SEVERE MOOD DISORDERS DURING PREGNANCY AND THE POSTPARTUM PERIOD

Janneke Gilden

Severe Mood Disorders During Pregnancy and the Postpartum Period

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The studies described in this thesis were performed at the Department of Psychiatry, Erasmus Medical Center, Rotterdam, the Netherlands and the Department of Psychiatry, Utrecht Medical Center, Utrecht, the Netherlands.

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Chapter 1

Introduction

The postpartum period is considered a time of increased risk for the development of both first-onset and recurrent severe psychiatric mood disorders (1). This thesis focuses on the relationship between postpartum psychosis and bipolar disorder (2). Although both have been described since the time of Hippocrates, studies on postpartum psychosis are scarce and there is no consensus about its classification and nosology (3). This chapter will, therefore, provide a brief clinical overview of both bipolar disorder and postpartum psychosis, followed by the study populations and the aims and outline of this thesis.

BIPOLAR DISORDER

Bipolar disorder (BD), previously also known as manic-depressive illness, is a severe chronic mood disorder characterized by episodes of mania, hypomania, and alternating or intertwining episodes of depression (4). It affects more than 1% of the world's population irrespective of nationality, ethnic origin, or socioeconomic status (5). Although bipolar disorder is one of the most heritable psychiatric disorders, a multifactorial model in which gene and environment interact is currently thought to best fit this disorder (6). It is one of the main causes of disability among young people (5), leading to cognitive and functional impairment (7, 8) and raised mortality, particularly death by suicide (9). In view of its recurrent nature, optimum long-term management is a preventive strategy that combines pharmacological, psychological, and lifestyle approaches from the first episode (10), with lithium being one of the most effective treatments of both manic and depressive episodes (11). The puerperal period has been identified as a high-risk period for women with bipolar disorder. There is strong, clear, and consistent evidence of a specific relationship between bipolar episodes and childbirth (1). Wesseloo et al. performed a quantitative analysis to examine the risk of postpartum recurrence in women with a history of bipolar disorder, reporting an overall rate of 37% (12). Additionally, in women with bipolar disorder and previous perinatal episodes, this recurrence risk will significantly increase after every subsequent pregnancy (13).

POSTPARTUM PSYCHOSIS

Postpartum psychosis (PP) is is the most severe form of postpartum psychiatric illnesses. It most frequently occurs in primiparous women without a psychiatric history. The incidence of first-onset postpartum psychosis ranges from 0.24 to 0.6 women per 1000 births (14-16). Within the first four weeks postpartum, women have a 23 times increased risk of a first-onset of affective psychosis, such as mania or psychotic depression, compared to any other period during a woman's life (15). Women already diagnosed with bipolar

disorder have a higher risk of recurrence postpartum compared to women with other psychiatric conditions, especially when these patients stop taking medication during pregnancy (12, 17). In general, the initial symptoms of postpartum psychosis like insomnia and mood fluctuations, have a sudden onset within 2 weeks after delivery (17). These initial symptoms are then followed by psychotic symptoms that can be divided into three phenotypic clusters: the depressive profile, the manic profile and the atypical profile (18). Within these profiles, core symptoms differ; with depressive and anxiety symptoms being most prevalent in the depressive profile; manic symptoms and agitation being most prevalent in the manic profile and disturbances of consciousness and disorientation being exclusively present in the atypical profile. Postpartum psychosis is a psychiatric emergency that often leads to admission to a psychiatric ward, when possible a Mother and Baby Unit (MBU). No clear guidelines for the treatment of this disorder have been established. Often a combination of benzodiazepines, antipsychotics and lithium are prescribed. In severe cases, ECT might even be warranted (17). Fortunately, nearly all patients (98.4%) achieve complete remission, with a median episode duration of 40 days (19).

POSTPARTUM PSYCHOSIS AND ITS CLASSIFICATION

Postpartum psychosis is currently not recognized by diagnostic systems. Given that the majority of women with postpartum psychosis have prominent manic or mixed episode features (18), by the current DSM-V criteria these women should therefore be diagnosed with bipolar disorder at the time of their first-onset postpartum psychosis. Bipolar disorder is characterized by its recurrent mood episodes during the lifespan. For some women with first-onset postpartum psychosis, the index episode is indeed the incipient episode of a recurrent affective disorder (17). However, in contrast, for other women their vulnerability is entirely limited to the postpartum period, a pattern described as "isolated postpartum psychosis" (12, 17). This distinction is of profound clinical relevance, because it has important implications for pharmacological treatment and prognosis.

Unfortunately, the magnitude of the recurrence risk after first-onset postpartum psychosis is currently unknown, and there is limited information on the longitudinal disease course (20-26). An overestimation of recurrence risk might lead to unfounded concerns for health care providers, patients, and their families, resulting in excessive medication use, unnecessary prevention strategies, or altered family planning. Conversely, underestimation of recurrence risk might lead to insufficient attention from health care professionals and insufficient maintenance treatment, potentially leading to impaired quality of life and increased risk for hospitalization or suicide (27).

Moreover, when a large percentage of women have no manic or psychotic recurrent episodes, or only during a subsequent postpartum period, it appears inaccurate to assign a lifelong diagnosis of bipolar disorder at the time of a first-onset postpartum psychosis. Therefore, and also because these episodes might have a different etiology (17, 28, 29), a distinct diagnostic category of postpartum psychosis within the bipolar spectrum might be more appropriate. To improve our understanding of the definition and classification of postpartum psychosis, in this thesis we will provide an evidence-based overview about the longitudinal course of both disease courses, specifically during the postpartum period.

AIM OF THIS THESIS

Understanding the relationship between postpartum psychosis and bipolar disorder has implications for perinatal and long-term treatment. This thesis aims at investigating the association of a fundamental link between postpartum psychosis and bipolar disorder, to provide further evidence whether postpartum psychosis should be classified as a distinct diagnostic category within the bipolar spectrum.

STUDY POPULATIONS

Women included in studies described in this thesis originated from different clinical cohorts:

OPPER (Onderzoeksprogramma Peripartum Psychiatrie Erasmus MC Rotterdam): an ongoing prospective multicenter cohort study (2005-present), which focuses on the prevention, treatment, and neurobiology of peripartum mood disorders (18, 19). Women are eligible for this study if they (a) are between 18–45 years of age; (b) have a postpartum onset of psychosis, mania, or severe depression as assessed with the Structured Clinical Interview for DSM-IV Axis I disorders (SCID) (30); and (c) are admitted to the Mother and Baby Unit (MBU) of Erasmus MC in Rotterdam or St. Antonius Ziekenhuis in Utrecht. Exclusion criteria are: (a) prenatal onset of psychosis, mania or severe depression; (b) drug/alcohol dependence in the last 3 months; (c) intellectual disability (IQ < 80); (d) serious somatic illness; and (e) inability to read or write. The Medical Ethical Committee of the Erasmus Medical Center Rotterdam approved the study (MEC-2005226). Written informed consent is obtained from all participants.

Dutch Bipolar Cohort (DBC) study: DBC was part of a collaboration between the University of California in Los Angeles and the Dutch health care institutes University Medical Center Utrecht, GGZ Altrecht, GGZ inGeest, University Medical Center

Groningen, Delta, Dimence, Parnassia (PsyQ) and Reinier van Arkel. Participants in DBC were patients with bipolar disorder from the age of 18 years and older. The objective of the study was to investigate genetic and phenotypic information of participants (31). The study was approved by the accredited Dutch Medical Ethical Trial Committee (METC) and all participants gave written informed consent (31). Data collection took place between June 2011 and July 2015. A total of 1396 patients with bipolar disorder participated in the DBC study, of which 793 were women.

OUTLINE OF THIS THESIS

In **Part I** of this thesis, we focus on first-onset postpartum psychosis. In **chapter 2** we present a systematic review and meta-analysis. The aim of this study is to quantify the risk of recurrence in women with a history of first-onset postpartum psychosis. The objective of **chapter 3** is to assess recurrence risk in our OPPER cohort. In addition, we identify potential clinical markers of 'isolated postpartum psychosis' versus a vulnerability for postpartum psychosis as an expression of a subsequent affective disorder with non-postpartum episodes. In **chapter 4** we present the effect of first-onset postpartum psychosis on mother-to-infant bonding.

Part II of this thesis focuses on bipolar disorder during the peripartum period. The aim of **chapter 5** is to provide an overview of recurrence risk during pregnancy and after childbirth, miscarriage and induced abortion in women with bipolar I disorder. In addition, we explore the preventive effect of lithium use during pregnancy and postpartum. In **chapter 6** we describe the association between lithium use during pregnancy and the risk of miscarriage in women with bipolar I disorder.

In **Part III** we tried to unravel the neurobiology of severe postpartum mood disorders. In **chapter 7** we describe the role of T-cell activity in the pathophysiology of postpartum depression.

In **chapter 8** we present the main conclusions of this thesis and summarize the current evidence regarding the relationship between first-onset postpartum psychosis and bipolar disorder. Finally, we provide directions for future research.

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Part I

First-onset postpartum psychosis

Chapter 2

Long-term outcomes of postpartum psychosis: a systematic review and meta-analysis

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ABSTRACT

Objective: There is limited information on the longitudinal disease course after first-onset postpartum psychosis (PP). Some women will experience severe affective episodes outside the postpartum period, while for other women their vulnerability to mania and psychosis may be restricted to the postpartum period. This meta-analysis estimates the risk of recurrence after first-onset PP.

Data sources: A computerized literature search was conducted using Embase, MEDLINE, Web of Science, PsycINFO, Cochrane Central, PubMed, and Google Scholar (first 100 hits) combining key terms regarding longitudinal studies of first-onset PP from inception through May 9, 2019. Two levels of screening were used on 2,807 citations.

Study selection: A total of 6 English-language articles including patients with a first-onset PP within 1 year after childbirth and a minimum follow-up period of 18 months or more after the index episode were included in the quantitative analysis.

Data extraction: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines were used for data extraction, and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used to independently assess the quality of the included studies. The primary outcome was recurrence, defined as any subsequent psychiatric episode after first-onset PP.

Results: Six studies and 645 patients could be included in the quantitative analyses; follow-up periods were 11–26 years. Of these patients, 279 did not experience subsequent severe episodes outside the postpartum period. Meta-analysis using random-effect estimation resulted in a weighted estimate of 43.5% (95% CI, 37.7% to 49.4%).

Conclusions: In this meta-analysis, more than 40% of women were classified as having "isolated postpartum psychosis," which could be considered a distinct diagnostic category with a more favorable prognosis. The remaining women had severe non-puerperal psychiatric episodes during longitudinal follow-up.

INTRODUCTION

Postpartum psychosis (PP) is an umbrella term for postpartum mania, psychosis, psychotic depression, or a mixed state that refers to an acute, severe, mainly affective episode shortly after childbirth (1-3). The incidence of first-onset PP from population-based register studies of psychiatric admissions varies from 0.3 to 0.6 per 1,000 births (4). Multiple studies (1, 5, 6) examining naturalistic cohorts of women with postpartum psychosis have documented the typical time of symptom onset as between 3 and 10 days after birth. The cardinal symptomatology is affective, and psychotic symptoms occur almost exclusively during periods of affective instability (7). Given the high relative risk for suicide and infanticide, early recognition and adequate treatment are of great importance (1, 8). In many countries, inpatient mother-baby joint admission units are the preferred treatment settings due to associations with improved patient satisfaction and reduced time to recovery (9-11). In the absence of a mother-baby unit, care is delivered in standard mental health treatment settings. With an adequate treatment regimen, nearly all women with PP achieve full remission, (12) and the majority of patients achieve good functional recovery (13). However, after remission, women with a first-onset PP are known to be at high risk of subsequent postpartum and non-postpartum psychiatric episodes. For some women, first-onset PP is the incipient episode of a life-long affective disorder, mainly within the bipolar spectrum (4). In contrast, other women will not be at risk of subsequent severe psychiatric episodes outside the postpartum period, and their vulnerability is entirely limited to the postpartum period, a pattern described as "isolated postpartum psychosis" (4, 14). Unfortunately, the magnitude of this risk is currently unknown, and there is limited information on the longitudinal disease course after first-onset PP, (2, 15-20) nor is much information available on prognostic markers for the disease course. An evidence-based overview of the occurrence of subsequent episodes after first-onset PP is therefore important, particularly with regard to risk-benefit analyses of maintenance pharmacotherapy. An overestimation of recurrence risk might lead to unfounded concerns for health care providers, patients, and their families, resulting in excessive medication use, unnecessary prevention strategies, or altered family planning. Conversely, underestimation of recurrence risk might lead to insufficient attention from health care professionals and insufficient maintenance treatment, potentially leading to impaired quality of life and increased risk for hospitalization or suicide. Therefore, we performed a systematic review and meta-analysis to improve the knowledge of the longitudinal course of women with first-onset PP. Our primary outcome was defined as recurrence of a psychiatric episode.

We categorically specified the window of recurrence as either during the postpartum period or outside the postpartum period. Additionally, we collected data on subsequent pregnancies, functional recovery, and suicide.

METHOD

Literature search

The computerized literature search was conducted from inception of database until May 9, 2019, in all large public medical electronic databases using search terms regarding first-onset postpartum psychosis. To identify as many relevant studies as possible, we used an exploratory search strategy and did not predefine the nature of the outcome. The full search strategies for all databases used are available in Supplementary Appendix 1. Details of the protocol for this systematic review were registered on PROSPERO (CRD42017057387).

Study selection

Studies were eligible for inclusion in the qualitative and quantitative analysis when (1) they had a longitudinal study design (cohort studies, randomized controlled trials, and birth register studies), (2) patients had a first-onset psychotic or manic episode within 1 year after childbirth (according to Diagnostic and Statistical Manual of Mental Disorders [DSM] criteria, International Classification of Diseases [ICD] criteria, or the Research Diagnostic Criteria [RDC]), (3) the follow-up period was 18 months or more after the index episode, and (4) the whole article was written in the English language.

Publications were included if the study population consisted of patients diagnosed with first-onset PP (postpartum mania, psychosis, psychotic depression, or a mixed state). First onset was defined as the absence of psychiatric hospitalization or absence of prior psychiatric symptoms prior to the index episode. Mixed patient samples were included when more than 75% of the patients in the sample met our criteria or when outcomes were reported separately for patients with first-onset PP.

Articles published after March 1986 used DSM, ICD, or RDC criteria and were considered eligible. Studies reporting either incidence or prevalence rates of recurrence were considered eligible for inclusion. Recurrence was defined as any subsequent psychiatric episode after first-onset PP, assessed using criteria of the DSM/ICD/RDC or a clinical interview and/or psychiatric hospitalization.

We divided recurrence into 3 categories: (a) at least 1 subsequent postpartum episode but no episodes outside the postpartum period, (b) at least 1 subsequent episode outside the postpartum period, and (c) no subsequent episode of mania, psychosis, or severe depression (sustained remission).

The EndNote X7 software package (Clarivate Analytics [formerly Thomson Reuter]; Philadelphia, Pennsylvania; 2013) was used for record management. Duplicate records and records without abstracts were removed. All remaining records were screened on the basis of title and abstract for eligibility. Next, full texts were screened. Screening was done by two researchers (J.G. and A.M.K.) independently. Disagreement between the two independent researchers was solved with the help from a third independent researcher (V.B.). Study selection was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (21) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) (22) guidelines.

Data extraction

Using a data extraction form, data were extracted by two researchers independently (J.G. and A.M.K.) who were not blind to authors, institutions, or journals. Differences in extracted data were discussed by all researchers (J.G., A.M.K., and V.B.). Patients experiencing recurrence events, including mania, psychosis, psychotic depression, a mixed state, and/or psychiatric hospitalization, were counted as the numerator. As the denominator, we used the total number of patients for whom information was available at the time of follow-up regarding our primary outcome.

Additionally, we extracted data on number of subsequent pregnancies, functional recovery, and suicide during the follow-up period as well as data on clinical and demographic predictors of recurrence, including primiparity, psychiatric family history, moment of illness onset, length and phenomenology of index admission, and medication at follow-up.

Quality assessment

The reviewers independently used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (23) to assess the quality of the included studies. The full quality assessment for all included articles is available in Supplementary Table 1. Potential bias of these quality criteria was assessed (24).

Procedure for meta-analyses

Primary outcomes were subjected to meta-analysis. To calculate the overall long-term risk of recurrence, we used fixed- and random-effects estimation. We reported the pooled estimate and 95% CI. A Q test was used to examine whether heterogeneity over the pooled studies was greater than would have been expected by chance. If there is substantial heterogeneity, random-effects analysis produces a more reliable estimate than fixed-effects analysis does. Additionally, associations between outcome and (potential) predictor variables were explored. In case of categorical predictor variables, fixed-effects estimation was used to compare differences across categories. In case of continuous predictor variables, random-effects meta-regression analysis was performed. Cochrane Q, I^2 statistics, and significance levels are reported. Statistical analyses were performed using the metaprop and metan package in Stata 15 (StataCorp LLC; College Station, Texas). Metaprop is specifically suited to handle the underlying binomial distribution of the outcome (25).

Publication bias

Publication bias was assessed visually with a funnel plot depicting the risk estimates (on the log scale) against their standard error. Publication bias was also formally assessed by the regression-based test of Egger et al. (26). Both assessments were used to consider if recurrence risk decreased with increasing sample size. When publication bias is low or absent, plots with a funnel shape are considered to occur. Studies in the bottom left-hand corner are often omitted, since nonsignificant studies are less likely to be published (27).

Heterogeneity and sensitivity analyses

Heterogeneity of the recurrence risk between the studies was assessed using both the χ^2 test and the I^2 statistic (28). We considered an I^2 value greater than 40% indicative of substantial heterogeneity. We conducted sensitivity analyses on the robustness of our results on the basis of study quality, design characteristics, and other relevant covariates as set forward in the preceding paragraphs.

RESULTS

Study selection

The literature search produced 5,050 articles, a total that was narrowed to 2,807 articles, after deduplication. Two independent raters (A.M.K. and J.G.) screened the titles and abstracts of these articles for eligibility, resulting in an initial selection of 64 articles. After review of the full-text articles, 7 articles were included in this systematic review (2, 15-20). There was no overlap in the included cohorts. Publication dates of the articles included in the qualitative synthesis were between 1992 and 2014. The PRISMA flowchart of the selection process for this quantitative analysis is shown in Figure 1. Interrater reliability was high (raw interrater agreement: 98%; $\kappa = 0.90$; 95% CI, 0.80 to 0.99).

Study characteristics

Detailed characteristics and results of the studies included in the qualitative and quantitative analyses are summarized in Table 1. In the 7 studies included in the qualitative analyses, the longitudinal disease course (mean follow-up = 16 years; range, 11–26 years) of 1,018 patients was described.

FIGURE 1. PRISMA Flowchart of the article selection process in a meta-analysis of risk of recurrence after first onset of postpartum psychosis

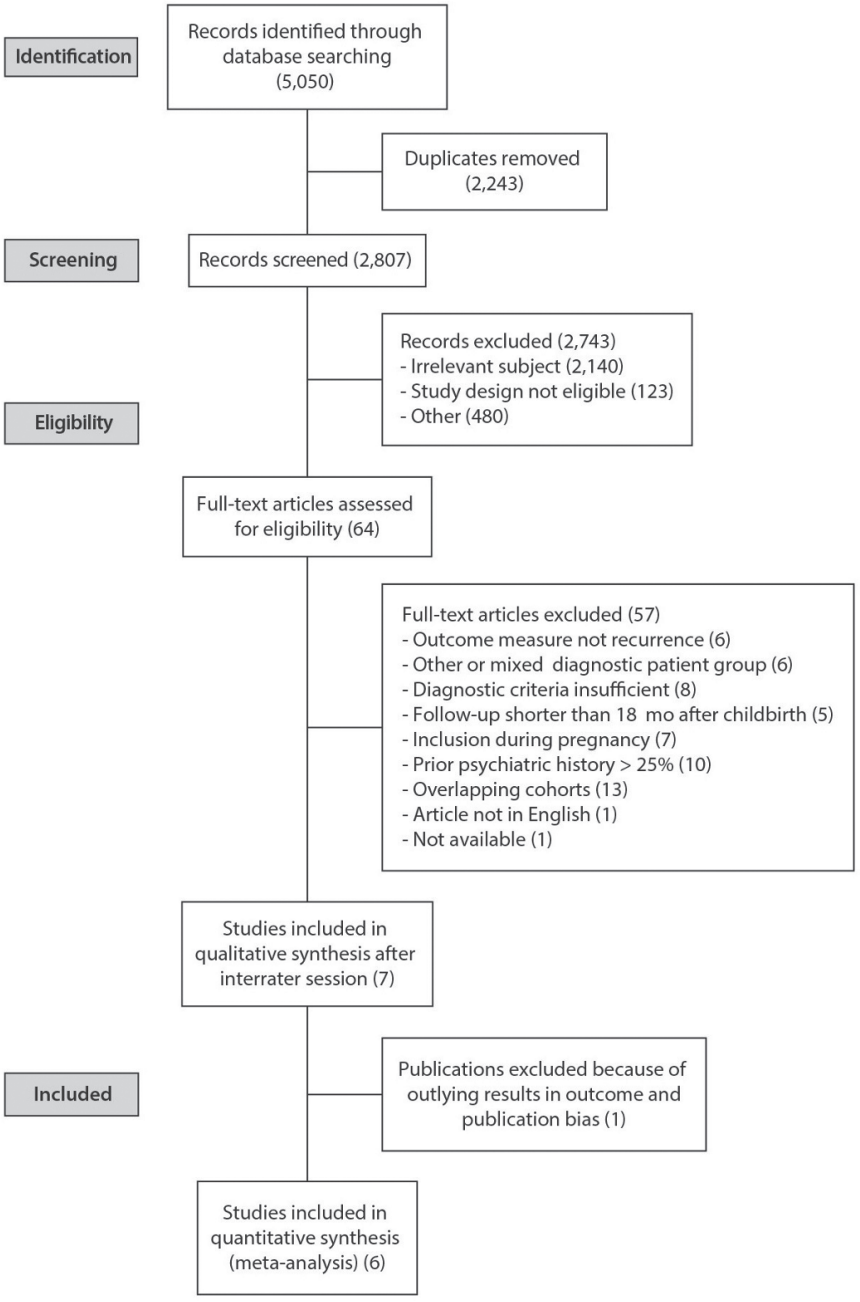


TABLE 1. Overview of characteristics of studies included in the qualitative synthesis

Study	Cohort/ Location	Study design	Time frame	Homogeneity of patient sample	Patients included with first-onset postpartum psychosis	Patients included in qualitative and quantitative analysis [a]	Moment of illness onset	Sustained remission (no recurrence), % (n/Total n)	≥ 1 Subsequent episode limited to the postpartum period, % (n/Total n)
Benvenuti et al. (1992)[15]	Florence, Italy	Retrospective cohort	1973-1987	100% first-onset	30	30	< 8 wk	37% (11/30)	13% (4/30)
Kapfhammer et al. (2014)[2]	Munich, Germany	Retrospective cohort	1975- 1995	61% first-onset, 39% with prior psychotic episode	60	55	< 4 wk	44% (24/55)	13% (7/55)
Kirpinar et al. (1999)[16]	Erzurum, Turkey	Retrospective cohort	1973-1994	100% first-onset	64	64	< 3 mo	19% (12/64)	39% (25/64)
Rohde and Marneros (1993)[17]	Cologne and Bonn, Germany	Prospective cohort	1950-1979	100% first-onset	86	61	< 6 wk	36% (22/61)	5% (3/61)
Schöpf and Rust (1994)[18]	Lausanne and Zurich, Switzerland	Retrospective cohort	1949-1990	87% first-onset, 13% with prior psychotic symptoms not leading to hospitalization	119	104	< 3 mo	31% (32/104)	3% (3/104)
Terp et al. (1999)[19]	Birth register (Denmark)	Birth register	NA	100% first-onset	609	345	< 91 d	36% (124/345)	8% (27/345)
Videbech and Gouliaev (1995)[20]	Birth register (Denmark)	Birth register	NA	100% first-onset	50	50	< 12 mo	40% (20/50)	4% (2/50)

TABLE 1. Overview of characteristics of studies included in the qualitative synthesis (continued)

Study	≥ 1 Subsequent episode outside the postpartum period, % (n/Total n)	Subsequent pregnancy, % (n/Total n)	Recurrence rate after subsequent pregnancy, % (n/Total n)	Functional recovery, % (n/Total n)[b]	Suicide
Benvenuti et al. (1992)[15]	50% (15/30)	23% (7/30)	57% (4/7)	NA	NA
Kapfhammer et al. (2014)[2]	44% (24/55)	38% (23/60)	52% (12/23)	67% (37/55)	8% (5/60)
Kirpinar et al. (1999)[16]	42% (27/64)	NA	NA	NA	NA
Rohde and Marneros (1993)[17]	59% (36/61)	36% (31/86)	26% (8/31)	NA	NA
Schöpf and Rust (1994)[18]	66% (69/104)	35% (42/119)	40% (17/42)	NA	11% (13/119)
Terp et al. (1999)[19]	56% (194/345)	36% (217/609)	22% (47/217)	NA	NA
Videbech and Gouliaev (1995)[20]	56% (28/50)	32% (16/50)	25% (4/16)	66% (31/47)	4% (2/50)

[a] Number is based on patients for whom information regarding the current study's primary outcome was available at time of follow-up.

