eerste week postpartum zichtbaar. Na enkele symptoomvrije dagen ontstaan er bijvoorbeeld slaapstoornissen, prikkelbaarheid, ontremming en achterdocht. Vervolgens worden na ongeveer een week psychotische verschijnselen waargenomen zoals verwardheid, hallucinaties, wanen, gestoorde realiteitsbeleving, maar ook een wisselend bewustzijn en symptomen van manie of depressie. De kans op agressie naar het kind en suïcide is toegenomen.

Opvallend aan het gepubliceerde onderzoek naar postpartum psychose is dat er veelal gebruik wordt gemaakt van slecht gedefinieerde termen en inconsistente classificaties. Dit komt omdat postpartum psychose niet als een op zichzelf staande aandoening wordt beschouwd binnen het huidige classificatie systeem, de DSM-IV. In de afgelopen eeuwen was dit anders, er zijn talrijke historische gevalsbeschrijvingen van postpartum psychose. In de 19^e eeuw was iedere psychiater er van overtuigd dat postpartum psychose een apart ziektebeeld is.

Vrouwen met een bipolaire stoornis (manische depressiviteit) hebben een hoog risico op het krijgen van een postpartum psychose. De meeste patiënten die een postpartum psychose doormaken hebben echter een blanco psychiatrische voorgeschiedenis. Bij deze groep is de postpartum psychose soms de eerste manifestatie van een onderliggende bipolaire stoornis. In de literatuur wordt beschreven dat dit bij 40-80% van die vrouwen het geval is.

Vanwege de ernst van beeld is opname in het geval van postpartum psychose vrijwel altijd nodig. In Nederland zijn in het Erasmus MC te Rotterdam, het RPC Woerden en RGC Apeldoorn gespecialiseerde psychiatrische afdelingen waar moeders met psychiatrische problemen samen met hun kind tot de leeftijd van 6 maanden opgenomen kunnen worden. Zo snel mogelijk na opname dient algemeen lichamelijk onderzoek en bloedonderzoek gedaan te worden. Uitgesloten moet worden dat er geen sprake is van een psychose door een onderliggende somatische oorzaak, zoals schildklierlijden, elektrolyt- lever- en nierfunctiestoornissen, medicatie- of middelengebruik, immunologische afwijkingen, infecties of neurologische ziekten. Medicatie, structuur, optimalisering van de moeder-kind interactie en aandacht voor de partner en de familie van de patiënte, zijn belangrijke peilers van de behandeling. Verder adviseren we de schildklierfunctie en autoantistoffen tegen de

schildklier tijdens de postpartum psychose en 6 maanden na de bevalling te controleren. Er bestaan geen specifieke richtlijnen voor de medicamenteuze behandeling van postpartum psychose. Vanwege de relatie tussen postpartum psychose en bipolaire stoornis, kan de richtlijn voor de behandeling van acute manie aangehouden worden in de acute fase van een postpartum psychose. In het Erasmus MC Rotterdam starten wij eerst met slaapmedicatie (benzodiazepinen), vervolgens antipsychotica en na 2 weken voegen we lithium toe, als er onvoldoende respons is.

In de literatuur is niets bekend over de behandeling van postpartum depressie met psychotische kenmerken. Een depressie met psychotische kenmerken buiten de kraamtijd wordt volgens de richtlijnen behandeld met antidepressiva. Wij hebben echter de ervaring dat gebruik van antidepressiva in de postpartum periode bij sommige postpartum vrouwen kan leiden tot een verslechtering van het klinische beeld. Wij raden daarom gebruik van antidepressiva af bij patiënten met een postpartum depressie met psychotische kenmerken. We adviseren deze groep patiënten ook te behandelen met antipsychotica en/of lithium.

In **hoofdstuk 3** beschrijven we onze zoektocht naar risicofactoren voor het krijgen van een postpartum psychose. In het Erasmus MC hebben we het enige prospectieve cohort van patiënten met een eerste postpartum psychose in de wereld. We hebben 51 vrouwen onderzocht met een postpartum psychose, zonder manische of psychotische symptomen voorafgaand aan de postpartum periode. We hebben gekeken naar fenomenologische karakteristieken en medicatie respons. Verder hebben we obstetrische-, neonatale- en aan borstvoeding gerelateerde risicofactoren in deze groep vergeleken met een groot bevolkingscohort, namelijk het "generation R cohort".