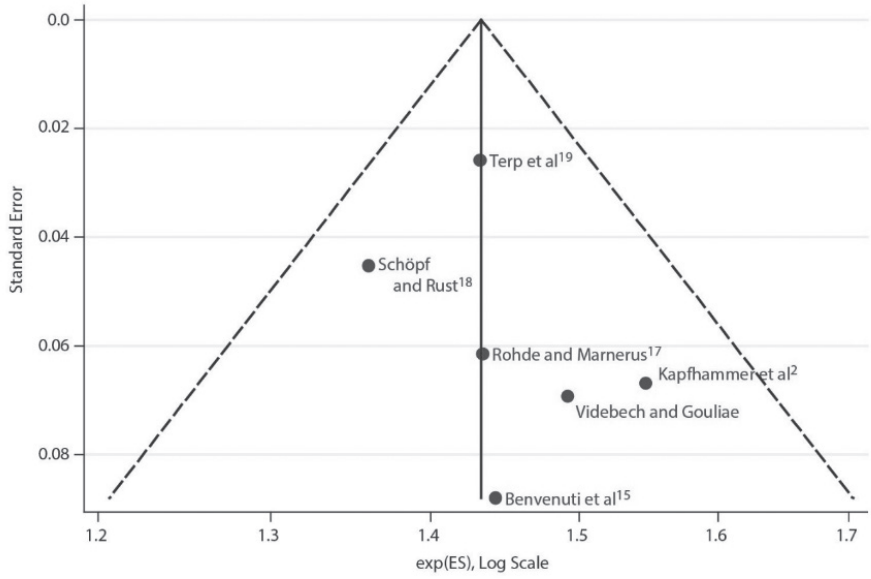
[b] Number is based on patients alive and for whom information was available at time of follow-up.

Abbreviations: NA = not available.

Quantitative analysis

Supplementary Figure 1 shows a forest plot of the outcomes of the 7 studies included in this review (2, 15-20). Supplementary Figure 2 shows the accompanying funnel plot. Kirpinar et al. (16) reported outlying results, both in terms of outcomes and based on the funnel plot (Supplementary Figure 2), resulting in high levels of heterogeneity. Specifically, the sample of Kirpinar et al. included 27 cases (42% of the total sample) with a final diagnosis of schizophrenia, which is known to be rare for first-onset affective psychosis. After removal of the study by Kirpinar et al., the funnel plot was symmetrical (Figure 2). We therefore present results from this meta-analysis both with and without the study by Kirpinar et al. (16). The remaining 6 studies involved a total of 954 patients, of whom 645 patients could be included in our longitudinal analysis.

FIGURE 2. Funnel plot with pseudo-95% confidence limits for studies included in meta-analysis (k=6)



Abbreviation: exp(ES) = the exponential of the effect size (effect size used for this analysis is sustained remission).

Recurrence risk

As shown in Figure 3, 412 of 645 women with first-onset PP experienced a recurrence during the follow-up period (64.0%; 95% CI, 60.3 to 67.7, according to both fixed- and random-effects estimation) in absence of heterogeneity (I^2 = 0%, P = .70). Of these, 46 of 645 women experienced subsequent episodes exclusively limited to the postpartum period. Meta-analysis using random-effects estimation resulted in a weighted estimate of 6.1% (95% CI, 3.3% to 8.9%) with substantial heterogeneity (I^2 = 47%, P = .10). More than half of the women (366/645) experienced ≥ 1 subsequent episode outside the postpartum period (weighted estimate: 56.5%; 95% CI, 50.6 to 62.3, using random-effects estimation). Women with subsequent episodes both inside and outside the postpartum period were also included in this category. Heterogeneity was substantial (I^2 = 44%, P = .10). The remaining 233 women did not experience a subsequent severe episode during the follow-up period. Meta-analysis using fixed- and random-effects estimation resulted in identical results (36.0%, 95% CI, 32.3% to 39.7%) in the absence of heterogeneity (I^2 = 0%, P = .70) (see Figure 4). Thus, these articles showed that 279 of 645 women with first-onset PP did not experience subsequent episodes outside the postpartum period. Meta-analysis using random-effects estimation resulted in a weighted estimate of 43.5% (95% CI, 37.7% to 49.4%) in presence of substantial heterogeneity (I^2 = 44%, P = .12) (due to substantial heterogeneity in a subset of the analysis, the weighted estimates do not necessarily add up).

Additional outcomes

Subsequent pregnancies and postpartum recurrence: For all studies, information on subsequent pregnancies was available (2, 15, 17-20). In these studies, 954 women were included, of whom 336 (35%) had a subsequent pregnancy. Of these 336 women with a subsequent pregnancy, 92 (27%) experienced a subsequent postpartum episode.

Functional recovery: Kapfhammer et al. (2) and Videbech and Gouliaev (20) provided information about functioning at follow-up. In the study by Kapfhammer et al. (2), functioning was measured with the Disability (DAS-M) (29) and 67% of women had no disturbance in psychosocial functioning after a mean of 12 years after the index episode. In the study by Videbech and Gouliaev (20), functioning was measured as working capacity during the follow-up assessment. In that study, 66% of women with first-onset PP regained full working capacity after a median of 11 years after the index episode. Both studies (2, 20) found an association between impaired functioning and psychiatric episodes during follow-up.

FIGURE 3. Disease course after first-onset postpartum psychosis (absolute numbers)

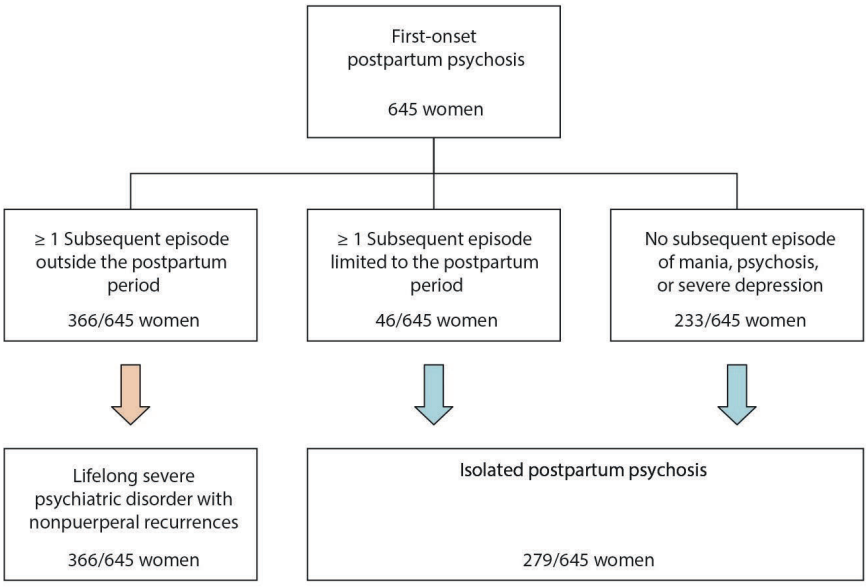
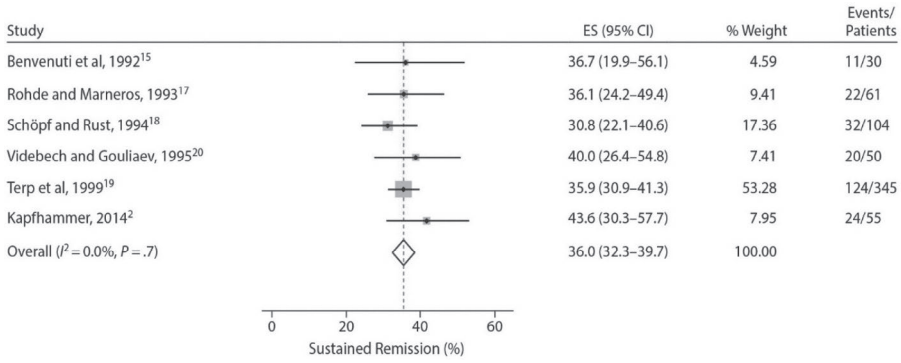


FIGURE 4. Sustained remission in women with first-onset postpartum psychosis



Abbreviation: ES=effect size (effect size used for this analysis is sustained remission).

Suicide: Four studies (2, 17, 18, 20) provided information about suicide. The study by Rohde and Marneros (17) was excluded from this analysis because they described suicide risk in a heterogeneous sample including women with a previous history of severe psychiatric illness and therefore the specific suicide risk for women with first-onset PP could not be determined. The remaining 3 studies reported 20 suicides in 229 patients.

Kapfhammer et al. (2) described suicide in 5 women (5/60), all within just a few weeks after discharge from the psychiatric hospital. As far as could be reconstructed from reports of the family, these women were in a state of depression at the time of their suicide. Similarly, Schöpf and Rust (18) described that 12 of the 13 suicides (13/119) within their study cohort occurred "during an episode of illness." They did not provide information on the type of episode. Videbech and Gouliaev (20) did not provide additional information of the 2 women (2/50) who committed suicide, although they reported a clinical picture of depression during the index episode for both patients. Additionally, the available data from these 4 studies were insufficient to allow for a distinction in relative suicide risk between women with isolated postpartum psychosis and those with recurrences outside the postpartum period.

Only Kapfhammer et al. (2) mentioned infanticide in their study sample. Three patients committed an extended suicide attempt that resulted in 2 infanticides. They described this infanticide risk in a heterogeneous sample including women with a previous history of severe psychiatric illness and therefore the specific infanticide risk for women with first-onset PP could not be determined.

Predictors

We analyzed the impact of parity and very early onset of symptoms (within the first week postpartum), but neither seemed to have an effect on subsequent episodes during follow-up (β = 0.25; 95% CI, −0.40 to 0.90; P = .35 and β = −0.06; 95% CI, −0.79 to 0.68; P = .78, respectively). Owing to insufficient data, we were not able to calculate the impact of other potential predictors, such as length and phenomenology of index admission, psychiatric family history, life events, or medication use, on the longitudinal disease course.

Sensitivity analyses

To estimate the robustness of our findings, we performed a series of sensitivity analyses based on the design and characteristics of the studies: year of publication, country of study (Germany vs Denmark), study design (cohort vs register), outcome measure (prevalence vs incidence), length of follow-up, definition of inclusion (ICD-8 vs DSM), and definition of recurrence (clinical interview vs DSM vs hospitalization).

Although the proportion of sustained remission increased across the period of study inclusion, with highest proportions of patients in sustained remission in the most recent studies, the year of publication did not show a significant impact on recurrence risk (β

= .005; 95% CI, −0.005 to 0.014; P = .25). Further, we found no significant differences regarding the country where the study was conducted (Q1 = 0.36, P = .55), whether the data involved cohort studies or register-based studies (Q1 = 0.08, P = .77), whether studies reported incidence or prevalence rates (Q1 = 0.39, P = .53), or whether dropout was explicitly reported (Q1 = 1.20, P = .27). Also, no differences were found regarding the criteria used for inclusion (ICD-8 vs DSM-II or DSM-IV) (Q1 = 0.08, P = .77) or recurrence (DSM vs clinical interview vs hospitalization) (Q2 = 1.80, P = .41). Finally, there was no impact of the duration of longitudinal follow-up (β = −0.005; 95% CI, −0.017 to 0.007; P = .30). Together, although power was limited, these sensitivity analyses supported the overall validity of our findings.

Publication bias

A visual inspection of the funnel plot revealed that the study by Kirpinar et al. (16) was an outlier (Supplementary Figure 2). After the removal of this study, the funnel plot was symmetrical (Figure 2). The Egger test did not suggest the presence of a small study bias (intercept = 0.18; 95% CI, −3.94 to 4.29, P = .92 [including the study by Kirpinar et al. (16)] or intercept = 0.59; 95% CI, −1.59 to 2.76; P = .49 [excluding the study by Kirpinar et al. (16)]).

DISCUSSION

This systematic review and meta-analysis shows that 36.0% (95% CI, 32.3% to 39.7%) of the patients with first-onset PP (weighted estimate) had no recurrences. These patients had a single episode and remained in remission during longitudinal follow-up (mean follow-up of 16 years). An additional 6.1% (95% CI, 3.3% to 8.9%) of women with a first-onset PP had a recurrence after a subsequent pregnancy but not outside the perinatal period. Together, 43.5% (95% CI, 37.7% to 49.4%) of women had an "isolated postpartum psychosis": they had episodes of mania, psychosis, or severe psychotic depression limited to the postpartum period. The remaining women had at least 1 subsequent episode outside the postpartum period. For these women, delivery was the incipient episode of a psychiatric disorder with a more disabling disease course and broader window of recurrence vulnerability.

Currently, the DSM-V is widely used as a classification system for psychiatric disorders (30, 31). Within the DSM-V, postpartum psychosis (including psychotic, manic, psychotic depressed, or mixed episodes) is not a distinct disease category (31). Given

that the majority of women with PP have prominent manic or mixed episode features (31), by the current DSM-V criteria these women should therefore be diagnosed with bipolar disorder at the time of their first-onset postpartum psychosis. However, our findings raise doubt about the validity of this approach. It appears inaccurate to assign a diagnosis of bipolar disorder at the time of a first-onset postpartum psychosis, given the finding that 43.5% of women have no manic or psychotic recurrence outside the postpartum period. Therefore, and also because these episodes might have a different etiology (4, 32, 33), a distinct diagnostic category might be more appropriate. To distinguish between isolated postpartum psychosis and lifelong psychiatric disorders, information about time to recurrence after first-onset PP is needed. Unfortunately, the information in the included studies was not detailed enough to investigate this highly relevant clinical outcome. A recent meta-analysis (34) reported recurrence rates of 59% after 2 years in women with first-onset manic or mixed episodes outside the perinatal period, with most recurrences occurring within the first year. This finding might guide diagnostic decision-making as well as conclusions on length of maintenance treatment after first-onset PP.

Subsequent pregnancy and the risk of recurrence

In our study, only 35% of women had a subsequent pregnancy. Women might have been anxious about experiencing another postpartum episode. In addition, some health care providers might have advised against further pregnancies (35). More women might have had a relapse if they had another child, which would have lowered the number (n = 233) of women in sustained remission. In those women who had a subsequent pregnancy, 27% experienced a severe postpartum recurrence. This percentage is similar to that found in a previous meta-analysis (14), in which the risk of recurrence of a PP episode in women with a history of postpartum psychosis after a subsequent pregnancy was found to be 29%. Given the high risk specifically in the postpartum period, we previously recommended (4) that women develop an individualized postpartum prevention plan in collaboration with their health care providers for implementation during a subsequent pregnancy to agree on specific preventive strategies for the postpartum period. One of the most effective interventions thus far identified is the initiation of prophylactic pharmacotherapy, preferably with lithium on the day of delivery (36).

Suicide

In our systematic review, only 3 studies (2, 18, 20) reported suicide rates for women with first-onset PP, and in these studies the suicide rates were very high (4%–11%). In contrast, a recent Danish register study (37), designed to investigate mortality after postpartum episodes, reported death by suicide in 29 (0.01%) of 2,699 women with a first psychiatric contact within 3 months after giving birth. The mean follow-up time for the women in that cohort was 26.26 years. One explanation for the lower suicide rates in that study is the severity of the episode, because both women with inpatient contact and those with outpatient contact were included. Another explanation could be the timing; the Danish register study collected data at the end of the 20th and beginning of the 21st century (1970–2011). In contrast, the 3 studies mentioned in the present review included data from the 20th century (1949–1995). An older Danish register study (data collection between 1973 and 1993) (38) reported a suicide rate of 3.3%. That study followed 1,567 women after postpartum admission to a psychiatric hospital. Our findings highlight the need to be very alert to the increased risk of suicidality in women with postpartum psychosis, especially during acute episodes, in the period following hospital discharge, and when depressive symptoms are present (39, 40).

Limitations

This systematic review is the first to describe the longitudinal course after first-onset PP. Although only a few studies could be included, sensitivity analyses confirmed the homogeneity and validity of our findings.

A limitation of this study is that we could not investigate other important clinical outcomes such as minor episodes, roughening, or treatment response, because these were not always sufficiently described in the included studies. In addition, even though the mean follow-up in the included studies was 16 years, we cannot draw definitive conclusions about long-term outcomes or lifetime prognosis. Follow-up in these studies also was not long enough to comment on recurrence risk during menopause, which is generally considered a period of high risk for mood episodes. Overall, given the mean length of the follow-up, we consider the risk of underestimating recurrence to be limited, which is supported by our sensitivity analysis.

All included studies were executed in Western Europe, and therefore our results may not be applicable to other contexts. Moreover, all studies were performed in the 1970s and 1980s, which hampered the generalizability of our results. More recent studies

have shown a lower recurrence rate of psychiatric episodes, (41) possibly because of prevention programs and prophylactic pharmacotherapy. It could be that recurrence risk is lower today.

Finally, it is not possible to study a true recurrence risk in a naturalistic setting, since many of the women included in these follow-up studies might have received targeted treatment to prevent recurrence.

CONCLUSIONS

This review describes the longitudinal course after first-onset PP and therefore provides novel prognostic insight. For a majority of women, postpartum psychosis was the incipient episode of a psychiatric disorder with subsequent severe non-postpartum recurrence. For the remaining sizeable proportion of women, their risk of recurrence appears limited to the period following delivery. Accordingly, a distinct diagnostic category might be more appropriate for this group (42). We found a high suicide risk, particularly after hospital discharge. This finding is alarming, given that PP is a condition with a generally optimistic prognosis following remission of the initial acute episode.

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SUPPLEMENTARY APPENDIX 1

A systematic electronic literature search was performed by a medical information specialist on longitudinal studies of postpartum psychosis. The following public medical electronic databases were systematically searched: Embase (via embase.com), Medline (via Ovid), Web-of-Science, PsycINFO (via OvidSP), Cochrane Central (via Wiley), PubMed, and Google Scholar (first 100 hits). Additionally, reference lists of key papers and review articles were screened for missing publications. The search was conducted from inception of database until May 9, 2019. Our search strategy combined terms regarding first-onset postpartum psychosis. To identify as many relevant studies as possible, we used an exploratory search strategy and did not predefine the nature of the outcome. The full search strategies for all databases used are available in this supplement. Details of the protocol for this systematic review were registered on PROSPERO (CRD42017057387).

Embase.com 2074

('puerperal psychosis'/de OR (('puerperium'/de OR 'puerperal disorder'/de OR childbirth/de OR 'puerperal depression'/de OR delivery/exp) AND 'psychosis'/exp) OR (((puerper* OR postpart* OR post-part* OR after-pregnan* OR childbirth* OR child-birth* OR new-mother* OR labor OR labour OR Caesarean OR delivery OR deliveries OR postnatal* OR post-natal* OR Parturition*) NEAR/6 (psychosis* OR psychotic* OR psychoses* OR bipolar* OR mania*))):ab,ti) AND [english]/lim NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim)

Medline Ovid 163

(((“Postpartum Period”/ OR “Puerperal Disorders”/ OR Parturition/ OR “Depression, Postpartum”/ OR exp “Delivery, Obstetric”/) AND “Psychotic Disorders”/) OR (((puerper* OR postpart* OR post-part* OR after-pregnan* OR childbirth* OR child-birth* OR new-mother* OR labor OR labour OR Caesarean OR delivery OR deliveries OR postnatal* OR post-natal* OR Parturition*) ADJ6 (psychosis* OR psychotic* OR psychoses* OR bipolar* OR mania*))).ab,ti.) AND english.la. NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt.

PsycINFO Ovid 134

("Postpartum Psychosis"/ OR (("Postpartum Depression"/ OR exp "Labor (Childbirth)"/) AND " Psychosis "/) OR (((puerper* OR postpart* OR post-part* OR after-pregnan* OR childbirth* OR child-birth* OR new-mother* OR labor OR labour OR Caesarean OR delivery OR deliveries OR postnatal* OR post-natal* OR Parturition*) ADJ6 (psychosis* OR psychotic* OR psychoses* OR bipolar* OR mania*))).ab,ti.) AND english.la. NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt.

Cochrane 18

((((puerper* OR postpart* OR post-part* OR after-pregnan* OR childbirth* OR child-birth* OR new-mother* OR labor OR labour OR Caesarean OR delivery OR deliveries OR postnatal* OR post-natal* OR Parturition*) NEAR/6 (psychosis* OR psychotic* OR psychoses* OR bipolar* OR mania*))):ab,ti)

Web of science 365

TS=(((((puerper* OR postpart* OR "post-part*" OR "after-pregnan*" OR childbirth* OR "child-birth*" OR "new-mother*" OR labor OR labour OR Caesarean OR delivery OR deliveries OR postnatal* OR "post-natal*" OR Parturition*) NEAR/5 (psychosis* OR psychotic* OR psychoses* OR bipolar* OR mania*))))) AND DT=(article)

Google scholar 53

First 100:
"puerperal|postpartum psychosis|psychotic|psychoses"
First 100:
"puerperal|postpartum psychosis|psychotic|psychoses" "first onset"

SUPPLEMENTARY TABLE 1. Quality assessment according to STROBE guidelines

Study	Study design	Homogeneity of patient sample	Definition of inclusion	Moment of onset of first-onset postpartum psychosis	Definition of recurrence	Follow-up range	Mean follow-up	Confounders reported	Missing data reported
Benvenuti et al. (1992)[1]	Retrospective cohort	100% first-onset	DSM III R	< 8 weeks pp	DSM III	4-18 years	13.4 years	None	Yes
Kapfhammer et al. (2014)[2]	Retrospective cohort	61% first-onset 39% former psychotic episode	DSM IV	< 4 weeks pp	DSM IV	7-24 years	12 years	None	Yes
Kirpinar et al. (1999)[3]	Retrospective cohort	100% first-onset	DSM IV	< 3 months pp	Clinical interview	2-23 years	11.2 years	None	Yes
Rohde and Marneros (1993)[4]	Prospective cohort	100% first-onset	DSM III, DSM III R	< 6 weeks pp	Clinical interview	12-41 years	25.6 years	None	Yes
Schöpf and Rust (1994)[5]	Retrospective cohort	87% first-onset 13% former psychotic symptoms not leading to hospitalization	DSM III R	< 3 months pp	Clinical interview	3-35 years	21.2 years	None	No
Terp et al. (1999)[6]	Birth register	100% first-onset	ICD 8	< 91 days pp	Hospitalization	10-20 years	15 years	None	No
Videbech and Gouliaev (1995)[7]	Birth register	100% first-onset	ICD 8	< 12 months pp	Hospitalization	7-14 years	11 years	Age Parity	Yes

Abbreviation: pp = postpartum.

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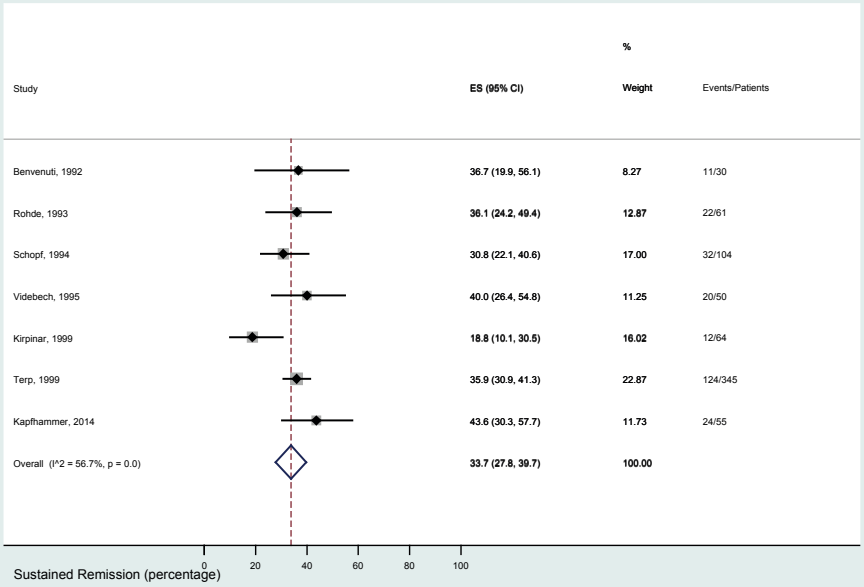
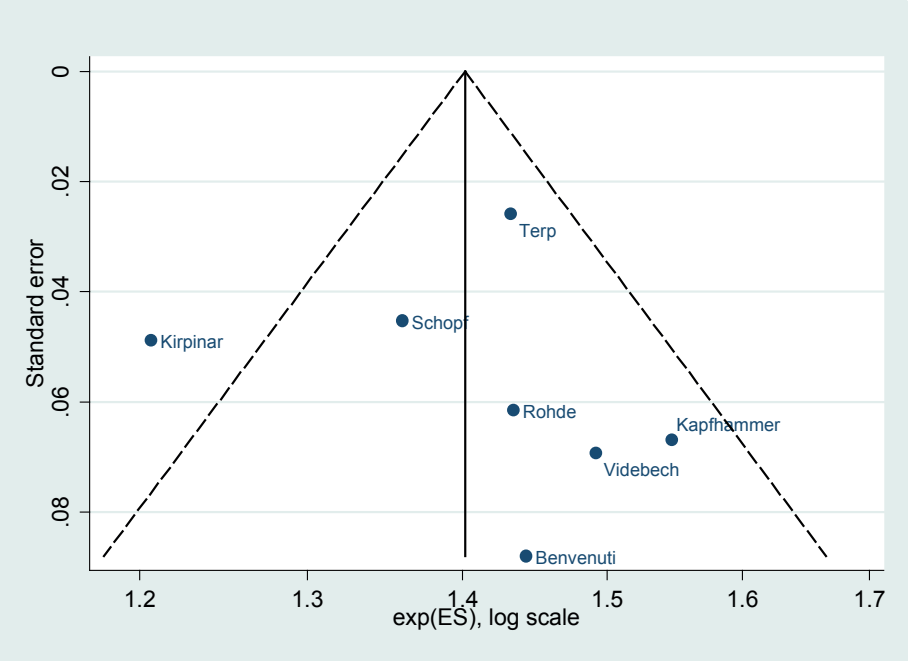
SUPPLEMENTARY FIGURE 1. Sustained remission in women with first-onset postpartum psychosis including Kirpinar



Abbreviation: ES = effect size. Effect size used for this analysis is sustained remission.

SUPPLEMENTARY FIGURE 2. Funnel plot with pseudo 95% confidence limits for studies included in the systematic review including Kirpinar (n=7)



Abbreviation: exp(ES) = the exponential of the effect size. Effect size used for this analysis is sustained remission.

Chapter 3

Long-term outcome of postpartum psychosis: a prospective clinical cohort study in 106 women

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ABSTRACT

Objective: We aimed to investigate the outcome of postpartum psychosis over a four-year follow-up, and to identify potential clinical markers of mood/psychotic episodes outside of the postpartum period.

Methods: One hundred and six women with a diagnosis of first-onset mania or psychosis during the postpartum period were included in this prospective longitudinal study. Women were categorized into either 1) recurrence of non-postpartum mood/psychotic episodes or 2) mania/psychosis limited to the postpartum period. We summarize the longitudinal course of the illness per group. We used a logistic regression model to identify clinical predictors of recurrence of mood/psychotic episodes outside of the postpartum period.

Results: Over two thirds of the women included in this study did not have major psychiatric episodes outside of the postpartum period during follow-up. The overall recurrence rate of mood/psychotic episodes outside the postpartum period was ~32%. Of these women, most transitioned to a bipolar disorder diagnosis. None of the women fulfilled diagnostic criteria for schizophrenia or schizophreniform disorder. No clinical markers significantly predicted recurrence outside of the postpartum period.

Conclusions: For the majority of women with first-onset postpartum psychosis, the risk of illness was limited to the period after childbirth. For the remaining women, postpartum psychosis was part of a mood/psychotic disorder with severe non-postpartum recurrence, mainly in the bipolar spectrum. No clinical predictors for risk of severe episodes outside the postpartum period emerged. Our findings add to previous evidence suggesting a fundamental link between postpartum psychosis and bipolar disorder, which may represent two distinct diagnoses within the same spectrum.

BACKGROUND

Postpartum psychosis is an umbrella term for postpartum mania, psychosis, psychotic depression and a mixed affective state, occurring shortly after childbirth (1-3). Postpartum psychosis is the most severe form of childbirth-related psychiatric disorders and has an incidence of ~ 0.3 to 0.6 per 1,000 births (1, 2, 4, 5). Women with postpartum psychosis may initially present with mood fluctuations, insomnia and obsessive concerns about the baby, followed by severe mood symptoms, and sometimes disorganized behavior, delusions and hallucinations (1, 6-9). The presence of severe mood symptoms differentiates postpartum psychosis from psychosis outside of the postpartum period (10). Postpartum psychosis is, therefore, a misnomer. Since psychotic symptoms in the postpartum period occur mostly within the setting of affective lability, the disorder is a bipolar-related mood disorder rather than a primary psychotic disorder (4, 5).

Due to the high relative risk for suicide and infanticide, early recognition and adequate treatment of postpartum psychosis is crucial (1, 11). With adequate treatment, nearly all women with postpartum psychosis achieve full remission (12), and a large proportion of patients achieve good functional recovery (13). For some women, postpartum psychosis is part of a severe, often life-long, psychiatric disorder (10, 14-16). For other women, the vulnerability is limited to the postpartum period (10, 17).

Despite the widespread use of the term 'postpartum psychosis', this diagnosis is not recognized in current classification systems, including the International Classification of Diseases, Tenth Revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (18). Instead, the majority of women with postpartum psychosis receive a DSM-V diagnosis of bipolar disorder, because they present with prominent manic or mixed affective episodes. Yet, according to our recent meta-analysis, 43.5% of women with postpartum psychosis have no manic or psychotic recurrence outside the postpartum period over a mean follow-up of 16 years (19), suggesting that a diagnosis of bipolar disorder might not always be warranted. It is important to note that most studies included in the meta-analysis were performed in the 1970s and 1980s, limiting the generalizability of the results. Further research is needed to reproduce these numbers in the current treatment setting. In addition, to improve long-term prognosis, it is pertinent to identify those women who may develop severe mood episodes outside the postpartum period.

Currently, little is known about which women are specifically at risk for recurrence outside the postpartum period. Previous studies identified being single/unmarried (20), a personal or family history of psychiatric disorders and older age (21) as potential risk factors for future recurrence after first onset postpartum psychosis (2, 22). However,

these studies were small and conducted retrospectively. Consequently, this prospective longitudinal study was designed to investigate recurrence in 106 women with postpartum psychosis over a four-year period. We further aimed to identify potential clinical markers of a psychiatric disorder with mood or psychotic episodes outside of the postpartum period.

METHODS

Study setting and procedure

The study was approved by the International Review Board of the Erasmus Medical Centre (Rotterdam, The Netherlands). All patients provided written informed consent. The study was performed on the Mother-Baby Unit (MBU), a five-bed inpatient unit that specializes in the care of patients with severe psychopathology in the postpartum period, located in the Department of Psychiatry in the Erasmus Medical Centre (Erasmus MC) in Rotterdam, The Netherlands. On the MBU, women are admitted with their babies, who stay in a fully staffed nursery adjoining the unit (1). Every patient admitted to the MBU between May 2005 and December 2016 was screened for study inclusion (n=315).

Participants

We included patients with a diagnosis of first-onset mania or psychosis during the postpartum period, who were aged between 18 and 45 years. 'Postpartum psychosis' was operationalized as any of the following DSM-IV diagnoses and requiring the specifier 'onset postpartum': manic episode, mixed episode, depressive disorder with psychotic features, psychotic disorder not otherwise specified (NOS) or brief psychotic disorder, as assessed with the SCID interview. Patients were excluded if they had a chronic psychotic disorder, mania or psychosis with onset during pregnancy or > 12 weeks postpartum, a history of psychosis or mania outside the postpartum period, or drug abuse.

A total of 315 women were admitted to the MBU between May 2005 and December 2016. One hundred thirty-seven of these patients received a diagnosis of postpartum psychosis. Of these, 14 women had a prior postpartum psychiatric episode but no episodes of mania or psychosis at other times. Of the 137 women, four patients declined participation. In addition, 21 women were excluded: 18 women were excluded because they had a history of mania or psychosis outside the postpartum period, one woman was excluded because of postpartum drug abuse, one woman was excluded because her symptom onset was > 12 weeks postpartum, one woman was excluded

because her symptoms started during pregnancy. Accordingly, 112 patients fulfilled the criteria for first-onset postpartum psychosis. Five patients were lost to follow-up (4.5%) and one patient (0.9%) was lost to suicide (baseline and clinical characteristics of these women can be found in Appendix A, Table A1). In this study, we therefore included 106 women admitted to the MBU between 2005 and 2016.

Symptomatology and clinical course of the initial episode

Patients were diagnosed by a clinician using the Structured Clinical Interview (SCID-1/P research version) (23). The SCID is a semi-structured interview guide for making diagnoses according to the diagnostic criteria published in the American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders (DSM). Previous hypomanic and manic episodes were also registered using the SCID. We further assessed demographics, psychiatric history, and family history of psychiatric illness (Table 1) (for more detail, see 12).

TABLE 1. Demographics and clinical characteristics of women with non-postpartum recurrence during follow-up and of women with no recurrence outside the postpartum period during follow-up (the table presents percentages and numbers of participants, unless stated)

	Non-postpartum recurrence (n=34)		**No recurrence outside the postpartum period (n=72)**		**p-value**
Baseline characteristics at time of initial episode					
Age in years	Mean=31.0	SD=4.8	Mean=31.9	SD=4.9	0.351
Country of origin (n)					0.018
Netherlands	79.4%	27	94.4%	68	
Other	20.6%	7	5.6%	4	
Marital status (n)					0.217
Married or in relationship	100.0%	34	91.6%	66	
Not in relationship	-	-	4.2%	3	
Missing	-	-	4.2%	3	
Education (n)					0.521
No education	3.0%	1	-	-	
Primary school	-	-	1.4%	1	
Secondary school	14.7%	5	9.7%	7	
Vocational training	29.4%	10	30.6%	22	
Higher education	52.9%	18	58.3%	42	
Parity (n)					0.343
1	79.4%	27	79.2%	57	
2	11.8%	4	16.7%	12	
≥ 3	8.8%	3	2.8%	2	
Missing	-	-	1.4%	1	

TABLE 1. Demographics and clinical characteristics of women with non-postpartum recurrence during follow-up and of women with no recurrence outside the postpartum period during follow-up (the table presents percentages and numbers of participants, unless stated) (continued)

	Non-postpartum recurrence (n=34)		No recurrence outside the postpartum period (n=72)		p-value
Psychiatric history before postpartum episode (n)					0.210
None	55.9%	19	76.4%	55	
Postpartum depression	8.8%	3	2.8%	2	
Postpartum psychosis/mania (not at other times)	8.8%	3	5.6%	4	
Depression	20.6%	7	9.7%	7	
Anxiety	5.9%	2	2.8%	2	
Hypomania	-	-	2.8%	2	
Family history of psychiatric disorders† (n)					
None	47.1%	16	34.7%	25	0.238
1st degree relative with depression or anxiety	41.2%	14	36.1%	26	0.616
1st degree relative with postpartum psychiatric episode	2.9%	1	13.9%	10	0.085
1st degree relative with bipolar disorder	8.8%	3	13.9%	10	0.444
Missing	2.9%	1	4.2%	3	0.745
Length of initial hospital admission in days	Mean=59.6	SD=25.6	Mean=57.3	SD=31.2	0.700
Phenomenology initial episode (n)					0.533
Manic with and without psychotic features	58.8%	20	61.1%	44	
Psychotic only	17.7%	6	12.5%	9	
Depressed-psychotic	5.8%	2	13.9%	10	
Manic-depressed (mixed)	17.7%	6	12.5%	9	
Relation between mood and psychotic symptoms (n)					
Presence of mood-incongruent psychotic symptoms	67.6%	23	62.5%	45	0.611
> 50% of time psychotic during initial episodes	52.9%	18	47.2%	34	0.596
First rank psychotic symptoms‡	8.8%	3	6.9%	5	0.730
DSM-IV diagnosis at baseline					
Bipolar I disorder	82.3%	28	77.8%	56	0.600
Bipolar II disorder	2.9%	1	1.4%	1	0.597
Major depressive disorder with psychotic features	2.9%	1	11.1%	8	0.159
Mood disorders NOS	8.8%	3	9.7%	7	0.883
Lithium treatment during admission (n)					0.617
No	20.6%	7	25.0%	18	
Yes	79.4%	27	75.0%	54	
Antipsychotics treatment during admission (n)					0.668
No	14.7%	5	18.1%	13	
Yes	85.3%	29	81.1%	59	
Follow-up					
Length of follow-up period in months	Mean=46.3	SD=20.3	Mean=44.5	SD=8.8	0.543
Subsequent pregnancies (n)					0.464
No	64.7%	22	58.3%	42	
Yes	32.3%	11	40.3%	29	
Missing	3.0%	1	1.4%	1	

TABLE 1. TABLE 1. Demographics and clinical characteristics of women with non-postpartum recurrence during follow-up and of women with no recurrence outside the postpartum period during follow-up (the table presents percentages and numbers of participants, unless stated) (continued)

	Non-postpartum recurrence (n=34)		No recurrence outside the postpartum period (n=72)		p-value
Recurrence period (n)					<0.001
Postpartum only	-	-	3.0%	2	
Non-postpartum only	90.9%	30	-	-	
Postpartum and non-postpartum	9.1%	3	-	-	
Recurrence phenomenology (n)					<0.001
No recurrence	-	-	97.2%	70	
Hypo(mania)	42.4%	13	-	-	
Depression/Anxiety	33.3%	11	2.8*%	2*	
Psychotic episode without affective components	15.2%	5	-	-	
Schizoaffective disorder	9.1%	4	-	-	
DSM-IV diagnosis at follow-up					
Bipolar I disorder	38.2%	13	4.2%	3	<0.001
Major depressive disorder	14.7%	5	16.7%	12	0.794
Anxiety/Panic disorder	11.8%	4	2.8%	2	0.063
Brief psychotic disorder	11.8%	4	-	-	<0.001
Psychotic disorder NOS	2.9%	1	-	-	<0.001
Schizoaffective disorder	11.8%	4	-	-	<0.001
Mood disorder NOS	2.9%	1	-	-	<0.001
Cyclothymic disorder	2.9%	1	-	-	<0.001
Observation of other suspected mental condition (V71.09)	2.9%	1	75%	54	<0.001
Lithium stop in follow-up period (n)					0.126
No	61.8%	21	45.8%	33	
Yes	38.2%	13	54.2%	39	
Recurrence within 6 months after lithium stop (n)					<0.001
No	23.5%	8	-	-	
Yes	14.7%	5	-	-	
Lithium treatment at follow-up (n)					0.027
No	38.2%	13	61.1%	44	
Yes	61.8%	21	38.9%	28	
Antipsychotics treatment at follow-up (n)					0.006
No	76.5%	26	94.4%	68	
Yes	23.5%	8	5.6%	4	
Still in treatment at follow-up (n)					<0.001
No	20.6%	7	68.0%	49	
Yes	76.5%	26	30.6%	22	
Missing	2.9%	1	1.4%	1	

† Percentages may exceed 100% because these categories are not mutually exclusive.

‡ The set of psychotic symptoms recognized as having special weight in the diagnosis of schizophrenia and schizoaffective disorder.

* Recurrence in the postpartum period.

Phenomenology of the initial episode was assessed using the Bipolar Affective Disorder Dimension Scale (BADDS) (24). The BADDS comprises four dimensions which provide a quantitative measure of psychopathology in each of four domains: 1) Manic-like episodes (the Mania dimension, M), 2) Depression-like episodes (the Depression dimension, D), 3) Psychotic symptomatology (the Psychosis dimension, P) and 4) the relationship (congruence of content and timing) between psychotic features (if present) and mood episodes (the Incongruence dimension, I). Each dimension provides a composite measure that takes both severity and frequency of relevant psychopathology into account. The dimensions are rated using integers in the range 0 to 100, with higher scores indicating more clinically important psychopathology – typically a mix of severity and frequency/duration.

Treatment regimen

During admission, women with a first-onset postpartum psychosis were treated according to a standardized treatment algorithm (12). All patients were initially treated with lorazepam at bedtime for three days. For patients receiving lorazepam monotherapy, who had persistent manic or psychotic symptoms, antipsychotic medication was recommended beginning on day four. Our primary recommendation for antipsychotic treatment was haloperidol at 2–6 mg/day. Patients who experienced side effects were switched to an atypical antipsychotic. A subset of patients who had already been treated with an antipsychotic for more than two days before admission (e.g., by acute services) were continued on the same antipsychotic they received before admission. After two weeks of combination treatment with a benzodiazepine and an antipsychotic, adjunctive lithium was recommended for those patients who did not have a significant clinical response. Lithium dosing was achieved based on plasma level (target, 0.8–1.2 mmol/L). After complete remission of symptoms, all women were advised to taper benzodiazepines to discontinuation. Women receiving antipsychotic monotherapy were advised to continue this treatment as maintenance therapy until nine months postpartum. Women who achieved clinical remission using both antipsychotics and lithium were advised to gradually taper off antipsychotic treatment, with maintenance lithium monotherapy until nine months postpartum. Lithium dosing for relapse prevention was achieved based on plasma level (target, 0.6–0.8 mmol/L).

Longitudinal course of the illness

Four years postpartum, women were re-evaluated using the SCID (23). Women were not seen in between hospital discharge and follow-up for the purposes of this study. Recurrence was defined as the occurrence of any depression, (hypo)mania, psychosis or mixed state episode fulfilling DSM-IV criteria, admission to hospital or a restart of medication. All women with a recurrence were asked retrospectively about the timing of their episode, including whether this was in relation to a subsequent pregnancy. Additionally, we collected information on the timing of tapering or stopping medication if applicable. The patient's medical records were consulted to validate the information.

Based on information collected at follow-up, women were categorized into one of two groups: 1) women with recurrence of non-postpartum mood or psychotic episodes within the follow-up period, or 2) women with mania/psychosis in the postpartum period and no mood or psychotic episodes outside the postpartum period during follow-up (vulnerability to affective psychosis only after childbirth).

Statistical analysis

We summarize the longitudinal course of the illness per group in Table 1. Differences between the two groups in terms of baseline demographic and clinical characteristics were assessed using Chi-squared and t-tests were appropriate (Table 1). A Kaplan-Meier Survival Curve of recurrence rates within the four-year follow-up period after first-onset postpartum psychosis was plotted. Additionally, we used a binomial logistic regression model to identify clinical predictors of postpartum psychosis group (recurrence of non-postpartum mood or psychotic episodes vs. mania/psychosis in the postpartum period only). Potential predictors of recurrence were based on the literature included admission length, maternal age, phenomenology of the index episode, and family history of psychiatric illness (2, 21, 22). To improve power in the family history variable, depression and anxiety were combined into the category 'depression or anxiety' and postpartum depression and postpartum psychosis were combined into the category 'postpartum psychiatric episode'. Mania/psychosis in the postpartum period only and psychiatric disorder with non-postpartum episodes were coded as 0 and 1 respectively. Results are presented in the form of odds ratios. All statistical analyses were performed using Stata/MP 15 (25). Lastly, we explored whether the set of psychotic symptoms recognized as having special weight in the diagnosis of schizophrenia and schizoaffective disorder (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; catatonia) was a precursor for a diagnosis within the psychotic disorder spectrum.

RESULTS

Follow-up

Seventy-two women (67.9%) did not experience recurrence during the four-year follow-up. Two women (1.9%) experienced a recurrence exclusively following later pregnancies. Both of these women subsequently received a diagnosis of depression at follow-up (Table 1).

Thirty-four women (32.1%) experienced at least one additional episode outside of the postpartum period during follow-up. The median time to recurrence during follow-up in women with episodes outside of the postpartum period was 20.3 months (IQR: 10.4-29.6) following initial hospitalization (Figure 1). Of the thirty-four women who had at least one episode outside of the postpartum period, 14 experienced an episode of (hypo) mania (13.2% of the overall sample), 11 experienced a depressive/anxiety episode (10.4% of the overall sample), and nine experienced a psychotic episode with or without affective components (8.5% of the overall sample) within the follow-up period.