Primipariteit (het krijgen van een eerste kind) bleek een belangrijke risicofactor voor het krijgen van postpartum psychose. We konden geen obstetrische-, neonatale- of aan borstvoeding gerelateerde risicofactoren vinden. We hebben verder gevonden dat klachten later beginnen bij vrouwen met een eerste postpartum psychose in vergelijking tot vrouwen met een bipolaire stoornis. Fenomenologisch valt op dat vrouwen met een postpartum psychose zonder voorgeschiedenis van manie of psychose vaak psychotische symptomen hebben die niet overeenkomen met de stemming (stemmingsincongruent). Alle vrouwen behalve één reageerden goed op onze medicamenteuze behandeling (benzodiazepine-antipsychotica-lithium). Vrouwen met depressieve symptomen hadden gemiddeld een langere ziekteduur vergeleken met vrouwen met manische kenmerken.

Hoofdstuk 4 behandelt het risico op terugval na een volgende zwangerschap. Vrouwen die eenmaal een postpartum psychose hebben gehad, lopen een groot risico op een nieuwe psychose na een volgende geboorte, net als vrouwen met bipolaire stoornis. Voor beide groepen is het risico op een nieuwe postpartum psychose tussen de 25 en 50%. Het was tot

nu toe onduidelijk wanneer men precies moest beginnen met medicatie om een psychose na de bevalling te voorkomen.

In dit onderzoek werden 70 vrouwen met een hoog risico op postpartum psychose behandeld in een speciaal programma om te voorkomen dat ze een postpartum psychose mee zouden maken. 29 vrouwen die een psychose hadden doorgemaakt na een bevalling (maar nooit een manie of psychose buiten de kraamtijd) bleven stabiel tijdens hun huidige zwangerschap, zonder medicatie. Vrouwen die meteen na de bevalling starten met lithium of antipsychotica kregen geen van allen een psychose na de bevalling. Vrouwen die geen preventieve medicatie gebruikten werden in 44% van de gevallen ziek.

In tegenstelling tot de vorige groep waren 41 vrouwen met een bipolaire stoornis helaas wel vaak instabiel tijdens de zwangerschap, met name de vrouwen die geen medicatie gebruikten. Na de bevalling kregen juist de bipolaire vrouwen die instabiel waren tijdens de zwangerschap vaker een postpartum psychose.

Deze bevindingen hebben geleid tot de volgende klinische adviezen: Vrouwen met een bipolaire stoornis kunnen het beste continue medicatie gebruiken, tijdens zwangerschap en in de postpartum periode om het risico op terugval zo laag mogelijk te houden. Het gebruik van deze medicatie dient echter te worden afgewogen tegen de risico's voor het ongeboren kind. Vrouwen met een postpartum psychose in de voorgeschiedenis (en geen psychose of manie op andere tijden) kunnen medicatie het beste onmiddellijk na de bevalling starten om terugval te voorkomen. Belangrijk is dat vrouwen met een postpartum psychose in de voorgeschiedenis geen medicatie tijdens de zwangerschap nodig hebben, het ongeboren kind wordt dus niet aan medicatie blootgesteld.

Klinische aanbevelingen
- Het is zinvol om in de diagnostiek onderscheid te maken tussen een eerste psychose of manie postpartum en een postpartum psychose in het kader van bipolaire stoornis.
- We stellen voor om patiënten met postpartum psychose te behandelen met achtereenvolgend benzodiazepines, antipsychotica en lithium.
- We adviseren bij patiënten met een psychotische depressie postpartum de richtlijnen te volgen voor de behandeling van bipolaire depressie. Pas op met gebruik van antidepressiva in deze groep, er kan een verslechtering van het beeld optreden.
- Controle van de schildklierfunctie is van groot belang. We stellen voor om TSH, f T4 en TPO abs tijdens opname en 6 maanden postpartum te bepalen.
- Een postpartum psychose preventieplan is noodzakelijk voor vrouwen met een hoog risico op postpartum psychose.
- Vrouwen met postpartum psychose of manie in de voorgeschiedenis maar geen episodes buiten de kraamtijd kunnen wachten met medicatie tot direct na de bevalling; zo word het ongeboren kind niet aan medicatie blootgesteld.

Deel II, pathofysiologisch perspectief

Hoofdstuk 5

Hoewel vele onderzoekers een neurobiologische oorzaak veronderstellen voor het acute ontstaan van psychose postpartum, is er slechts weinig onderzoek verricht met teleurstellende resultaten. Dit komt omdat postpartum psychose relatief zeldzaam is en vrouwen zó ziek zijn dat ze moeilijk te includeren zijn in onderzoek. De neurobiologie van postpartum depressie is veel vaker onderzocht. Dit is echter een heterogeen ziektebeeld. De klachten beginnen vaak al tijdens de zwangerschap en psychosociale factoren spelen een grote rol. Onderzoek op dit gebied heeft dan ook niet geleid tot de ontdekking van een uitlokkende factor die postpartum leidt tot psychiatrische ziekte.