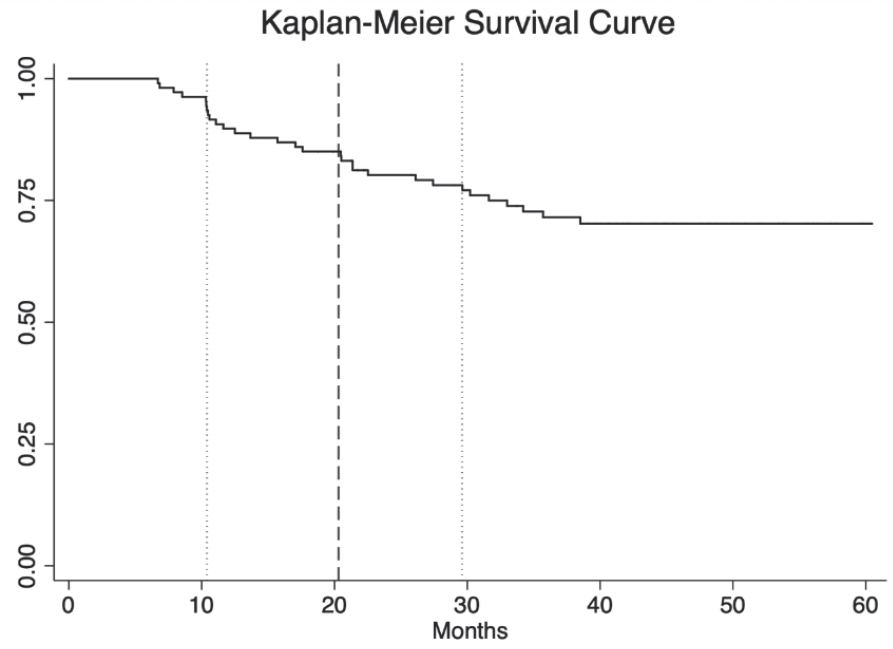
Medication use

The majority of patients were treated with lithium (76.4%) and antipsychotics (83.0%) during their MBU admission. Over the course of the follow-up period, most women were able to successfully taper lithium: out of the 52 women who stopped lithium, five relapsed within six months of discontinuation (Table 1).

Potential predictors of relapse

To identify potential clinical predictors of recurrence of non-postpartum mood or psychotic episodes, we carried out a logistic regression. We did not find significant predictors of recurrence outside the postpartum period (Table 2).

FIGURE 1. Kaplan-Meier Survival Curve of recurrence rates within the four-year follow-up period after first-onset postpartum psychosis (median time to recurrence is represented by a dashed line, the interquartile range is represented by dotted lines)



Psychotic symptoms

Eight women (7.5%) in this cohort experienced first rank psychotic symptoms during their postpartum psychosis as measured by the BADDS. These include one or more of the schizophrenia-like symptoms, including thought insertion, withdrawal or broadcasting, passivity experiences, hallucinatory voices giving running commentary, discussing subject in third person and bizarre delusions. Of these eight women, five experienced no recurrence, while two women experienced (hypo)mania within the first year after their initial episode. One woman experienced depressive episodes both during a subsequent postpartum episode, as well as outside the postpartum period. None of the women with first rank psychotic symptoms met criteria for a schizophrenia spectrum illness, including schizophreniform, schizophrenia, and schizoaffective disorder, during follow-up.

TABLE 2. Logistic regression analysis of the clinical predictors for recurrence of non-postpartum mood or psychotic episodes within the follow-up period

	ß	z	p	OR	OR 95% CI
Admission length	0.001	0.07	0.943	1.00	0.98; 1.02
Age	-0.06	-1.16	0.245	0.94	0.86; 1.04
Phenomenology at admission					
Psychotic only	0.46	0.74	0.460	1.59	0.47; 5.42
Depressed-psychotic	-0.48	-0.55	0.580	0.61	0.11; 3.47
Manic with and without psychotic features	0.55	0.81	0.418	1.74	0.46; 6.61
Family history					
Postpartum episode	-1.65	-1.50	0.133	0.20	0.02; 1.65
Depression/Anxiety	0.17	0.36	0.717	1.18	0.48; 2.94
Bipolar disorder	-0.70	-0.94	0.345	0.50	0.12; 2.12
Lithium treatment of initial episode	0.21	0.35	0.727	1.24	0.37; 4.11
Antipsychotic treatment initial episode	0.26	0.42	0.677	1.30	0.38; 4.42

DISCUSSION

In this prospective longitudinal study, we investigated the long-term outcome of 106 women with postpartum psychosis over a four-year period. Over two thirds of the women included in this study did not have psychiatric episodes outside the postpartum period during follow-up. For the remaining subset of women (~32%), postpartum psychosis was part of a psychiatric disorder with a more disabling disease course and broader window of recurrence vulnerability, both in and outside of the postpartum period. This recurrence rate for mood or psychotic episodes outside the postpartum period is lower than the recurrence rate we recently reported in our meta-analysis (56.5%) (19).

The differences between this study and our recent meta-analysis (19) may be due to the differences in the follow-up period, which was four years in this study but ranged from 11 to 26 years in the meta-analysis. It is conceivable that recurrence rates increase with longer follow-up periods. The relatively lower relapse rates may also be attributed to preventive follow-up, including continued medication use, and specialized health care for these women in the current treatment setting (1).

Of the 34 women with a recurrence, 14 experienced an episode of (hypo)mania (13.2% of the overall sample), 11 experienced a depressive/anxiety episode (10.4% of the overall sample), and nine experienced a psychotic episode with or without affective components (8.5% of the overall sample) within the follow-up period. Of the nine women who experienced a psychotic episode, four women met diagnostic criteria for schizoaffective disorder, four women met diagnostic criteria for brief psychotic disorder,

and one met diagnostic criteria for psychotic disorder not otherwise specified. None of these women fulfilled diagnostic criteria for schizophrenia or schizophreniform disorder. Currently, the DSM-V does not recognize postpartum psychosis (including psychotic, manic, psychotic depressed, or mixed episodes) as a distinct disease category (6). Women with psychotic symptoms without an affective component are currently diagnosed as either psychosis not otherwise specified, brief psychotic disorder or schizophreniform disorder, if schizophrenia-like symptoms are present. A primary diagnosis within the psychotic DSM may not be accurate.

The majority of women with postpartum psychosis have prominent manic or mixed affective features (6). Based on current best practice, these women are, therefore, diagnosed with bipolar disorder at the time of their first-onset postpartum psychosis. However, the fact that over 67% of our sample (and 43.5% in our recent meta-analysis (19)) had no depressive, manic or psychotic recurrence outside the postpartum period raises questions about the validity of this approach. The diagnosis 'bipolar disorder' suggests a vulnerability to mood episodes at all times, not only during the postpartum period. Consequently, we believe a diagnosis of bipolar disorder should only be given following severe mood episodes outside of the postpartum period, either mania or depression. For women with vulnerability for episodes limited to the postpartum period, a distinct classification within the bipolar spectrum would be more accurate and reduce stigma.

To investigate predictive factors of episodes outside of the postpartum period, we assessed the association between various clinical and demographic characteristics with recurrence outcome. Unlike previous retrospective studies (9, 20, 21), we did not find that the length of the disease episode or a woman's age were significantly associated with higher risk for developing a more severe psychiatric disorder with non-postpartum episodes. This may be due to our standardized treatment algorithm, as well as the lack of variance in maternal age in our sample. Moreover, phenomenology of the index episode was also not predictive of the disease course, but this may be attributed to a lack of statistical power. The risk of recurrence for women with mania (both with or without psychotic symptoms) or psychosis without affective symptoms was very similar. Surprisingly, a schizophrenia-like presentation was neither predictive of recurrence, nor of receiving a schizoaffective diagnosis during follow-up. In line with prior longitudinal studies (2, 20, 22, 26-29), we found that the vast majority of non-postpartum episodes during follow-up occurred within the bipolar spectrum. In our cohort, none of the women received a diagnosis of schizophrenia during follow-up, similar to most prior studies,

except Kirpinar et al. (26), who found a relationship between postpartum psychosis and a diagnosis of schizophrenia during follow-up.

Understanding who is at risk of a mood or psychotic disorder during follow-up, and whose vulnerability is limited to the postpartum period, is particularly important in guiding treatment decisions including long-term pharmacotherapy. Unfortunately, no biomarkers are currently available to help guide these decisions. In clinical practice, this means that long-term monitoring is warranted for everyone with postpartum psychosis. Another reason for long-term monitoring are the high suicide rates during follow-up, reported by other studies (2, 28, 29).

Our findings must be interpreted in light of a number of limitations. Firstly, our sample size was relatively small. Nevertheless, this is the largest prospective longitudinal study of women with postpartum psychosis to date. Secondly, this is a naturalistic study, rather than a randomized control trial, in which patients' preferences may have influenced treatment decisions. Due to the low incidence of postpartum psychosis, a randomized control trial for its treatment would be challenging, and no such trial has been published (10). Lastly, our cohort was recruited from a single, inpatient site in the Netherlands. Patients were more highly educated and more likely to be partnered/married than the general population, potentially limiting the generalizability of our findings.

CONCLUSION

In this prospective longitudinal study of first-onset postpartum psychosis, we investigated the long-term outcomes of 106 women with postpartum psychosis over a four-year follow-up. We found that for the majority of women with first-onset postpartum psychosis, the risk of illness was limited to the period after childbirth. For the remaining women, postpartum psychosis was part of a mood or psychotic disorder with severe non-postpartum recurrence, mainly in the bipolar spectrum. No clinical predictors of a woman's risk of severe episodes outside the postpartum period were found. Our findings add to previous evidence suggesting a fundamental link between postpartum psychosis and bipolar disorder, which may represent two distinct diagnoses within the same spectrum.

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Chapter 4

Mother-to-infant bonding in women with postpartum psychosis and severe postpartum depression: a clinical cohort study

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ABSTRACT

Mother-to-infant bonding is important for long-term child development. The aim of this study was to investigate bonding in women admitted to a Mother and Baby Unit with postpartum depression (PD, n = 64) and postpartum psychosis (PP, n = 91). Participants completed the Postpartum Bonding Questionnaire (PBQ), the Edinburgh Postnatal Depression Scale (EPDS) and the Young Mania Rating Scale (YMRS) weekly during admission. At admission, 57.1% of women with PD had impaired bonding, compared to only 17.6% of women with PP (p-value < 0.001). At discharge, only 18.2% of women with PD and 5.9% of women with PP still experienced impaired bonding (p-value = 0.02). There was a strong association between decrease of depressive and manic symptoms and improved bonding over an eight-week admission period. In a small group of women (5.7%) impaired bonding persisted despite being in remission of their psychiatric disorder. The results from our study show that impaired bonding is a more present and evidently severe problem in postpartum depression but not so much in postpartum psychosis. Treatment of depressive symptoms will improve bonding in almost all women, but clinicians should assess if impaired bonding is still present after remission because for a small group special care and treatment focused on bonding might be required.

INTRODUCTION

Affective and protective feelings towards the child usually begin during the first trimester of pregnancy (1). These feelings gradually increase during pregnancy, particularly in response to fetal movements (2). After giving birth, the term "bonding" refers to the unidirectional feelings experienced by a mother towards her child (3). Mother-to-infant bonding is considered to form the foundation for the child's later attachment (4). The development of bonding is important, as impaired bonding can impact the child's emotional, cognitive, and behavioral long-term development. For example, studies have shown associations between impaired mother-to-infant bonding and child behavior problems in early childhood (5), and an increased child's risk of developing psychopathology in adulthood (6). Moreover, mothers who reported impaired mother-to-infant bonding experienced high levels of parenting stress during toddlerhood (7), and these children are at risk for maltreatment later in life (8). While in most situations adequate bonding develops gradually after birth, bonding can be impaired when the mother suffers from a psychiatric disorder (8).

The postpartum period is considered a time of increased risk for the development of severe psychiatric disorders (9). Postpartum depression (PD) is one of the most common disorders and affects approximately 10% of new mothers (10). A less common but more severe postpartum illness is postpartum psychosis (PP). Postpartum psychosis is the umbrella term for postpartum mania, psychosis, and depression with psychotic features (11). First onset postpartum psychosis has an incidence ranging from 0.24 to 0.6 women per 1000 births (12-14). The prevalence of PP in women with a prior diagnosis of bipolar disorder is high, our meta-analysis reported 17% (15). Given the severity of the illness and the high relative risk for suicide and infanticide, early recognition and adequate treatment is of great importance (16, 17). Both severe PD and PP are indications for psychiatric hospitalization (12, 18). Joint inpatient mother–baby admission to a Mother and Baby Unit (MBU) is preferred for PP and PD, as these admissions are associated with reduced time to recovery, when opposed to mother-only admission (19-21). With an adequate treatment regime, nearly all women with postpartum mood disorders achieve full remission (22).

While the association between PD and impaired bonding is well established in current literature (3, 23-27), there is hardly any research on the association between PP and impaired bonding. As the underlying nature of PD and PP differ substantially, it is uncertain whether the magnitude of the problem is comparable in both groups. In addition, previous studies have not investigated how the relationship between PD/PP and impaired bonding is affected by the treatment of the depressive and manic symptoms.

Acquiring this data could provide insights into driving factors behind impaired bonding and underline the importance of particular treatment regimens. In this inpatient study on a Mother and Baby Unit (MBU), we therefore examined the differences in mother-to-infant bonding between women with postpartum psychosis and women with severe postpartum depression. Additionally, we investigated the association between change in depressive and manic symptoms and mother-to-infant bonding scores over the course of MBU admission.

METHODS

Study design and participants

The present study was embedded in an ongoing prospective multicenter cohort study (OPPER), which focuses on the prevention, treatment, and neurobiology of peripartum mood disorders (22, 28). Women are eligible for this study if they (a) are between 18–45 years of age, (b) have a postpartum onset of psychosis, mania, or severe depression as assessed with the Structured Clinical Interview for DSM-IV Axis I disorders (SCID) (29), and (c) are admitted to the MBU. Exclusion criteria are: (a) prenatal onset of psychosis, mania or severe depression, (b) drug/alcohol dependence in the last 3 months, (c) intellectual disability (IQ < 80), (d) serious somatic illness and (e) inability to read or write. The Medical Ethical Committee of the Erasmus Medical Center Rotterdam approved the study (MEC-2005226). Written informed consent was obtained from all participants.

For the current study, all women who participated in OPPER between May 2005 and January 2013, and who had completed a Postpartum Bonding Questionnaire (PBQ) (30), were included.

Data collection and procedures

Psychiatric diagnosis was established at intake using the SCID (29). Bonding was measured with the Postpartum Bonding Questionnaire (PBQ) (30). The PBQ is a self-report instrument that consists of 25 statements that are rated on a 6-point Likert scale (from "always" to "never"). It has four scales representing (1) impaired bonding, (2) rejection and anger, (3) anxiety about care, and (4) risk of abuse. The maximum total score is 125 with a cut-off of 26 to identify mothers with medium impaired bonding and a cut-off of 40 for mothers with severe impaired bonding. Depressive symptoms were measured with the widely-used Edinburgh Postnatal Depression Scale (EPDS) (31). A score of 13 or higher

is indicative of depressive disorder (31, 32). Manic symptoms were measured using the Young Mania Rating Scale (YMRS) (33), a well-validated 11-item interviewer rated scale designed to assess the severity of manic symptoms in bipolar patients. A state of euthymia usually requires a score below the cut-off of 12 (34). During hospitalization, the PBQ and EPDS were completed weekly by the participant and the YMRS was completed weekly by a trained rater.

Treatment

Women in this study received pharmaceutical treatment according to medical guidelines, as described previously (35). Women with PP were treated with antipsychotics and/or lithium, while women with PD were treated with either tricyclic antidepressants or a selective serotonin reuptake inhibitor. In addition, non-pharmacological interventions to optimize mother-baby interaction took place as part of the regular program of the MBU. These interventions included guidance from nursing staff, video interaction guidance, baby massage and a support group for mothers. Women with PD and PP were equally exposed to these interventions. Information on the effect of each individual treatment intervention on mother-to-infant bonding was not collected in this observational study.

Statistical analysis

Descriptive statistics of the study population are provided. Differences in demographic and clinical characteristics between the PD and the PP group were tested using t-tests, Mann-Whitney U tests, chi-square tests and Fisher's exact test. We then tested differences in PBQ scores (both dichotomized using the cut-off score of 26 and the cut-off score of 40) between women with PD and women with PP at admission and at discharge, using chi-square tests and Fisher's exact test. Additionally, we tested whether bonding scores showed a different course during the MBU admission period for PD and PP women by testing a diagnosis*time interaction term using linear mixed effect modelling analysis (LMM, fixed intercept, fixed slope, AR(1), covariance matrix, maximum likelihood estimation). To examine the association between change in depressive and manic symptoms and bonding scores over the course of MBU admission, we used linear mixed effects modelling as well. This model ensures optimal use of the weekly repeated assessments over the course of admission (36). Because depressive symptoms were present in both the PP and the PD groups, we tested the association between depressive symptoms and bonding in both groups separately. Manic symptoms are, by definition,

exclusively present in the PP group. We therefore tested the association between manic symptoms and bonding in the PP group only. Analyses were adjusted for maternal age and primiparity (16, 37-39). We report coefficients and their confidence intervals. To visualize these associations, we created graphs displaying mean EPDS, YMRS, and PBQ scores over the first eight weeks of admission in both the PD and the PP group. We chose to display eight weeks as this was the mean length of admission. Statistical Package for Social Sciences (SPSS) version 24.0 was used for data analysis. All hypotheses were tested with an alpha of 0.05 (two-sided).

RESULTS

Participants were 155 women with a severe postpartum mood disorder, of which 91 were diagnosed with postpartum psychosis and 64 were diagnosed with postpartum depression. Relevant demographic and clinical characteristics are presented in Table 1. Infant age at admission was significantly higher for women with PD compared to women with PP. As expected, depressive symptoms (EPDS) were higher in women with PD. There were no substantial differences in maternal age, length of admission, relationship status, education level, gender of the infant and psychiatric history of the women.

Prevalence of impaired mother-to-infant bonding at admission and discharge

At admission, 17.6% of women with PP compared to 57.1% of women with PD had a PBQ score above the cut-off of 26 (p-value < 0.001), which is associated with medium to severe impaired bonding (Figure 1). At discharge, only 5.9% of women with PP compared to 18.2% of women with PD still had a PBQ score above this cut-off (p-value = 0.02).

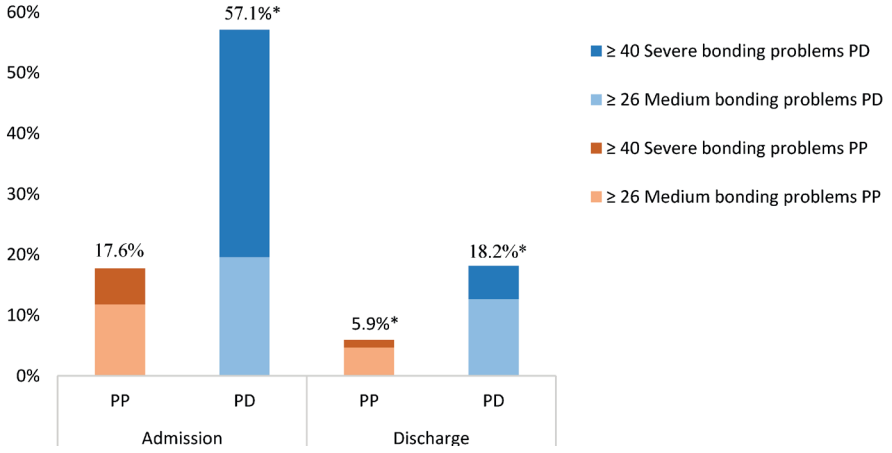
The percentage of women with severe impaired bonding (PBQ score above the cut-off of 40) at admission in women with PP was 5.9% compared to 37.5% in women with PD (p-value < 0.001). At discharge, these percentages decreased to 1.2% in women with PP compared to 5.5% in women with PD (p-value = 0.30). Mean PBQ scores during the first eight weeks of admission per group can be seen in Figure 2. The PBQ scores went down gradually during the first five weeks of MBU admission for both PP and PD patients, but showed no further decline up to eight weeks of admission. Formal testing showed that the course of bonding problems during the admission period differed significantly between PP and PD women ($F(672) = 8.632$; $p = 0.003$).

TABLE 1. Demographic and clinical characteristics

	Postpartum psychosis (n=91)	**Postpartum depression (n=64)**	**p-value**
Maternal age at admission (yr), mean (SD)	31.0 (4.7)	30.0 (8.0)	0.32
Length of admission (wks), mean (SD)	7.9 (4.3)	7.5 (4.8)	0.52
Dutch nationality, n (%)	83 (92.2)	55 (90.2)	0.66
Relationship, yes, n (%)	88 (97.8)	55 (93.2)	0.21
Primary/Secondary education only, n (%)	44 (48.4)	33 (60.0)	0.17
Primiparous, n (%)	68 (78.2)	40 (64.5)	0.09
Psychiatric history, n (%)			
None	44 (48.4)	25 (39.1)	0.14
Prior postpartum episode	11 (12.1)	4 (26.7)	
Prior non-postpartum episode	36 (39.6)	35 (54.7)	
EPDS score at admission, mean (SD)	14.9 (6.0)	19.0 (4.9)	0.001 *
YMRS score at admission, mean (SD)	17.7 (11.5)	NA	NA
Family history of psychiatric disorder, n (%)	51 (56.0)	20 (35.0)	0.013 *
Infant age at admission (wks), median (IQR)	2.0 (3.7)	6.0 (5.2)	<0.001 *
Gender infant, male, n (%)	45 (50.0)	26 (43.3)	0.51

* = Significant result ($p < 0.05$).

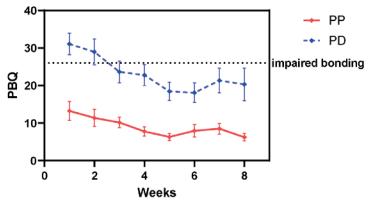
FIGURE 1. Proportion of women with PP and PD presenting with medium to severe impaired bonding at hospital admission and discharge



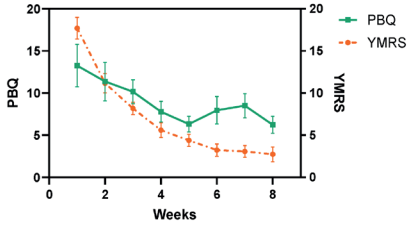
* = Significant result ($p < 0.05$).

Abbreviations: PP = postpartum psychosis; PD = postpartum depression; Note: PBQ scores were missing at random at both time-points. During admission PP (n = 68)/PD (n = 56), at discharge PP (n = 85)/PD (n = 55).

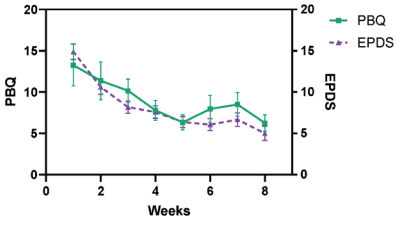
FIGURE 2. Change in mean mother-to-infant bonding scores and depressive (EPDS) and manic (YMRS) symptoms in women with postpartum psychosis and postpartum depression (including standard error bars)



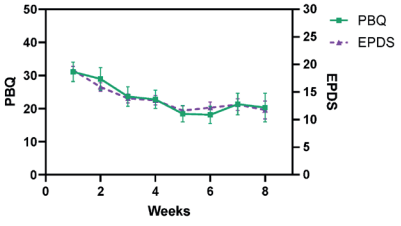
(a) Bonding problems in women with PP and PD



(b) Manic symptoms and bonding in women with PP



(c) Depressive symptoms and bonding in women with PP



(d) Depressive symptoms and bonding in women with PD

Abbreviations: PP = postpartum psychosis; PD = postpartum depression; PBQ = Postpartum Bonding Questionnaire; YMRS = Young Mania Rating Scale; EPDS = Edinburgh Postnatal Depression Scale.

Persistent impaired bonding at discharge

At discharge, 15 women in total (10.7%) continued to experience impaired bonding (5 women with PP and 10 women with PD). In seven of these women (5.0%), depressive symptoms (EPDS > 12) were also still present. In eight women (5.7%), impaired bonding remained present in the absence of depressive symptoms. None of these women had manic symptoms.

Postpartum depressive and manic symptoms and the association with mother-to-infant bonding

Depressive symptoms decreased gradually over the course of admission. At admission, the mean EPDS score in the PD group was 19.0 (SD 4.9) and 14.9 (SD 6.0) in the PP group, which decreased to 10.3 (SD 6.0) and 4.1 (SD 4.6) respectively. In the PP group, manic symptoms decreased gradually over the course of admission as well, from a mean YMRS of 17.7 (SD 11.5) at admission to a mean YMRS of 1.1 (SD 1.6) at discharge. Table 2 demonstrates the results of the association of maternal depressive (EPDS) and manic (YMRS) symptoms and mother-to-infant bonding (PBQ) during inpatient follow-up, based on linear mixed effects modelling. There was a significant association between a decrease in depressive symptoms and improvement of bonding over the 8-week admission period in PD patients (Figure 2d). A similar, but slightly weaker association between a decrease in depressive symptoms and improvement of bonding was seen in the PP group (Figure 2c). In addition, we found a significant association between a decrease in manic symptoms and improvement of bonding in PP patients (Figure 2b), independent from the association with depressive symptoms. However, the correlation between depressive symptoms and impaired mother-to-infant bonding was much stronger (compared to the correlation between manic symptoms and impaired mother-to-infant bonding).

TABLE 2. The effect of depressive (EPDS) and manic (YMRS) symptoms on mother-to-infant bonding (PBQ)

Fixed effects	Unadjusted estimate	Sig.	Adjusted estimate	Sig.
Linear mixed effects model in PP group				
Intercept	2.62	0.02	7.96	0.22
EPDS	0.76	0.00	0.76	0.00
YMRS	0.16	0.02	0.16	0.02
Linear mixed effects model in PD group				
Intercept	8.30	0.00	1.98	0.88
EPDS	1.05	0.00	1.05	0.00

Abbreviations: PP = postpartum psychosis; PD = postpartum depression; EPDS = Edinburgh Postnatal Depression Scale; YMRS = Young Mania Rating Scale; PBQ = Postpartum Bonding Questionnaire. Adjusted estimates: adjusted for maternal age and primiparity.

DISCUSSION

Differences in bonding problems between PP and PD

In this prospective cohort study, we found that impaired mother-to-infant bonding is a major problem in inpatient women with severe postpartum depression (57.1%), while less than 1 out 5 women with postpartum psychosis reported impaired bonding (17.6%).

Moreover, in women with postpartum depression we found a higher proportion with severe impaired bonding compared to women with PP. This is in line with previous research, which reports that depressed mothers perceived their bonding to the baby more negatively than psychotic mothers during admission (40). In this study, they observed impaired bonding rates in 61.1% of women with PD and 29.4% of women with PP. We agree with Hornstein et al. (40) that this intergroup difference is an expression of the nature of the psychopathology. Mothers with PD have feelings of inadequacy, negative cognitions, and self-doubt resulting in a negative bonding experience, while most mothers with PP lack these cognitions, especially if they mainly have manic symptomatology.

At discharge, the number of women reporting impaired bonding had greatly reduced in both groups (5.9% in PP vs. 18.2% in PD). Studies on impaired bonding in the general population have shown prevalence rates from 12.2% at 48 hours postpartum (41) to 7.1% and 8.9% at 2 and 12 weeks postpartum respectively (42, 43). Thus, the prevalence rate of impaired bonding at discharge in women with a diagnosis of PP could be considered equal to that of the general population.

The effect of treating depressive and manic symptoms on mother-to-infant bonding

A recent systematic review identified 29 previous cross-sectional studies that investigated the correlation between depressive symptoms and postnatal mother-to-infant bonding (27). Out of these 29 studies, 21 studies observed a moderate to strong correlation (r = −0.61 to −0.14, ß = −0.39 to −0.26). None of these studies examined the correlation over time. In our longitudinal study, we observed the correlation between depressive symptoms and mother-to-infant bonding over time, and found an almost exact concordant movement of both scores over an 8-week admission period. This indicates that improvement in mother-to-infant bonding is highly dependent on improvement of depressive symptoms. Impaired bonding seems to be an integral part of postpartum depression and could therefore be an indication of the presence of a postpartum depression. We also found a correlation between manic symptoms and mother-to-infant bonding over time, although this correlation was much weaker.

In a small group of women (5.7%), impaired bonding persisted despite effective treatment of the depressive and/or manic symptoms. This finding is in agreement with the earlier observations by other researchers (3, 8, 44), and with reported prevalence rates of impaired bonding in the general population, which suggest that impaired bonding can exist independent of psychiatric symptoms. Therefore, at discharge, and also when patients are in remission, the quality of the mother-to-infant bonding should be assessed. For these women, besides treatment of their psychiatric disorder, interventions aimed at improving bonding are important.

Strengths and limitations

Although the findings should be interpreted with caution, this study has several strengths. This is the first prospective cohort study to investigate the association of longitudinal depressive and manic symptoms (at the symptom level) with mother-to-infant bonding in patients admitted with postpartum psychosis or severe postpartum depression. Another strength of this study is the use of the PBQ (30), an extensive screening instrument, assessing all domains of bonding. Nonetheless, the current study also has several limitations. Differentiation between the most effective interventions for impaired bonding could not be established, because inpatient treatment at the MBU included both interventions aimed at reducing depressive, manic and/or psychotic symptoms, and interventions focused on optimizing the mother-baby interaction. However, our positive results for improvement on

both domains underline the added value of joint inpatient mother–baby admission to an MBU as opposed to mother-only admission. Furthermore, we encountered missing data points for measurements during admission. Fortunately, mixed models allow data for all subjects to be included in the analysis regardless of whether they completed all study time points.

Clinical implications

The results from our study implicate that women with severe postpartum psychiatric disorders, and especially women with severe postpartum depression, are at risk of impaired mother-to-infant bonding due to the nature of their symptoms. While both manic and depressive symptoms were strongly associated with impaired bonding, the association with depressive symptoms was stronger both in the PD and the PP groups. Over the course of eight weeks of inpatient mother–baby admission at our Mother and Baby Unit (MBU), the combined pharmacological and non-pharmacological treatment greatly improved both depressive and manic symptoms and mother-to-infant bonding. While these results are encouraging, admission to an MBU is only reserved for mothers with severe postpartum psychiatric disorders and contingent on the presence of an MBU. Many women with mild to moderate symptoms of depression will go undetected and untreated, or will receive treatment untailored to the postpartum period, posing a threat to adequate mother-to-infant bonding, putting the child at risk for adverse short- and long-term outcomes. Our findings support the necessity to establish MBUs, or at least tailored treatment programs, for optimal patient care. Since the prevalence of prenatal depression is similar or even higher than postpartum depression (45-47), and mother-to-infant bonding already starts in the first trimester of pregnancy, we strongly encourage that diagnosis and interventions should take place as early as possible during the perinatal period to avoid harmful consequences. Screening for depression during pregnancy and the postpartum period is unfortunately not yet standard clinical practice in many settings. Interventions should primarily be focused on the treatment of the psychiatric disorder. Nonetheless, after remission has been achieved, it is important to check for residual impaired bonding and to act accordingly.

Implications for future research

The results from our study indicate that mother-to-infant bonding is a major problem in women with postpartum psychiatric disorders, especially in women with severe PD. Our

data suggests that treatment of depressive symptoms improves mother-to-infant bonding in almost all women. There is an urgent need for studies comparing improvement in psychiatric symptomatology and mother-to-infant bonding in MBU settings compared to regular outpatient treatment settings. In addition, longer follow-up studies in women with impaired mother-to-infant bonding should be initiated and include measurements of the cognitive and emotional development of the child, to investigate the long-term effect of impaired bonding on the offspring later in life.

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Part II

Bipolar I disorder during the peripartum period

Chapter 5

Bipolar episodes after reproductive events in women with bipolar I disorder, a study of 919 pregnancies

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ABSTRACT

Background: Women with bipolar I disorder are at high risk for severe episodes after childbirth, but there is no study that provides an overview on bipolar episode risk both during pregnancy and after childbirth, miscarriage and induced abortion. The aim of this study was to determine the episode risk during all pregnancy outcomes subdivided by first and subsequent pregnancies.

Methods: Participants were 436 women with bipolar I disorder from the Dutch Bipolar Cohort, having 919 pregnancies of which 762 resulted in a live childbirth, 118 ended in a miscarriage and 39 ended in induced abortion. Women reported on the occurrence of manic or depressed episodes during the perinatal period. Information about medication use was obtained by questionnaires.

Results: Episode risk was 5.2% during pregnancy, and 30.1% in the postpartum period, with a peak in the early postpartum period. Risk of an episode was highest after live birth (34.4%), and lower after miscarriage (15.2%) and induced abortion (27.8%). Women with an episode during pregnancy or postpartum were less likely to have a second child compared to women with an uneventful first pregnancy (cOR=0.34; 95%CI: 0.22-0.51; $p<0.001$); if they had a second child their risk of an episode was significantly elevated with a subsequent pregnancy (cOR=6.17; 95%CI: 3.64-10.45; $p<0.001$).

Limitations: Retrospective cross-sectional design with assessment (partial) through self-report in a homogeneous population.

Conclusions: Women with bipolar I disorder have a six times higher risk of an episode after delivery compared to during pregnancy, therefore preventive strategies are particularly important immediately after delivery.

INTRODUCTION

Bipolar I disorder is a severe chronic mood disorder characterized by episodes of mania, hypomania, and alternating or intertwining episodes of depression (1). It affects more than 2% of the world's population irrespective of nationality, ethnic origin, or socioeconomic status (2). In view of its recurrent nature, optimum long-term management is a preventive strategy that combines pharmacological, psychological, and lifestyle approaches from the first episode (3), with lithium being one of the most effective treatments of both manic and depressive episodes (4). The postpartum period has been identified as a high-risk period for women with bipolar disorder. There is strong, clear, and consistent evidence of a specific relationship between childbirth and the risk of a bipolar episode (5), with an overall recurrence risk of 37% (range 29-45%) (6). In contrast to the postpartum period, information about the recurrence risk during pregnancy is limited and the wide variation in the reported rates (4-73%) hampered previous efforts to do a meta-analysis (7, 8). In addition, very few studies have investigated the risk of a bipolar episode after miscarriage and induced abortion. This is remarkable since both miscarriage and induced abortion are common pregnancy outcomes. The risk of miscarriage among recognized pregnancies was 12.8% in a large Norwegian register based study (9). Globally, about one in five pregnancies ended in induced abortion in 2008, corresponding with an abortion rate of 28 per 1000 women aged 15-44 years (10). In the Netherlands the abortion rate in 2016 was 3.3 times lower than the global abortion rate (8.5 per 1000 women aged 15-44 years) (11). A clinical cohort study reported that the risk of a bipolar episode after miscarriage was 20.1% and after abortion this was 24.2% (12). Lastly, there is no study that provides an overview on episode risk both during pregnancy and after childbirth, miscarriage and induced abortion. This is a problem because women make decisions regarding family planning and prevention strategies based on their individual risk profile during the entire perinatal period. This is particularly relevant during pregnancy, when risk of fetal medication exposure should be weighed to both the episode risk during pregnancy and after delivery (6, 13, 14). In this large clinical cohort we investigated the risk of a bipolar episode during the perinatal period in a sample of patients with bipolar I disorder. Additionally, we wanted to determine the effect of subsequent pregnancies on the episode risk and investigate the association between lithium use during pregnancy and episode risk.

PATIENTS AND METHODS

Study design

This retrospective cohort study was part of the Dutch Bipolar Cohort (DBC) study, a collaboration between the University of California - Los Angeles and the Dutch health care institutes University Medical Center Utrecht, GGZ Altrecht, GGZ inGeest, University Medical Center Groningen, Delta, Dimence, Parnassia (PsyQ) and Reinier van Arkel. The objective of the DBC study was to investigate genetic and phenotypic information of patients with bipolar disorder type I (BD-I), first-degree relatives and controls (15, 16). Patients were recruited via clinicians, the Dutch patient association, pharmacies and advertisements. Inclusion criteria for all participants were 1) age 18 years or older 2) at least three Dutch-born grandparents 3) a good understanding of Dutch language. Patients with a somatic illness that could have influenced the diagnosis of BD were excluded (15). The study was approved by the accredited Dutch Medical Ethical Trial Committee (METC) and all participants gave written informed consent. Data collection took place between June 2011 and July 2015. A total of 1396 patients with bipolar disorder participated in the DBC study, of which 793 were women.

Participants and aims

For the current study, we analyzed data from the DBC study of women with (a) a lifetime diagnosis of DSM-IV bipolar I disorder, (b) who had at least one pregnancy, and (c) for whom information on the occurrence of a perinatal bipolar episode was available (see Supplementary Figure 1. CONSORT flow diagram for participant selection in this study). The primary aim of our study was to explore the self-reported risk of a manic or depressive episode during the perinatal period in women with bipolar I disorder. The perinatal period was defined as the period from the first day of pregnancy until 6 months after induced abortion, miscarriage or the birth of a living child. Postpartum was defined as the period from the first day of delivery until 6 months after induced abortion, miscarriage or the birth of a living child. Secondary, we wanted to determine the effect of subsequent pregnancies on the episode risk. Finally, we investigated the association between lithium use during pregnancy and episode risk during pregnancy and postpartum.

Data collection and procedures

For all patients, clinical bipolar I disorder diagnosis was confirmed at inclusion using the Structured Clinical Interview for DSM-IV (SCID) (17), conducted by at least one well-

trained independent rater of the DBC study (18). Other clinical features (i.e. age of onset, the total number of manic and depressive episodes, lifetime rapid cycling, family history of psychiatric illness and educational level) were also assessed at inclusion with the Dutch version of the Questionnaire for Bipolar Illness (QBP-NL, Dutch translation by Akkershuis, Groenesteyn, Nolen, 1997; an adaptation of the Enrolment Questionnaire as previously used in the Stanley Foundation Bipolar Network) and the SCID-I (17, 19, 20). For our primary and secondary outcome - occurrence of perinatal mood episodes during the first and subsequent pregnancies - data was collected retrospectively. Women were asked to report the date of birth of a living child, miscarriage or induced abortion and whether they experienced a manic episode (with or without prominent psychotic features) or depressive episode during pregnancy or the postpartum period. When the episode occurred after delivery of a living child, women were asked to specify the timing of onset (<4 weeks or 1-6 months after childbirth). For our third outcome – the association between lithium use and episode risk – we assessed medication use in two different ways: all participants were asked to 1) complete online questionnaires during inclusion and study assessment, including a list of current and lifetime medication use, and 2) complete a lithium satisfaction questionnaire including questions on current and past use of lithium. Detailed information regarding the timing and duration of use, was only available for lithium and was used to determine the prophylactic use of lithium during pregnancy as accurate as possible and to restrain misclassification (21). For the other types of medication, lifetime use could be determined, but data was not detailed enough to determine use during pregnancy. Lifetime medication use was defined as the exposure to medication in the period from the first episode until the assessment of pharmacological treatment during the DBC study. Data was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (22).

Data-analysis

Data management and descriptive statistics were performed using Statistical Package for Social Sciences (SPSS) version 24.0. Comparisons of demographic and clinical variables between women who experienced a perinatal episode and those who did not, were completed by means of chi-squared or Fisher's exact test for categorical data; continuous variables were examined with two-sample t-tests or Mann-Whitney U tests. For our primary outcome, the risk of mood episodes during pregnancy, after live birth, miscarriage and induced abortion were determined. Episode risks related to the different pregnancy outcomes were compared using a chi-squared test. We report crude incidence

risks and incidence risks adjusted for the occurrences of multiple pregnancies within the same women. Adjusted incidence risks were estimated using multilevel logistic regression models, for which we included women as level in our analyses to cluster the pregnancies. Self-reported phenomenology and timing of episodes was reported in a descriptive manner. In order to investigate whether the episode risk increased during the second perinatal period in women who experienced an episode in the first perinatal period, we calculated the odds ratio of a second perinatal episode. The association between lithium prophylaxis and the occurrence of an episode was examined in a subgroup of women who had a bipolar I disorder diagnosis before conception, using logistic regression analysis. Analyses were conducted unadjusted, and repeated adjusting for possible confounders (age of onset, total number of episodes, family history of bipolar disorder, and multiple pregnancies within unique women) using a multivariable multilevel regression model. We report crude and adjusted odds ratios (cOR or aOR) with corresponding 95% confidence intervals. Statistical analyses were considered significant with an alpha of 0.05 (two-sided). We report absolute numbers and percentages.

RESULTS

Demographic and clinical characteristics

Participants were 436 women with bipolar I disorder with a total of 919 pregnancies. Out of the 919 pregnancies, 762 resulted in a live birth, 118 in a miscarriage (miscarriage rate 12.8%), and 39 in an induced abortion (abortion rate 4.2%). A detailed overview of demographic and clinical characteristics of these 436 women is presented in Table 1. The average age at the time of assessment was 51.7 years (SD=10.0), the average age of onset was 27.1 years (SD=9.5), the median number of episodes at assessment was 8 (IQR=5-15), and the percentage of women with rapid cycling was 19%. Out of the 436 women in this study, 241 experienced at least one episode during or after pregnancy (group 1). Women who experienced a perinatal episode had on average a lower age of illness onset, more previous bipolar episodes and were more likely to have a family history of bipolar disorder when compared to women who did not experience an episode during pregnancy or postpartum (group 2). Both groups had a comparable education level, age at first pregnancy, parity and percentage of rapid cycling (Table 1).

Information regarding the lifetime use of mood stabilizers, antidepressants, antipsychotics and benzodiazepines was available for all 436 women. Lifetime mood stabilizer exposure was 87.2% (n=380) in our study population, with lithium being the most prescribed mood stabilizer. The majority of women (n=259) were also treated with

antipsychotics (59.4%) at some point during their mood disorder, and to a lower extent with antidepressants (n=186, 42.7%). Benzodiazepines were prescribed to 252 of the 436 women (57.8%) as a pharmacological treatment during mood episodes.

Information on the use of lithium during pregnancy could be extracted for 462 pregnancies in 272 women with a diagnosis of bipolar I disorder before conception. In total, 18.8% of these pregnancies (87/462) were supported by lithium prophylaxis.

TABLE 1. Demographic and clinical characteristics

	No episode		At least one episode during pregnancy or postpartum		Test
	Mean/n	SD/%	Mean/n	SD/%	
Women with BDI diagnosis	195	44.7	241	55.3	
Pregnancies	571	62.1	348	37.9	
Demographic characteristics					
Educational level†					$Chi^2(1)=0.469$; p=0.493
Lower and intermediate education	106	60.9	130	57.5	
Higher education	68	39.1	96	42.5	
Clinical characteristics related to fertility					
Age at first pregnancy (years)†	27.0	4.9	28.0	4.6	T(381)=-.684; p=0.494
Pregnancy before illness onset	87	53.7	105	48.8	$Chi^2(1)=0.875$; p=0.349
Number of childbirths	1.8	1.0	1.8	0.9	T(434)=0.004; p=0.997
Clinical characteristics related to disorder					
Age at onset of illness† (years)	29.2	11.4	25.4	7.3	T(400)=4.172; p<0.001
Number of total bipolar episodes (median: IQR)					
Manic†	3	1.5-5	3	2-6	Z=2.290; p=0.022
Depressive†	4	2-7	4	2-8	Z=0.335; p=0.738
Any†	7	4-13.25	8	5-16	Z=2.070; p=0.038
Rapid cycling†	35	20.5	48	21.9	$Chi^2(1)=0.121$; p=0.728
Family history					
Bipolar disorder†	54	32.7	95	44.8	$Chi^2(1)=5.668$; p=0.017
Depressive disorder†	99	59.6	114	53.8	$Chi^2(1)=1.320$; p=0.254
Psychotic disorder†	35	21.5	57	26.5	$Chi^2(1)=1.278$; p=0.258
Substance abuse†	41	25.2	60	28.0	$Chi^2(1)=0.392$; p=0.531

† Missings: Educational level n=36; Age of onset n=34; Duration of illness n=34; Age at first pregnancy n=53; Number of manic episodes n=73; Number of depressive episodes n=154; Any episode n=163; Rapid cycling n=46; Family history bipolar n=59; Family history depressive n=58; Family history psychotic n=58; Family history substance abuse n=59.

Recurrence risk during all reproductive events

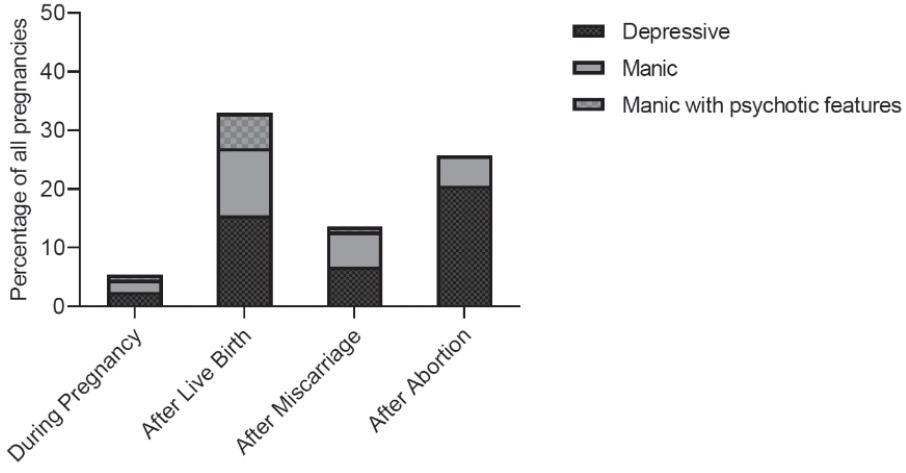
As shown in Figure 1, the crude risk of an episode during pregnancy was 5.2% (48/919 pregnancies; adjusted risk: 5.6%). The risk of an episode after live birth was 34.4% (251/730 live births). When pregnancy resulted in a miscarriage, the episode risk was

15.2% (16/105 miscarriages), while the risk of an episode after induced abortion was 27.8% (10/36 abortions). The risk of a bipolar episode was significantly higher after a live birth compared to miscarriage (Chi2(1)=18.16; p<0.001) but not compared to induced abortion (Chi2(1)=0.34; p=0.439). For 23 women who experienced a perinatal episode, information on the onset was missing.

Phenomenology of episodes

The majority of the bipolar episodes had a manic phenomenology (with or without prominent psychotic features), which applied to both episodes during pregnancy (54.2%; 26/48 episodes), as well as to episodes after delivery (51.6%; 143/277 episodes) (Figure 1). The other episodes were depressive (45.8% (22/48) during pregnancy and 48.4% (134/277) after delivery). Episodes with manic phenomenology were not significantly more present related to live birth than related to miscarriage or induced abortion (FET Chi2(2)=4.131; p=0.122).