Postpartum psychose is een fenotypisch goed gedefinieerd ziektebeeld. Een van de meest consistente bevindingen in het neurobiologisch onderzoek is de genetische kwetsbaarheid voor postpartum psychose bij vrouwen met een bipolaire stoornis. Verder is het onderzoek met name gericht op de hormonale veranderingen postpartum als mogelijke oorzaak. De geslachtshormonen (oestrogeen, progesteron en HCG) en de stress hormonen (ACTH en cortisol) dalen sterk na de bevalling, de "borstvoedingshormonen"(oxytocine en prolactine) stijgen juist. Helaas heeft geen enkel onderzoek een relatie kunnen aantonen tussen deze hormonale veranderingen en het ontstaan van postpartum psychose.

Dit is voor ons de reden geweest om een alternatieve hypothese te onderzoeken zoals beschreven in **hoofdstuk 6.** Als een ziekte in de geneeskunde vaker voorkomt of vaker ontstaat specifiek in de periode rondom de bevalling, dan is er een associatie met verstoorde autoimmuniteit. Schildklierziekten, reumatische ziekten, multiple sclerose zijn enkele voorbeelden van ziekten waarvan symptomen vaak zichtbaar worden of verergeren in de kraamtijd. Zou het kunnen zijn dat postpartum psychose ook te maken heeft met een verstoorde (auto) immuniteit?

Tijdens de zwangerschap ontstaat een selectieve rem op het immuunsysteem omdat vrouwen anders hun kind afstoten. Na de bevalling slaat die afweer aanvankelijk door en ontstaat een soort overreactie. Bij sommige vrouwen, die daar gevoelig voor zijn, leidt dat tot het ontstaan van een auto-immuunziekte. Het lichaam maakt dan antistoffen aan tegen eigen cellen.

In **hoofdstuk 7** onderzochten we de schildklierfunctie van vrouwen met postpartum psychose en ontdekten we dat zij kort na de bevalling ruim drie keer vaker dan gezonde kraamvrouwen antistoffen in het bloed hebben tegen hun schildklier (19 % thyroperoxidase antistoffen vergeleken met 5 % bij een postpartum controle groep). Ruim twee derde van de kraamvrouwen met een verhoogde concentratie antistoffen ontwikkelde later

een schildklierafwijking. Mogelijk speelt het gebruik van lithium, wat schadelijk voor de schildklier is, hierbij ook een rol. Het tegelijk voorkomen van postpartum psychose en auto immuun schildklier ziekte is een aanwijzing voor een mogelijke gemeenschappelijke afwijking in de immuun cellen.

Een tweede, belangerijk argument voor het onderzoeken van een immunhypothese voor postpartum psychose is de uitkomst van recent onderzoek naar de bipolaire stoornis (manische depressiviteit). Zoals eerder genoemd is er een sterke correlatie tussen postpartum psychose en bipolaire stoornis: Vrouwen met een bipolaire stoornis hebben een heel hoog risico op een postpartum psychose na zwangerschap en vice versa blijkt postpartum psychose vaak het begin te zijn van een bipolaire stoornis.

Er zijn diverse studies die afwijkingen in het immuunsysteem beschrijven bij bipolaire patienten. Ontstekingsmoleculen (cytokinen) komen vaker voor in het bloed dan bij controle patienten en hetzelfde geldt voor verschillende soorten autoantistoffen. Verder zijn er afwijkingen gevonden in de aantallen T cellen. Immuun gerelateerde genen en de expressie van deze genen in witte bloed cellen blijken bij sommige patienten af te wijken van gezonde controles.

In **hoofdstuk 8** zochten we naar immuunafwijkingen in het bloed van patienten met postpartum psychose. We vergeleken onze patienten met gezonde controles postpartum en niet postpartum. We hebben naar ontstekingsmediatoren in het bloed, aantallen T cellen en expressie van ontstekingsgerelateerde genen gekeken.

We hebben in dit onderzoek, net als bij eerdere onderzoeken immuun activatie gevonden in de normale postpartum periode. Bij vrouwen met een postpartum psychose was er sprake van een dysregulatie van het immuunsysteem postpartum. We vonden in de monocyten van vrouwen met postpartum psychose meer expressie van immuungerelateerde genen dan aanwezig is in de normale postpartum periode. Het aantal T cellen was lager.