FIGURE 1. Phenomenology of episodes during the reproductive period



Overall episode risk and timing of onset

The crude overall risk of a perinatal episode (both during pregnancy and postpartum) was 37.9% (348/919 pregnancies; adjusted risk: 39.9%). The crude risk of an episode during pregnancy was 5.2% (48/919 pregnancies; adjusted risk: 5.6%), while the crude risk was 30.1% (277/919; adjusted risk: 31.6%) postpartum (taking into account all pregnancy outcomes). Most episodes started within 4 weeks postpartum (crude

risk 20.3%, 187/919 pregnancies), while episodes between 4 weeks and 6 months postpartum were less common (crude risk 9.8%, 90/919 pregnancies).

Bipolar episodes during and after subsequent pregnancies

Of the 436 women with a first pregnancy, 69.0% did have a subsequent pregnancy (301/436). If the first perinatal period was uneventful, the risk of a perinatal bipolar episode decreased to 20.5% (41/200) with a subsequent pregnancy. If women had an episode during or after their first pregnancy, the risk of an episode with a subsequent pregnancy increased to 61.4% (62/101) (cOR=6.17; 95%CI: 3.64-10.45; p<0.001). This pattern is further amplified over subsequent pregnancies and shown in Figure 2. Overall, the risk of bipolar episodes in subsequent pregnancies increased after a previous perinatal episode (cOR=4.9; 95%CI: 3.3-7.4; p<0.001). Additionally, we found the onset of a previous perinatal episode to be associated with the onset of a subsequent episode. Thus, antepartum episodes increased the risk for subsequent antepartum episodes (Chi2(1)=17.6; p<0.001) and to a lesser extent, postpartum episodes increased the risk for subsequent postpartum episodes (Chi2(1)=3.0; p=0.078). Of all the women with an uneventful first perinatal period, 78.7% had another pregnancy. Women who reported having suffered from an episode during the first perinatal period were significantly less likely to have a second pregnancy as only 55.5% did have a subsequent pregnancy (cOR=0.34; 95%CI: 0.22-0.51; p<0.001).

Efficacy of lithium prophylaxis on recurrence risk during the perinatal period

Information on the use of lithium during pregnancy could be extracted for 462 pregnancies in 272 women with a diagnosis of bipolar I disorder before conception. In total, 18.8% of these pregnancies (87/462) were supported by lithium prophylaxis. Prophylactic lithium use during pregnancy was associated with a lower risk of a perinatal episode. The episode risk was 26.4% (23/87) in lithium supported pregnancies compared to 46.7% (175/375) in unsupported pregnancies (cOR=0.41; 95%CI 0.25-0.69; p=0.001). This association remained after adjusting for age of onset, total number of episodes, bipolar family history, and multiple pregnancies within unique women (aOR=0.47; 95%CI: 0.26-0.83; p=0.009). We also distinguished between the association of lithium prophylaxis on episodes during pregnancy and after delivery. For all the pregnancies in which information about the use of lithium and the timing of onset was available (n=449), 2.3% (2/86) of

FIGURE 2. Episode risk with subsequent pregnancies

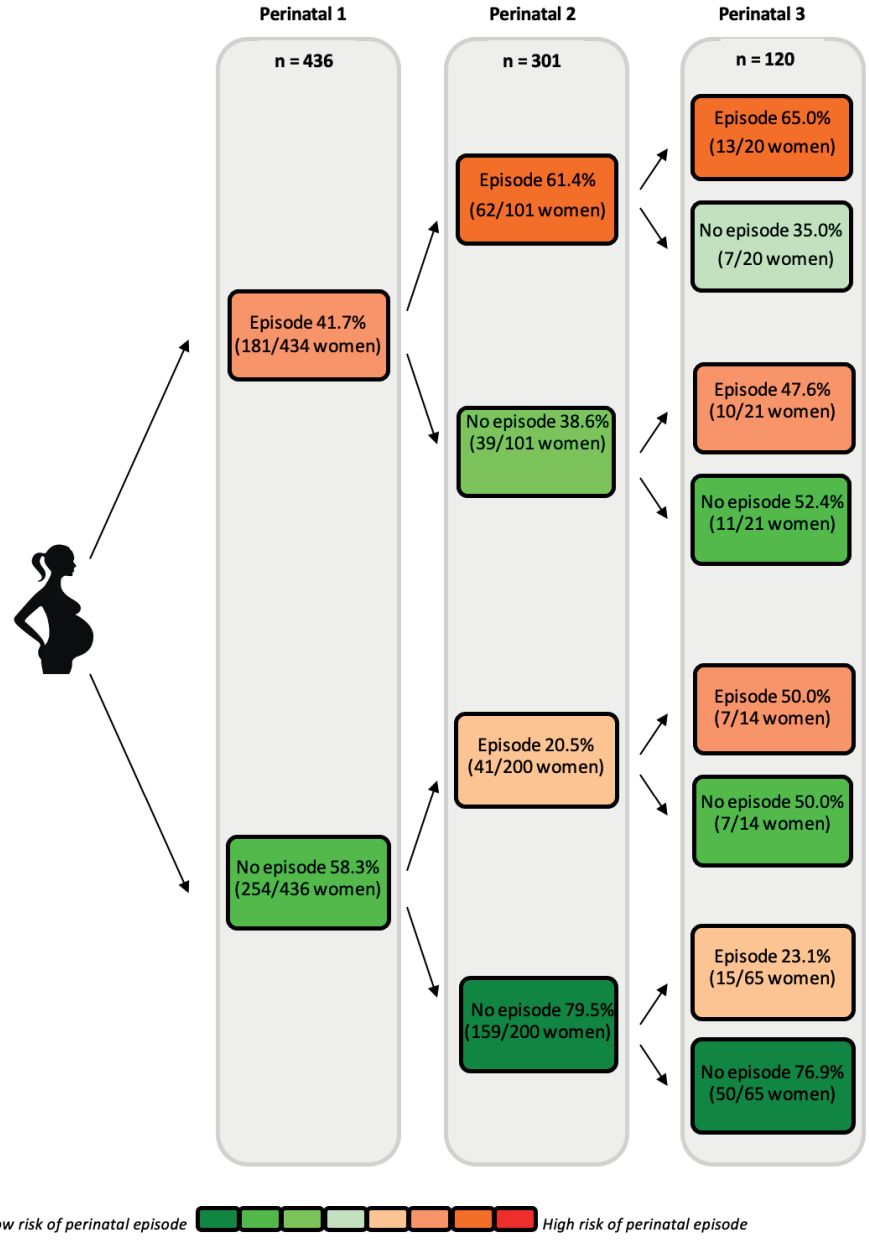


Figure 2 describes the risk of any bipolar episode during the first perinatal period and subsequent perinatal periods.
Perinatal 1 = first perinatal period, perinatal 2 = second perinatal period, perinatal 3 = third perinatal period.

women with lithium use during pregnancy experienced an episode during pregnancy, compared to 8.0% (29/363) of women without lithium use (cOR=0.27; 95%CI:0.06-1.17; p=0.081). Similarly, 23.8% (20/84) of women with lithium use during pregnancy and postpartum experienced a postpartum episode, compared to 40.1% (134/334) of women without lithium use (cOR=0.47; 95%CI: 0.27-0.81; p=0.006). Women who had experienced an episode during pregnancy were censored in the analysis regarding postpartum recurrence risk.

DISCUSSION

In this large retrospective cohort study, we found that women with bipolar disorder had a particularly high risk for developing an episode during the postpartum period (30.1% of pregnancies), which was six times the risk during pregnancy (5.2% of pregnancies). Especially, the early postpartum period (< 4 weeks) was a high-risk period for recurrence (20.3% of pregnancies). The risk for postpartum recurrence is consistent with previously published studies (6) but the recurrence risk of 5.2% during pregnancy is rather low. Previous studies reported both low recurrence rates (5, 23, 24) as well as quite high rates (25-27) during pregnancy among women with bipolar I disorder (range 4-73%). The higher risk in these latter studies could be a consequence of prospective study design (25-27), which is more sensitive to detecting less severe episodes compared to retrospective studies. In addition, some of these studies included mostly women from a tertiary referral hospital specializing in perinatal psychiatry (25). These women likely had a more severe form of bipolar I disorder in comparison with the women in our study. Besides, some studies included women with bipolar II disorder in their study population (5, 23, 25, 26), which has been found to be a predictor for an increased risk of recurrence during pregnancy when compared to women with bipolar I disorder (risk ratio 1.5, p<0.002) (25).

This study shows that the risk of a bipolar episode is highest after a live birth (34.4%) and lower after miscarriage (15.2%) and induced abortion (27.8%). These risks are comp arable to the risks reported in a retrospective cohort study by Di Florio and colleagues, based on data gathered by interview and case-notes review (12). In addition, a Danish population-based cohort study showed that risk of readmission is similar before and after first-time first-trimester abortion, contrasting with a marked increase in risk of readmission postpartum (28). Our results emphasize the importance of mental health care during reproductive events in this population and indicate that care should not solely focus on childbirth, but on all pregnancy outcomes. The end of pregnancy, including live childbirth, induced abortion or miscarriage, is evidently a very strong trigger for bipolar episodes

and this likely has a biological base. The postpartum period is specifically characterized by sleep loss and sleep loss could be a trigger for the recurrence of mood episodes (29). Interestingly though, in our study we also found induced abortion and miscarriage to be associated with a high recurrence risk even though induced abortion and miscarriage are not specifically characterized by sleep loss. This suggests that sleep loss by itself cannot fully explain the risk of recurrence of mood episodes. The risk of post-pregnancy episodes might be largely explained by the major physiological changes that occur with the transition from the state of pregnancy to a non-pregnant condition. After delivery or pregnancy termination the level of sex hormones changes, with rapid falls of estrogen postpartum (30). This may cause a change in mood regulation (31). Additionally, the immune system is triggered after live childbirth or termination which results in an overreaction, also called the 'rebound' phenomenon (32-39). In some women this results in exacerbation of pre-existing autoimmune disease or a first manifestation of an episode of autoimmune disease. The postpartum immune activation is postulated to produce the clinical manifestations of physical auto-immune diseases as rheumatoid arthritis, multiple sclerosis and thyroiditis and may play a central role in the pathogenesis of bipolar disorder (40). In addition to physical changes, psychological changes during the perinatal period may also play a role as a trigger for bipolar episodes. A systematic review found an increased risk of the onset of bipolar disorder within 6 months of stressful life events (41) and a more recently published meta-analysis found that patients experience more life events prior to bipolar episodes than during euthymic periods (42). Another large case-control study supported this association between life events and bipolar episodes, as it found that stressful life events, as suicide of a first-degree relative, but also divorce, marriage, disability or unemployment were associated with a first hospitalization for a manic episode (43). Pregnancy, childbirth, miscarriage and induced abortion are all considered major life events.

Previous reports from the National Institute of Mental Health (NIMH), revealed that depression is the predominant affect of bipolar I disorder (44, 45). Patients with these conditions experience depressive symptoms much more frequent than manic or hypomanic symptoms, with a ratio of 3:1 (44, 45). Interestingly, in our study 51.4% of episodes during the perinatal period were of manic phenomenology (with or without prominent psychotic features), suggesting that manic episodes are more frequent during pregnancy or after childbirth than during other periods in life. In a retrospective cohort study by di Florio et al. information was gathered by semi-structured interview, questionnaires and case-note review from 887 women with bipolar disorder. The risk of perinatal recurrence was

analyzed in women with bipolar I disorder and similar results to the current study were found (46). Of all women having an episode in the first perinatal period in that study, half of the women had an episode with manic phenomenology (46). A similar distribution of manic versus depressive bipolar episodes in the perinatal period was found in a meta-analysis of Wesseloo and colleague (6). Our results emphasize the distinctive character of perinatal bipolar episodes.

Women who reported having suffered from an episode during the first perinatal period were significantly less likely to have a second pregnancy (55.5%), compared to 78.7% women with an uneventful first perinatal period. This is in line with a retrospective cohort study of Blackmore et al. in which clinical diagnostic interviews and medical case notes reviews were used to estimate that around half of those with postpartum psychosis in their first pregnancy had a subsequent pregnancy (47). Evidently, this may also influence the association between primiparity and perinatal bipolar episodes which has been described in previous studies (48). In our study, we showed that women who reported having experienced an episode related to their first perinatal period have an increased risk of an episode in a subsequent pregnancy (61.4%). In contrast, the risk was lower (20.5%), but not absent, after a first uneventful perinatal period. This pattern was further amplified over subsequent pregnancies. Similar results have been found by di Florio et al. (46), who described that rates were significantly higher in women with previous perinatal psychiatric history (55%), but women without such episodes were still at risk of developing perinatal illness (31%). These findings are particularly important for clinicians and patients, because these risks influence family planning and prevention strategies during the perinatal period.

A meta-analysis (6) reported previously that lithium prophylaxis during pregnancy is important for maintaining mood stability during pregnancy and after delivery in women with bipolar I disorder. The association between lithium prophylaxis and lower episode risk found in this study confirms these findings but should be interpreted with caution due to several methodological limitations. Moreover, in general, the benefits of the protective effect of lithium prophylaxis during pregnancy should be weighed against the risk of congenital malformations (13, 14) and an increased risk of miscarriage (49). Prophylactic medication immediately after delivery is recommended in clinical practice, given the high recurrence risk postpartum. Ideally, women with bipolar I disorder of reproductive age have access to specialized women's mental health care facilities in order to weigh both risk and benefits of medication, with a reproductive psychiatrist.

Methodological considerations

A few limitations need to be considered when interpreting the results of this study. Data was collected retrospectively at one point in time, with information on childbearing history and related mood episodes being assessed through a self-report questionnaire. This means that data on this matter may have been subject to recall bias. It would have been preferable if perinatal episodes were confirmed by parallel interview of partners or family members. We do, however, not expect that recall bias had a major impact on our results as it has been shown that perinatal illness is a remarkable event for mothers, and therefore its severity and duration seem to be recalled accurately (50). Second, assumptions on lithium use during pregnancy may have been inaccurate due to the fact that it was assessed through self-report, with the duration of lithium use not always being described as precisely as hoped for. Additionally, we did not have information on dosing and blood levels of lithium during pregnancy. However, in this study two different assessments of lithium use were combined to determine the use of current and past medication as accurate as possible and restrain misclassification (21). Information on the use of other mood stabilizing medication during pregnancy was unfortunately collected in less detail and therefore we could not investigate the association with other medication and episode risk. To our knowledge, there is no single other study that has been able to provide this information. Third, since lithium may have been predominantly prescribed in women with more severe previous bipolar episodes, confounding by indication is possible. This would most likely have led to an underestimation of the protective effect of lithium. Another limitation is that selection bias toward those willing to participate in a study is always possible (51). Together with the finding that most women in the sample are Caucasian, this may affect the generalizability of our results to all women with bipolar I disorder in the childbearing age, even though there was a large variety in treatment settings and great variety in socioeconomic status in our sample. Our data did not allow us to compare perinatal recurrence risks to recurrence risk in a similar period of time in women of reproductive age who are not pregnant or postpartum. Interestingly, inpatient admission risks during pregnancy have been studied in a population based study, and the authors found a decreased risk for inpatient admission during pregnancy compared to a year after delivery (RR 0.53, 95%CI 0.-0.7) (52), but this study investigated all new inpatient admissions, not specifically bipolar episodes.

CONCLUSIONS

This study shows that women with bipolar I disorder are at high risk of a bipolar episode after childbirth, miscarriage and induced abortion, but not during pregnancy. Consistent with previous studies, the risk is especially high in the first four weeks postpartum. This pattern is known from autoimmune disorders such as autoimmune thyroiditis, rheumatoid arthritis and multiple sclerosis. Future prospective studies should focus on the underlying biology of this remarkable flair pattern. After a first perinatal episode, the risk of a recurrent episode increases with subsequent pregnancies. Our data supports the need for preventive strategies immediately after delivery, given the high recurrence risk within 4 weeks postpartum. Women with bipolar I disorder should be informed about all risks associated with pregnancy, preferably before conception. Together with their treating physician women should weigh the benefits and risks of mood stabilizing therapy during pregnancy and develop an individualized plan to prevent episodes following delivery. Future studies are needed on the effect of all mood stabilizing medication during pregnancy on the recurrence risk in the perinatal period.

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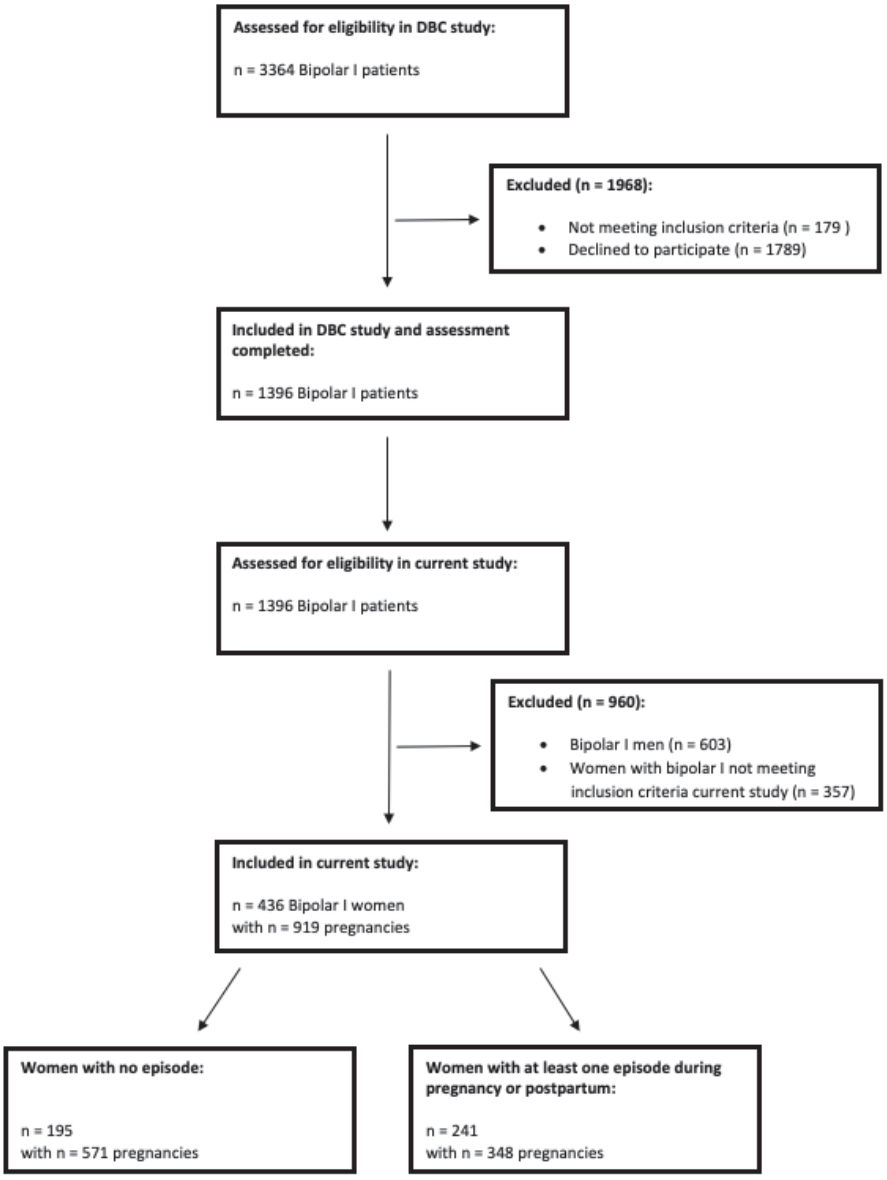
SUPPLEMENTARY FIGURE 1. CONSORT flow diagram



Chapter 6

Lithium use during pregnancy and the risk of miscarriage

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ABSTRACT

Recent studies have provided new data on the teratogenicity of lithium. Less is known about the risk of miscarriage after lithium use during pregnancy. The aim of this study was to investigate the association between lithium use during pregnancy and miscarriage. Participants were women with bipolar I disorder and one or more pregnancies, of which information on medication use and pregnancy outcome was available (n = 443). The unadjusted odds ratios for miscarriage after lithium use during pregnancy was calculated. Multilevel logistic regression was used to calculate the odds ratio, adjusted for the age at conception and the clustering of pregnancies per woman. Miscarriages occurred in 20.8% of the lithium-exposed pregnancies (16/77), compared with 10.9% of the unexposed pregnancies (40/366) (OR = 2.14; 95% CI: 1.13–4.06). The adjusted odds ratio of miscarriage after lithium use during pregnancy was 2.94 (95% CI: 1.39–6.22). Lithium use during pregnancy may increase the risk of miscarriage.

INTRODUCTION

Women with bipolar disorder have a high risk of recurrent episodes in the perinatal period (1). Treatment with mood-stabilizing medication during pregnancy might be necessary to reduce this risk, but this warrants special attention, as these medications may be potentially harmful to the developing fetus. Valproate and carbamazepine are highly teratogenic. Lithium has a well-established evidence base in the prevention of episodes in bipolar disorder (2) and is often prescribed during pregnancy, especially because, in 2012, a meta-analysis concluded that there was not enough evidence to say that lithium is teratogenic (3). However, last year, the two largest studies to date were published, and they both showed the teratogenicity of lithium during the first trimester of pregnancy (4, 5). The first study compared 663 lithium-exposed pregnancies with 1945 lamotrigine-exposed pregnancies, and found a dose-dependent association between first trimester lithium exposure and cardiac malformations (4). The second study reported an increased risk of major malformations (including cardiac malformations) in 727 first trimester lithium-exposed pregnancies, compared with 21,397 unexposed pregnancies in mothers with a mood disorder (OR = 1.62; 95% CI: 1.12–2.33) (5). A few years earlier, a smaller study had found a similar, non-significant effect (6). Interestingly, this study by Diav-Citrin et al. was the first to show an increased risk of miscarriage after first trimester lithium use (OR = 1.94; 95% CI: 1.08–3.48) (6). In this prospective cohort study, 183 lithium-exposed pregnancies of women who had contacted the Israeli Teratology Information Service were followed up and compared with 72 disease-matched and 748 nonteratogenic-exposed pregnancies. Pregnancy outcome was assessed by maternal interview. The rate of miscarriage was 16.4% in lithium-exposed pregnancies, versus 8.3% in the bipolar disorder comparison group, and 5.7% in nonteratogenic-exposed pregnancies. In contrast, another prospective cohort study by Jacobson et al. did not find a difference in the rate of miscarriage between lithium-exposed and control pregnancies (7). In this study, women were also recruited for study participation if they had contacted a teratogen information center, and pregnancy outcome was assessed by telephone interview. The rate of miscarriage was 9% in the lithium-exposed group (n = 138), versus 8% in a control group of women who used nonteratogenic drugs during pregnancy (n = 148). Other studies did not report on miscarriages, because they were designed to investigate live births only (8). Information on the risk of miscarriage associated with lithium use during pregnancy is relevant for both clinicians and women with bipolar disorder of childbearing age. Based on the magnitude of this risk, further decisions regarding family planning and prevention strategies can be made. In this study, we present new information on miscarriages after lithium use.