Ons **toekomstig onderzoek** zal ook gericht zijn op de behandeling van postpartum psychose, de prognose en de preventie. We zullen het effect van onze behandeling van postpartum psychose evalueren 9 maanden na de bevalling. Na 4 jaar postpartum hopen we iets over de prognose te kunnen zeggen en voorspellers van terugval/ziekte te kunnen identificeren. Tenslotte zijn we van plan om in meerdere ziekenhuizen de uitkomsten van postpartum psychose preventie plannen te evalueren. We zijn benieuwd of antipsychotica net zo goed werken als lithium voor preventie van postpartum psychose. Verder verzamelen we gegevens over lithium en antipsychotica gebruik bij bipolaire zwangeren wat ons in staat stelt het effect van de medicatie op moeder en kind te onderzoeken.

We hopen in toekomstig onderzoek beter te kunnen voorspellen welke vrouwen een

eenmalige postpartum psychose doormaken en welke vrouwen meerdere manische, psychotische of depressieve episodes gaan doormaken. Bij deze laatste groep is de postpartum psychose, achteraf gezien het begin geweest van een bipolaire stoornis.

We zullen daarom niet alleen naar klinische karakteristieken zoeken die beloop voorspellen maar ook naar verschillende merkers in het bloed. We zullen ook genetisch onderzoek doen omdat we denken dat immunologische of hormonale mechanisme alleen tot ziekte leidt bij vrouwen die daar genetisch gevoelig voor zijn. Genetisch onderzoek is alleen zinvol bij grote groepen patienten (of bij families). Dit genetisch onderzoek zullen we dan ook in samenwerking doen anderen. Uiteindelijk hopen we dat dit type onderzoek leidt tot een manier om de start van bipolaire stoornis in de kraamtijd te voorkomen, dan wel het ziektebeloop gunstig te beinvloeden.

Dankwoord

Het krijgen van een kind, zeker voor de eerste keer, is een ingrijpende gebeurtenis. Vrouwen die in deze tumulteuze periode ook nog eens ernstig psychiatrisch ziek worden hebben wel wat anders aan hun hoofd dan meedoen aan onderzoek. Daarom vind ik het heel bijzonder dat er zoveel vrouwen hebben meegedaan aan het onderzoek en wil ik jullie als eerste bedanken.

Mijn promotoren wil ik graag bedanken. Hemmo Drexhage, het vernieuwende onderzoek van jouw groep naar de immunologie van de bipolaire stoornis is de basis geweest van de "immuun hypothese van postpartum psychose". Je hebt me meteen opgenomen in je onderzoeksgroep en me later de verantwoordelijkheid gegeven voor het postpartum gedeelte van "Moodinflame". Jij hebt me veel geleerd over immunologie. Ik hoop de prettige samenwerking nog lang te continueren.

Michiel Hengeveld, je hebt me als jonge psychiater aangenomen en me de vrijheid gegeven om onderzoek op te zetten. Onze samenwerking was prima maar toch heb je het stokje overgegeven aan Steven, omdat je wilde investeren in het onderzoek op de lange termijn. Je bent gelukkig nog steeds erg betrokken en geïnteresseerd in het reilen en zeilen van onze afdeling en in de ontwikkelingen in de zwangerschapsgerelateerde psychiatrie.

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Curriculum Vitae

Curriculum Vitae

Veerle Bergink werd geboren op 14 juni 1973 te Oak Ridge, Tennessee, USA. Zij groeide op in Oss alwaar zij in 1991 haar Gymnasium diploma behaalde. Zij volgde de studie geneeskunde aan de Rijks Universiteit Groningen. Tijdens haar studie werkte ze voor Eurotransplant Leiden (cornea transplantaties) en was student assistent bij chirugie en anaesthesie, UMC Groningen. Na een onderzoeksstage kindergeneeskunde in Zuid-Afrika en co-schappen in Deventer, behaalde zij in 1998 haar artsexamen (cum laude). Ze werkte een jaar als arts-assistent neurologie in het Sint Lukas Andreas Ziekenhuis, Amsterdam om vervolgens weloverwogen voor psychiatrie te kiezen. In 1999 starte zij haar opleiding psychiatrie met een keuze jaar biologische psychiatrie (angststoornissen) in het UMC Utrecht. Na de basisopleiding te hebben afgerond deed zij haar stage sociale psychiatrie in 2004 bij Mentrum te Amsterdam. Sinds 2004 is zij als psychiater en staflid verbonden aan het Erasmus Medisch Centrum, Rotterdam. Vanaf 2005 werkt ze aan de door haar opgezette OPPER studie (Onderzoeksprogramma Postpartum Psychose Eramus MC Rotterdam). Ze is hoofdonderzoeker voor postpartum psychiatry binnen "moodinflame", een Europees consortium, lid van de internationale werkgroep fenotypering van postpartum depressie en actief lid van de WPA sectie Immunologie en Psychiatrie. Veerle woont samen met Matthijs Laban en hun 2 dochters, Marijn (9) en Fenna (7).

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