EXPERIMENTAL SECTION

Study design and participants

This retrospective cohort study was part of the Dutch Bipolar Cohort (DBC) study, a collaboration between the University of California in Los Angeles and several Dutch health care institutes (University Medical Center Utrecht, Geestelijke gezondheidszorg (GGZ) Altrecht, GGZ inGeest, University Medical Center Groningen, Delta, Dimence, Parnassia (PsyQ) and Reinier van Arkel) (9). Participants in the DBC study were patients with bipolar disorder, aged 18 years and older, between June 2011 and July 2015. The objective of the DBC study was to investigate the genetic and phenotypic information of the participants. The study was approved by the accredited Dutch Medical Ethical Trial Committee (METC 10-285) and all participants provided written informed consent (9). In the current study, we selected a subcohort of women who had experienced one or more pregnancies, with a diagnosis of bipolar I disorder before pregnancy, and for which detailed data on lithium use and pregnancy outcomes were available. Analyses were performed on the total number of pregnancies that ended in live birth or miscarriage.

Data collection and procedures

For all patients, bipolar I disorder diagnosis was established using the Structured Clinical Interview (SCID) for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), conducted by at least one well-trained independent rater (9). In a self-report Questionnaire on Postpartum Mood Disorders, developed by one of the authors (V.B.), women were asked about the dates of the abortions, miscarriages, and births of their children. All participants were asked to complete a questionnaire, in which they were asked for detailed information on their current and lifetime medication use. In addition, they filled in a lithium satisfaction questionnaire, with specific questions on both their current and past use of lithium. Both questionnaires were combined to assess their current and past lithium use as accurately as possible and to restrain misclassification.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (version 24.0, IBM Corp., Armonk, NY, USA). In order to investigate the association between lithium use during pregnancy and miscarriage, the odds of miscarriage were determined for pregnancies with and without lithium use. For our primary analysis,

the unadjusted odds ratio for miscarriage after lithium use was calculated using a logistic regression model. Since an underlying maternal medical condition or genetic predisposition could cause multiple miscarriages within the same woman, this is a potential source of bias. In a sensitivity analysis, we adjusted for the occurrence of multiple miscarriages within one woman by means of a multilevel logistic regression analysis taking the clustering of pregnancies per woman into account. A generalized linear mixed model was defined with age at conception as a covariate in order to calculate the adjusted odds ratio. This generalized linear mixed model analysis was performed on a subgroup of pregnancies without comorbid lifetime valproate and carbamazepine use. Even though these medications are generally not prescribed during pregnancy in the Netherlands, they are teratogenic, and therefore we wanted to exclude any influence these medications might have had on the risk of miscarriage. Odds ratios were reported with their corresponding 95% confidence intervals. A two-sided p-value of 0.05 was considered to be statistically significant.

RESULTS

In Table 1, we present the characteristics of our study sample. We analyzed the data of all the pregnancies of the women in the DBC study with a diagnosis of bipolar I disorder before pregnancy (n = 509), for which detailed data on lithium exposure and pregnancy outcomes were available (n = 443). Of these 443 pregnancies in 241 women, 56 ended in a miscarriage (12.6%; 56/443). The remaining pregnancies ended in a live birth (87.4%; 387/443). Lithium exposure varied over successive pregnancies. In total, 77 pregnancies were exposed to lithium (17.4%; 77/443) and 366 pregnancies were unexposed to lithium (82.6%; 366/443). Lifetime valproate or carbamazepine use was present in 26% of the lithium-exposed pregnancies and in 21% of the pregnancies not exposed to lithium. Miscarriages occurred in 20.8% of the lithium-exposed pregnancies (16/77), compared with 10.9% of the unexposed pregnancies (40/366), (OR = 2.14; 95% CI: 1.13–4.06, p = 0.018). After adjusting for the age at conception and the clustering of pregnancies per woman, the odds ratio of miscarriage after lithium use during pregnancy was 2.94 (95% CI: 1.39–6.22, $p < 0.005$).

TABLE 1. Characteristics of study sample

	Total	Lithium-exposed	Unexposed
N pregnancies	443 in 241 women	77 in 50 women	366 in 202 women
N miscarriages	56 in 41 women	16 in 11 women	40 in 30 women
Age at conception, Mean (SD)	30.7 (4.9)	33.2 (4.6)	30.1 (4.9)
Age at onset bipolar disorder, Mean (SD)	21.8 (6.3)	21.9 (5.1)	21.7 (6.5)
Lifetime valproate or carbamazepine use n (%)	97 (21.8)	20 (26.0)	77 (21.0)

DISCUSSION

In the general population, miscarriage can be expected in 10–15% of pregnancies (10), which is similar to the rate of occurrence of miscarriage in our group of women with bipolar I disorder without lithium exposure. We found the rate of miscarriage to be increased in lithium-exposed pregnancies. This is consistent with data from the study by Diav-Citrin et al., who also reported the rate of miscarriage to be twice as high in lithium-exposed pregnancies (n = 183) when compared with disease-matched unexposed (n = 72) (OR = 1.94; 95% CI: 1.08–3.48) (6). When we add the results of the current study to the previously published literature, we can conclude that two out of the three studies show an increased risk of miscarriage in lithium-exposed pregnancies (6, 7). This information warrants attention from clinicians treating women with bipolar I disorder of childbearing age. The risks associated with lithium use should be weighed against the risks of maternal recurrence. Maternal mood stability is also crucial for the wellbeing of mother and child, and the prevention of recurrence is especially important in women with a history of severe mood episodes. Lithium use during pregnancy lowers the risk of recurrence during pregnancy and postpartum for women with bipolar disorder (1, 11), and lithium is less teratogenic than carbamazepine or valproate. Clearly, the risks and benefits of lithium use during pregnancy should always be weighed on an individual basis.

The association between lithium use during pregnancy and miscarriage in this study remained present after adjusting for the age at conception, the clustering of pregnancies per woman, and their lifetime use of valproate and carbamazepine. Importantly, the age at onset (an important indicator of the severity of illness in women with bipolar disorder) was similar in the lithium-exposed and unexposed groups, suggesting that the severity of illness does not explain the increase in miscarriages in the lithium-exposed group. Our results might, therefore, suggest a specific effect of lithium use during pregnancy.

The mechanism of the association between lithium use during pregnancy and miscarriage has not yet been investigated. We would like to propose a hypothetical mechanism of this association. Lithium use has been associated with overt and subclinical hypothyroidism in several studies (12) and (sub)clinical hypothyroidism has been associated with pregnancy loss (13). Thyroid function might, therefore, have a mediating role in the association between lithium use during pregnancy and miscarriage. Unfortunately, thyroid levels during pregnancy were not available in this study. Further research is needed to study this hypothesis.

A few limitations need to be considered. In this study, data on pregnancy outcome and medication use were collected retrospectively by questionnaire and, therefore, recall bias might be present. However, a miscarriage is a major life event, and is likely to be remembered and reported by all women. Due to the fact that lithium use was assessed by questionnaire, we did not have information on lithium level and dosage during pregnancy and were not able to investigate a dose–response relationship. Additionally, information on maternal medical conditions, body mass index, smoking, alcohol and substance use at the time of miscarriage was not available and, therefore, it was not possible to investigate the potential mediating, moderating or confounding influence of these factors on our results.

CONCLUSIONS

Our findings suggest that, in addition or related to its teratogenic effect, lithium may increase the risk of miscarriage. These findings underscore the need for caution, but there is no imminent need to change clinical guidelines for lithium use during pregnancy, as current guidelines already warn against prescribing lithium during the first trimester of pregnancy. The possible risks associated with lithium use during pregnancy, such as the risk of miscarriage and congenital malformations, need to be carefully weighed against the risk of maternal recurrence. The current study provides important information that should be discussed with all women with bipolar disorder of childbearing age.

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Part III

Neurobiology of severe postpartum mood disorders

Chapter 7

T-cell defects and postpartum depression

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ABSTRACT

Background: Most studies of immune dysregulation in perinatal mood and anxiety disorders have focused on peripheral cytokines, but literature from non-perinatal mood disorders also implicates T-cell defects. We sought to characterize proportions of T-cell subtypes in women with postpartum depression.

Materials and methods: We enrolled 21 women with postpartum depression (PPD), 39 healthy postpartum controls, and 114 healthy non-postpartum women. Blood was collected in sodium-heparin EDTA tubes and was analyzed using flow cytometry. We conducted statistical tests including linear regression analysis that were aimed at determining differences in proportions of T-cell populations among groups.

Results: Mean counts of T-cells (all CD3+ T-cells), T-helper cells, (CD3+CD4+ T-cells), and T-cytotoxic cells (CD3+CD8+ T-cells) were significantly increased in healthy postpartum women compared to healthy non-postpartum controls ($p < 0.001$, $p = 0.007$, and $p = 0.002$, respectively), but not in women with PPD. The increases in healthy postpartum women were driven by increases in T_H1 cells and T regulatory cells, increases that were nonexistent or attenuated in women with postpartum depression. Mean counts of CD4+ T-helper memory cells were also increased in healthy postpartum women ($p = 0.009$), but slightly decreased in women with PPD ($p = 0.066$), when compared to healthy non-postpartum controls.

Conclusions: Our study confirms that the postpartum period in healthy women is a time of enhanced T-cell activity. Women with postpartum depression failed to show physiological enhanced T-cell activity postpartum, and future research is needed to elucidate etiological mechanisms and consequences.

INTRODUCTION

It is now well established that immune system dysregulation plays a role in major depressive disorder, with numerous studies linking peripheral cytokine alterations to depressed mood (1, 2) and others showing that anti-inflammatory treatment can help some depressed patients (those with elevated inflammatory markers at baseline) (3, 4). Because immune dysregulation appears to play a role only for certain subsets of depressed people, it has been a logical progression to investigate the role of the immune system in psychiatric illness during the perinatal period. It is a time of known immune dysregulation and one of the few periods in life when there is an obvious biological trigger (parturition) that can be linked to psychiatric symptoms – specifically, to symptoms of perinatal depression, including the diagnosed depressive disorders that occur in up to 15–20% of women (5), with potentially devastating effects on women and families.

Early research on the physiological immune dysregulation of the peripartum focused on immune suppression during pregnancy, then on a supposed shift away from T-helper type 1 (T_H1) activity and toward T-helper type 2 (T_H2) activity (6). More recent work has focused on a more complex model, with enhancement of innate immune barriers but reduced effectiveness of some elements of adaptive immunity across pregnancy (7-10). In the postpartum, healthy women appear to have a rebound of adaptive immunity, in particular a rebound in T-cell activity, that has been identified in both animal and human literature (11-13). Moreover, research on T-cell activity in depressive and anxiety disorders outside of pregnancy indicates deficiencies of T regulatory cells as well as dysregulation of T_H17 cells (14, 15). T regulatory cells have also been shown to decrease in response to acute stress (16).

In light of this work on immune dysregulation in healthy pregnancy and in mood and anxiety disorders, numerous researchers have attempted to link immune dysfunction to both antenatal and postpartum depression, with mixed success. Most of these studies have focused on a small number of peripheral cytokines as markers of immune function (17). A few recent studies have measured large numbers of peripheral markers and attempted to come up with summary variables (18, 19) – an improvement in technique that has nevertheless not yet yielded a useful measurement tool. In addition, many studies in the perinatal period have conflated antenatal and postpartum depression, therefore making it diffcult to draw conclusions about new-onset depression in the postpartum, a type of illness that may carry its own unique genetic signature representing distinct biological pathways (20).

Despite the relatively large number of studies – including our own (21) – that have focused on peripheral cytokines, this may not be the ideal way to measure the relationship between immune function and psychopathology. It is unclear whether there is a correlation between levels of cytokines in the periphery and those in the central nervous system. One recent study, in perinatal depression, found no correlation between cytokines in the periphery and those measured in cerebrospinal fluid (22). Relatively few studies, by contrast, have examined either antenatal or postpartum depression in relationship to shifts among classes of immune cells. One early study found a negative association between T-cell count and dysphoria, but did not examine shifts among different types of cells within the T-cell compartment (23). Examining such shifts may give us important information about the biological mechanisms of perinatal depression, and may also yield novel therapeutic targets.

When first released from the thymus, T-cells are "naive"; upon presentation with antigen, they proliferate and differentiate into effector cells. Once the antigen has been cleared, 95% of the effector cells die, and the remainder take up long-term residence as memory cells (24). The effector subgroups are identifiable by the panel of cytokines they secrete. Cytotoxic T-cells are characterized by the surface marker CD8+, and directly attack damaged cells. Helper T-cells (CD4+) coordinate the immune response, and are further subdivided into several groups. T-helper 1 cells (T_H1) and T-helper 17 cells (T_H17) are involved in the activation of macrophages and secrete IFN-γ, among others, and IL-17, respectively. T-helper 2 cells (T_H2) cells secrete IL-4 and IL-5, among others, and are involved in the activation of B cells. The regulator subgroup is formed by the natural T regulatory cells, which dampen the activity of T_H1, T_H2, and T_H17 cells (15, 25-27). Our own group and one other have examined shifts among T-cell classes in postpartum psychosis (PPP), another devastating but rare postpartum psychiatric illness (11, 28). Our study showed that women with PPP failed to show the T-cell elevation characteristic of healthy postpartum women. Kumar's group found that women with PPP failed to show an elevation in naive T-helper cells that was characteristic of healthy postpartum women, but also showed higher levels of both cytotoxic T-cells and T regulatory cells. In addition, T-cell dysregulation has also been shown in numerous studies of mood disorders outside the perinatal period (14, 29, 30).

Given this paucity of information, we therefore sought to expand the available evidence concerning immune cells and particularly T-cell populations in postpartum depression by comparing women with severe PPD (with postpartum onset only) to both healthy postpartum controls and healthy women who were neither pregnant nor postpartum.

MATERIALS AND METHODS

Participants

This study protocol was approved by the institutional review board of the Erasmus Medical Center, Rotterdam (original protocol number MEC-2005226). After receiving a complete description of the study, all subjects provided written informed consent. Twenty-one (n = 21) women with an acute postpartum onset of severe depression (PPD) were recruited from the Mother-Baby Inpatient Unit of the Department of Psychiatry of the Erasmus University Medical Center in Rotterdam, the Netherlands, between April 2007 and February 2012. All subjects were diagnosed according to DSM-IV-TR using the Structural Clinical Interview for DSM-IV (SCID – 1/P research version). Symptoms were additionally tracked using the Edinburgh Postnatal Depression Scale (EPDS). Those subjects diagnosed with PPD via the SCID had a mean EPDS score of 18 (SEM 1.3). The relevant DSM-IV-TR diagnoses included both major depressive disorder alone (n = 13) and major depressive disorder comorbid with anxiety disorders (n = 8). Recent research in postpartum depression has indicated that there are distinct clinical phenotypes (31), most of which include a significant anxiety component, and we therefore deemed it important to include both of these populations.

All women had an onset of symptoms within six months following delivery, and 14 had an onset within 4 weeks postpartum (67%). Those with a history of bipolar disorder, non-puerperal psychotic episodes, substance abuse, or psychiatric symptoms during pregnancy were excluded from the study. The median onset of symptoms occurred at day 7 postpartum (IQR 0.5–40.0). Mean time of blood collection occurred at day 61 postpartum. Of these 21 subjects, at the time of blood collection, nine were using benzodiazepines (median 2 days), two were using antipsychotics (seven and nine days), and one was using antidepressant medication (one day). Women admitted to our ward with depressive symptoms have an antidepressant-free observation period, which enabled us to enroll the majority of subjects before the start of antidepressant treatment. Eleven subjects had a previous history of non-puerperal depressive or anxiety symptoms. Physical examination and routine laboratory screening were performed at the time of study enrollment to confirm the absence of infection or other hematological abnormalities. All subjects were in an acute disease state at the moment of blood collection.

The healthy postpartum control group (HPC) consisted of 39 age-matched healthy postpartum women recruited between January 2009 and March 2012 (Erasmus MC, Rotterdam), with an EPDS score $\leq$10 (mean 3.8; SEM 0.4) at the time of postpartum blood sampling at mean 31 days postpartum.

One hundred twenty-four age-matched healthy non-postpartum women were included as an additional control group (HC). Inclusion criteria for both healthy postpartum and healthy non-postpartum women included the absence of any medical, neurologic, psychiatric, or autoimmune disorders, as well as having no current or recent clinical evidence of acute infection. All blood draws, from cases and controls, occurred in the morning, allowing us to minimize diurnal variations in immune factors.

Blood collection and preparation

Blood was collected in sodium-heparin tubes (30 ml) in the morning and transported to the laboratory at room temperature. Peripheral blood mononuclear cell (PBMC) suspensions were isolated using low-density gradient centrifugation by Ficoll (GE Healthcare, Uppsala, Sweden) within 8 hours. PBMCs were counted and frozen in medium (RPMI-1640 containing 25 mM Hepes and UltraGlutamine (Lonza, Verviers, Belgium), with the addition of 10% fetal calf serum (Lonza), 10% dimethylsulfoxide (Merck, Hohenbrunn, Germany) and 1% Penicillin/Streptomycin) and stored in liquid nitrogen to enable testing case and control immune cells in the same experiment.

Flow cytometric analysis

PBMCs were defrosted and washed once with medium. Average recovery of cells after thawing was 82% and viability 97%, as determined by Trypan blue staining. Differences between different groups were not observed. Two different staining procedures were used: staining A determined percentages of different types of T-cells, and staining B determined T-helper subsets. (Details of the staining methods are included in Supplemental information.)

All specific staining antibodies used are routinely tested for effectiveness by the manufacturer and titrated for optimal concentrations in our laboratory. Specificity of the staining antibodies was controlled using five isotype controls provided by the manufacturer (BD) and background positivity was negligible (between 0.2% and 1% of the specific staining depending on the isotype control, both in patient samples and controls).

Stained samples were analyzed by 8-color flow cytometry on a FACS Canto II (BD biosciences) and analyzed by FlowJo software (Tree Star, Ashland, OR, USA). Gating strategy for staining B is given in Supplemental Figure 1. T-cell subsets of staining B were expressed as percentages of total lymphocytes, which could reliably be detected as a clear population in forward sideward scatter after the 4-h culture.

Data exploration of flow cytometry data also revealed 10 outlier HC women (> 3 SD). In accord with our statistician we decided to exclude all data of these healthy controls from further analysis including sociodemographic characteristics, leaving an n = 114 in our HC group.

Statistical analysis

Statistical analysis was performed using SPSS version 24.0. Sample characteristics were evaluated using Chi^2 tests or Fisher's exact test (if cell sizes were < 5), and independent samples *t*-tests. Immune cell data were mean and standard error of the mean (SEM). To compare immune cell data between PPD women, HPC women, and HC women, we used separate linear regression analyses (e.g. HC vs HPC and PPD; and HPC vs PPD). Comparisons with HC women were adjusted for body mass index (BMI). Comparisons between HPC and PPD women were adjusted for BMI, postpartum day of blood draw, and educational level. Confounders (e.g. BMI, postpartum day of blood draw, and educational level) were selected based on the existence of a significant associations with both predictor (sample) and outcome variable (immune cell data, see Supplemental Table 1). We report Cohen's delta alongside p-values to represent the size of the difference. Normality of the data was explored visually using histograms and Q-Q plots, and tested statistically using Shapiro-Wilk tests. Normality of the error distribution was checked in the context of the regression analyses. Analyses were performed using untransformed immune cell data.

RESULTS

Sample characteristics

We analyzed 21 PPD subjects, 39 HPC, and 114 HC. There were no differences in age, weight, ethnicity, marital status, gravidity, parity, delivery by Cesarean section, and delivery by vacuum extraction between women with PPD and HPC women (Table 1). Women with PPD had a higher BMI compared to HPC ($p = 0.029$). The HPC women were more likely to have education beyond high school ($p = 0.020$). Blood draw took place later after partus in PPD women than in HPC women ($p < 0.001$). The majority of HPC women were breastfeeding (71.8%), while very few PPD subjects were (4.8%, $p < 0.001$). Demographic characteristics for HC women included only weight and BMI, hence we were unable to compare other demographic characteristics with the HC women.

TABLE 1. General and obstetric characteristics of subjects with first-onset postpartum depression (PPD), healthy postpartum controls (HPC), and healthy non-postpartum controls (HC)

	HC (n=114)		HPC (n=39)		PPD (n=21)		Difference between HPC and PPD
	Mean	SEM	Mean	SEM	Mean	SEM	p
Age (years)	30.25	(0.61)	33.00	(0.67)	32.09	(1.12)	0.492
Weight	67.88	(0.92)	71.55	(1.67)	74.66	(2.81)	0.322
BMI	23.12	(0.27)	23.88	(0.50)	26.97	(0.96)	**0.029**
Blood withdrawal, days postpartum			30.97	(2.84)	61.00	(8.50)	**< 0.001**
			n	%	n	%	
Dutch ethnicity			35/39	89.7%	17/20	85.0%	0.594
Education beyond high school			37/39	94.9%	14/19	73.7%	**0.020**
Married/cohabiting			36/39	92.3%	18/20	90.0%	0.763
Primiparity			24/39	61.5%	16/21	76.2%	0.251
Primigravidity			22/39	56.4%	13/21	61.9%	0.681
Caesarean section			5/39	12.8%	5/21	23.8%	0.276
Vacuum extraction			4/39	10.3%	3/21	14.3%	0.687
Breastfeeding			28/39	71.8%	1/21	4.8%	**< 0.001**
Medication use					12/21	57.1%	

Bold values are statistically significant at the $p < 0.05$ level.

HC = healthy non-postpartum controls, HPC = healthy postpartum controls, PPD = patients with postpartum depression.

Percentages of overall T-cells among peripheral blood mononuclear cells (PBMCs)

Mean counts of T-cells (all CD3+ T-cells), T-helper cells, (CD3+CD4+ T-cells), and T-cytotoxic cells (CD3+CD8+ T-cells) were significantly increased in HPC compared to HC women ($p < 0.001$, $p = 0.007$, and $p = 0.002$, respectively; see Table 2 and Figure 1). For PPD women, this was not the case; the mean count of CD8+ cells fell somewhat below that of HC women, while the mean count for CD4+ cells was intermediate between those of HC and HPC women, with no significant differences in either case. Mean counts of CD4+ T-helper memory cells (measured in staining B) were increased in HPC women compared to HC women, ($p = 0.009$), but somewhat decreased in the PPD women compared to HC women ($p = 0.066$). The mean count of T- helper naive cells (calculated) was increased in PPD women as com- pared to HC ($p = 0.045$), with HPC women's levels in between the other two groups.

TABLE 2. Proportions of T-cell subsets across all three groups

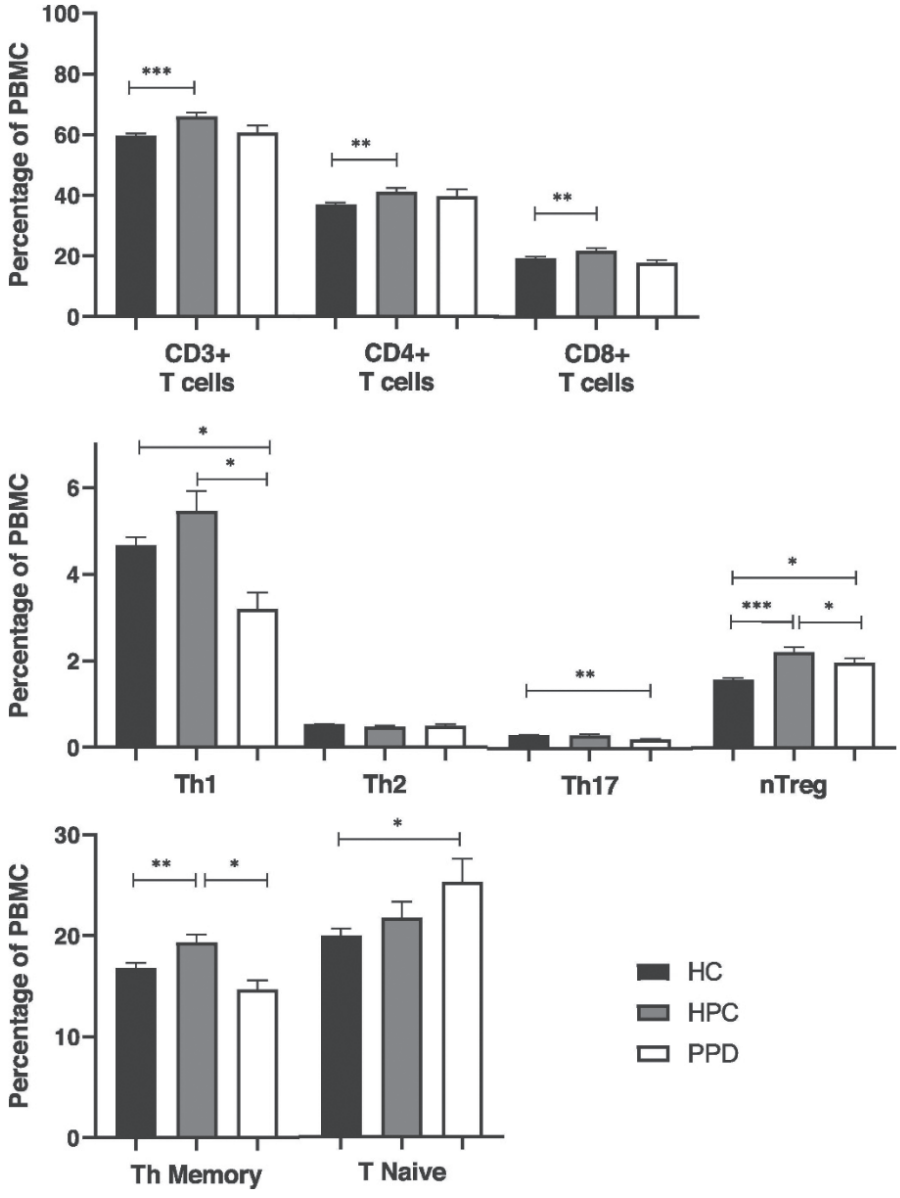
Percentage of Peripheral Blood Mononuclear Cells (PBMCs)	HC (n=114)	HPC (n=39)	PPD (n=21)	HC vs. HPC		HC vs. PPD		HPC vs. PPD	
	M (SEM)	M (SEM)	M (SEM)	p-value[1]	Cohen's *d*	p-value[1]	Cohen's *d*	p-value[2]	Cohen's *d*
CD3+ T-cells	59.74 (0.62)	66.02 (1.35)	60.65 (2.36)	**< 0.001**	0.83	0.458	0.10	0.122	0.56
CD4+ T-cells	36.87 (0.65)	41.02 (1.30)	39.65 (2.20)	**0.007**	0.55	0.431	0.33	0.260	0.15
CD8+ T-cells	19.35 (0.42)	21.68 (1.06)	17.85 (0.91)	**0.002**	0.41	0.994	0.35	0.428	0.70
T_H1	4.67 (0.19)	5.47 (0.46)	3.20 (0.38)	**0.032**	0.33	**0.031**	0.81	0.069	0.99
T_H2	0.53 (0.01)	0.48 (0.03)	0.50 (0.04)	0.082	0.30	0.390	0.19	0.826	0.12
T_H17	0.31 (0.01)	0.31 (0.03)	0.21 (0.02)	0.896	0.01	**0.006**	0.57	0.365	0.55
T reg	1.57 (0.04)	2.21 (0.11)	1.96 (0.11)	**< 0.001**	1.09	**0.030**	0.82	**0.044**	0.42
T_H memory	16.83 (0.48)	19.32 (0.81)	14.68 (0.94)	**0.009**	0.49	0.066	0.46	**0.017**	0.99
T_H naive (calculated)	19.91 (0.69)	21.70 (1.53)	25.22 (2.27)	0.333	0.21	**0.045**	0.60	0.356	0.36

Bold values are statistically significant at the $p < 0.05$ level.

[1] Adjusted for BMI.

[2] Adjusted for BMI, postpartum day of blood draw, and educational level.

FIGURE 1. Percentage of T-cells and T-cell subset populations (as percentage of lymphocytes) in three populations



Postpartum depression (PPD, n = 21, in white); healthy postpartum controls (HPC, n = 39, in gray); and healthy non-postpartum controls (HC, n = 114, in black).

Percentages of T_H1, T_H2, T_H17, and T regulatory cells

We next sought to separate out T-cell subsets by testing in staining B for the capacity of CD4+ cells to produce the characteristic cytokines of T_H1, T_H2, and T_H17 cells, and for the intracellular presence of the transcription factor FOXP3 (characteristic of regulator cells). We saw substantial differences between HC and HPC and between PPD and HPC (Table 2). In HPC women, the rise in CD4+ T-helper cells was due to a rise in T_H1 cells and T regulatory cells ($p = 0.032$ and $p < 0.001$, respectively) compared to HC women. Mean counts of T_H2 and T_H17 cells did not differ between these two groups. In PPD women, by contrast, these rises were nonexistent or attenuated. T_H1 cells were even lower than in HC women ($p = 0.069$ vs. HPC and 0.031 vs. HC), and T regulatory cell counts were intermediate between the other two groups ($p = 0.044$ vs. HPC and 0.030 vs. HC). T_H2 cells again did not differ between groups, but T_H17 cells were somewhat lower in PPD women than in both other groups ($p = 0.365$ vs. HPC and 0.006 vs. HC). While not all differences reached statistical significance, effect sizes in some cases were substantial (see Table 2).

DISCUSSION

Our study clearly confirms that the postpartum period in healthy women is a time of altered immune activity, with increases in T-cells compared to the non-postpartum period. The postpartum increases in T-cells involved both the CD8+ cytotoxic and CD4+ helper T-cells and were seen in both the T-helper naive and memory populations. We also found that both the pro-inflammatory T_H1 and the immune suppressive T regulatory cells were increased. Previous research, though scarce, has also shown that pregnancy and the postpartum condition persistently affect these lymphocyte populations. In the 1990s a Japanese group (32) showed that T regulatory cells were increased in early pregnancy, while the number of T-cytotoxic cells decreased. In late pregnancy, T-helper cell numbers decreased. After delivery, T-helper cells, T-cytotoxic cells, and T-suppressor cells increased for a period of up to half a year. The investigators took these observations as indicating that early pregnancy alterations were related to the tolerance of the fetus, late pregnancy alterations to maintenance of pregnancy, and postpartum alterations to the combat of infections. The postpartum alterations could also explain the increased incidence of some autoimmune disorders postpartum (including multiple sclerosis and autoimmune thyroiditis) (33-35).

Additional literature has supported a pattern of lymphocyte suppression during pregnancy followed by rebound after delivery in T-helper memory cells in particular. Matthiessen and colleagues found that T-helper memory cells decreased substantially during pregnancy and began to rebound early in the postpartum (at 2–7 days), still remaining lower than pre-pregnancy levels (36). Kieffer and colleagues (37) looked much later in the postpartum (6 months) and found significantly higher proportions of T-helper memory cells in parous compared to nulligravid women, indicating that pregnancy persistently affects the pre-pregnancy CD4+ memory cell pool in human peripheral blood. Collectively, the two studies on T-helper memory cells support our own finding of a clear increase in T-cells, including T-helper memory cells, in healthy women in the postpartum period, and it is tempting to speculate that these increases serve a physiological role in healing processes and in combatting infections in this vulnerable period and may also represent a tolerance induction toward paternal antigens (as speculated by Kiefer et al. (38).

Women with postpartum depression, however, displayed a remarkably different pattern. The failure of postpartum depressed subjects to mount a physiological T-cell activation in the postpartum period is consistent with our earlier findings in postpartum psychosis subjects (11). The abnormal apportioning of subsets here is also comparable to that found in our postpartum psychosis subjects: Cells with a T_H1 potential (IFN-γ production) were reduced in PPD compared to HPC and HC women controls, as were T_H17 cells, while cells with an immune suppressive capability (T regulatory cells) were significantly less activated as compared to the HPC women.

It was particularly notable that T-helper memory cells failed to rise and were even reduced when compared to HPC women. Memory T-cells, which remember previously encountered antigens through exposure to semen, fetal cells in pregnancy, or microchimerism, are thought to play a key role in fetal-maternal tolerance. Preeclampsia is considered to be a disease of immune maternal-fetal incompatibility, and a recent study showed lower memory T-cells not only during pregnancy but also postpartum in women who had preeclampsia during pregnancy compared to healthy controls (38). We earlier showed high co-occurrence of preeclampsia and postpartum mood disorders (39), and lower memory T-cells (and maternal-fetal incompatibility) might be evidence of a relationship in their underlying pathophysiology.

Some of the differences we found were more pronounced than others, and it may be that with a larger sample size these less pronounced differences would become more clear. The one category in which we saw not even a glimmer of difference between the

two postpartum groups was in the T_H2 cells, indicating that this is primarily a story of cells associated with pro-inflammatory action (i.e., T_H1 and T_H17) and the cells that suppress that action (T-reg).

This inability of postpartum depressed and postpartum psychotic women to mount a physiological T-cell immune activation in the postpartum period suggests a defect in the T-cell system. Indeed, older research on functional T-cell parameters (such as lymphocyte stimulation assays) delivers evidence for such a defect in the T-cell system intrinsic to those with a major mood disorder (40). We reported that subjects with a major depressive episode (outside the postpartum period) were characterized by decreased serum levels of the T-cell growth factors IL-7 and sCD25 and by mildly reduced levels of T-helper and T regulatory cells (14). Snijders and colleagues similarly reported reduced levels of T-cells and T-helper cells in children of a bipolar parent (at high risk for a mood disorder) from adolescence to young adulthood (29), and another study from the same group showed that the familial liability to develop bipolar disorder determined the reduced levels of T-cells (30). Two other groups also confirmed shifts in the T-helper populations, with T regulatory cells decreased and T_H17 and T_H2 cells increased in bipolar disorder (41, 42) in contrast to the decreases in T_H17 cells characteristic for unipolar depression (41). In sum, there is ample evidence that T-cell defects mark mood disorders, and our data here indicate that this pattern extends to postpartum depression as well.

Of course, merely establishing a connection between T-cell defects and postpartum affective disorders does not significantly advance our science about either the results or the causes of such disorders. If women with PPD have T-cell defects, are they in fact more vulnerable to postpartum infections? Is their tolerance to paternal antigens in future pregnancies less robust than that of healthy women? To our knowledge there are no data supporting a higher infection rate or an increased spontaneous abortion rate in subsequent pregnancies for women suffering from a postpartum depression (though a higher infection rate has been described in major depressed individuals in general) (43). T-cell defects might also have substantial effects on brain development and white matter integrity. Poletti and colleagues (44) found the percentage of circulating T_H17 cells to correlate positively with white matter integrity, particularly in fiber tracts connecting the forebrain with the limbic system, in both healthy controls and bipolar depressed subjects. The frequency of circulating T regulatory cells correlated positively with white matter tract disruption in these areas and to lower neuronal responses to negative versus positive morally tuned stimuli in the right dorsolateral prefrontal cortex of bipolar depressed subjects.

With regard to the origin of the T-cell defects in subjects with mood disorders, particularly in the postpartum, a few putative mechanisms come to mind. Tryptophan is an essential growth factor for T-cells, and reduced tryptophan levels are a hallmark of mood disorders. In a previously published paper we showed reduced tryptophan levels in both postpartum depression and postpartum psychosis (45), and it is tempting to speculate that these reduced tryptophan levels are related to the T-cell defects. Other groups have had similar findings (46, 47). It may also be that non-depressed people have the ability to buffer a decrease in tryptophan that occurs for all women after childbirth, as increases in cortisol spur immune activity that downregulates the metabolism of tryptophan into serotonin (46). Substantial work is clearly needed on the connection between these T-cell defects and other findings showing increases in inflammatory activity postpartum, measured primarily in cytokines (17, 18) – we may need to look more at the function of different immune cell populations than at number. In this case, the population may prove illuminating, as our sample was limited to women who developed new-onset symptoms in the postpartum, and many cytokine studies include women who were or may have been depressed in pregnancy as well.

Another possibility is the interaction with pregnancy hormones. Sex steroids and prolactin are known to influence T-cell growth and differentiation (48), and altered levels of these hormones have been suggested in at least some studies of postpartum mood disorders, though evidence is mixed (49-51). Studies that link endocrine alterations to those of the immune system in postpartum mood disorders do not yet exist.

Our study has a number of limitations. While we were able to include reasonably large control groups, the sample of women with postpartum depression is quite small, given the stringent inclusion criteria (postpartum onset, severe depression, largely antidepressant-free). Because we wanted to restrict to postpartum onset, our group of cases does not match the DSM-V definition, which requires onset during pregnancy or within 4 weeks postpartum. We may, therefore, have missed small differences among groups that would have been evident in a larger population (but thus also avoided the heterogeneity common to studies on PPD that have less strict inclusion criteria). In addition, we did not have sociodemographic details other than weight and BMI for our non-postpartum healthy controls, so it is possible that some of our results reflect differences between groups that are affected by these characteristics. Only one of our subjects was taking anti-depressant medication, so we were unable to control for this variable in our analyses. Other limitations may come from possible differences among samples in the amount of time spent in storage (though we are aware of no literature that addresses

whether such differences actually exist), or from the timing difference in the blood draw between groups. We are reassured on the latter point, however, because we controlled for this difference in our analyses, and limited previous literature actually supports an increase in T-helper activity across the postpartum period, which would mean that our PPD subjects (who had the later blood draw) should show HIGHER and not LOWER activity than our healthy subjects (32). In addition, our T-cell data do not represent absolute counts per ml of blood but are instead relative to numbers of PBMCs and lymphocytes; future studies would benefit from measuring the absolute numbers of leukocytes per ml blood at the time of testing.

Despite these limitations, our work adds to the small but growing number of investigations of immune alterations in perinatal mood disorders that attempts to reach beyond measures of peripheral cytokines to look at other immune system defects that may play an etiological role in these devastating illnesses. Our clear results showing that healthy postpartum women show a rebound of T-cell activity, particularly in pro-inflammatory activity (T_H1) and compensatory mechanisms (Treg), is consistent with previous literature on pregnancy. Our finding that postpartum depressed women do not mount this response adds to our previous similar results in a population of women with postpartum psychosis, and adds to the growing body of literature indicating that T-cell dysregulation may be an important feature of mood disorders. Future research characterizing these differences in larger populations, and extending into different classes of immune cells, will be instructive.

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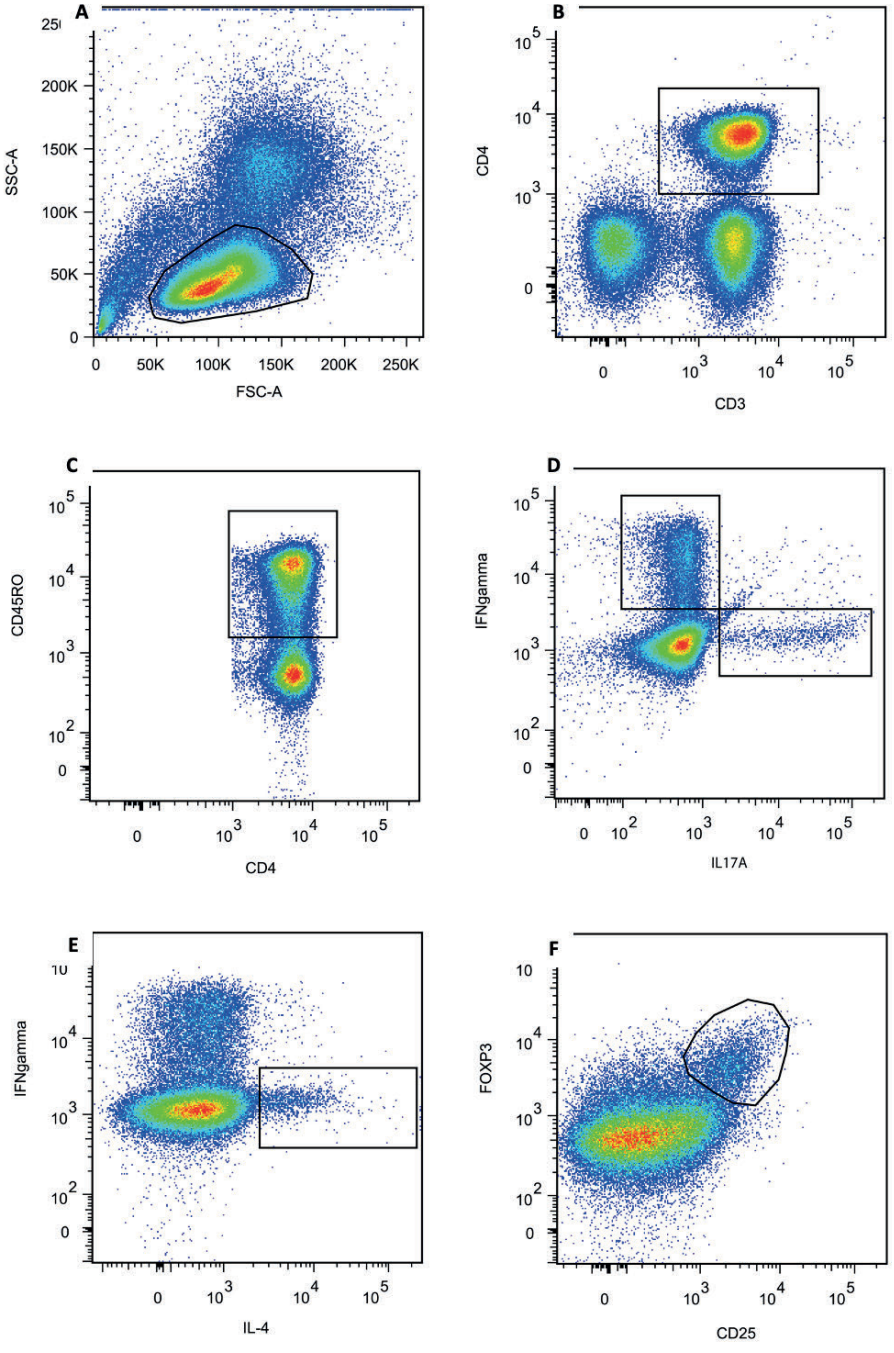
FIGURE S1. Definition of T-cell subsets by intracellular staining and gating strategy



Examples of gating in flow cytometry to detect the different T-cell subsets in a patient. First, single cell events were selected by gating out cell aggregates on the basis of event area versus event height (data not shown). Within the single cells, further analysis was performed. **(A)** Selection of lymphocytes by forward scatter (FSC: proportional to cell size) and side scatter (SSC: proportional to cellular granularity). **(B)** Selection of T-helper cells within the lymphocyte gate. CD3+CD4+ cells were selected. **(C)** Selection of T-helper memory cells within the T-helper gate (see B). CD4+CD45RO+ cells were designated T-helper memory cells. **(D)** Selection of T-helper 1 (T_H1) and T-helper 17 (T_H17) cells within the T-helper cells (see B). Cells expressing intracellular IFNg (upper left gate) represent T_H1 cells, cells expressing IL-17A (lower right gate) represent T_H17 cells. **(E)** Selection of T-helper 2 (T_H2) cells within the T-helper gate (see B). The gated IL4+IFNg- cells represent T_H2 cells. **(F)** Selection of FoxP3+CD25^{high} regulatory T-cells (Treg) within the T-helper gate (see B). Within the helper T-cells, CD25^{high} cells were selected and in this subset FOXP3+ were designated regulatory T-cells.

SUPPLEMENTAL TABLE 1. Correlations between characteristics and T-cell subsets

	Age	Weight	BMI	Blood withdrawal, days postpartum	Dutch ethnicity#	Education beyond high school#	Married/ cohabiting#	Primiparity#	Primi-gravidity#	Caesarean section#	Vacuum extraction#	Breast-feeding#	Medication use‡
CD3+ T-cells	.05	-.004	-.02	-.21	.16	-.09	.04	-.07	.03	-.07	-.06	.14	.21
CD4+ T-cells	.15*	.19**	.18**	-.08	.16	-.05	.25**	-.02	-.06	-.07	.002	-.04	.17
CD8+ T-cells	-.10	-.24**	-.24	-.20	.06	.01	-.31**	-.23*	-.03	-.01	-.25*	.20	-.07
T_H1	.13*	-.06	-.15*	-.14	-.08	.23*	-.06	-.17	.01	.19	-.18	.10	.14
T_H2	.10	-.10	-.02	.13	-.15	.11	-.10	.08	.04	.20	.11	-.02	.02
T_H17	.05	-.04	-.04	-.34**	.15	.18	.15	-.21	-.09	.05	-.08	-.02	-.02
T reg	.01	.22**	.24***	-.08	.02	-.07	.35***	.05	.12	-.07	.02	.11	.25
T_H memory	.10	.02	-.01	-.11	-.13	.29**	-.01	-.36***	-.14	.10	-.11	.10	.38*
T_H naive	.07	.16**	.17**	-.003	.19	-.16	.18	.12	.004	-.13	-.02	-.11	.04

* p<.10; ** p<0.05; *** p<0.001

in postpartum women (HPC and PPD) only (n=60)

‡ in postpartum depressed women (PPD) only (n=21)

SUPPLEMENTAL METHODS AND MATERIALS

Staining A: To determine percentages of CD14+ monocytes, CD3+ T-cells, CD3+CD8+ T cytotoxic lymphocytes, and CD3+CD4+ T-helper lymphocytes, 50,000 PBMCs were stained for 15 min at room temperature in tube A containing staining buffer (PBS 0.2%, 0.1 % sodium-azide, pH 7.8) with CD45-Pacific Orange (Invitrogen, Carlsbad, CA, USA) 1:80, CD3-PercP-Cy5.5 (BD Biosciences, San Jose, CA, USA) 1:16, CD4-Pacific Blue (BD Biosciences) 1:200, CD8-PC7 (Beckman Coulter, Brea, CA, USA) 1:80, CD14-APC-H7 (BD Biosciences) 1:16 and CD15-FITC (BD Biosciences) 1:400. Furthermore, we calculated percentages of T-cells (CD3+), cytotoxic T-cells (CD3+CD8+), and T-helper cells (CD3+CD4+) as frequencies of PBMCs.

Staining B: To determine T-helper cell subsets (T-helper memory cells and T_H1, T_H2, T_H17, T regulator cells), 1 x 106 PBMCs were cultured for 4 hours at 37 °C stimulated in the RPMI-1640 culture medium (as was used for freezing the cells down, see before) with 50 ng/ml phorbol 12-myristrate 13-acetate (PMA; Sigma Aldrich, St. Louis, MO, USA) and 1.0 μg/ml ionomycin (Sigma) in the presence of Golgistop (BD Biosciences). Cells were harvested and stained for membrane markers with CD45-RO-FITC (Dako, Glostrup, Denmark) 1:10, CD3-APC-H7 (BD Biosciences) 1:40, and CD25-APC (BD Biosciences) 1:20 antibodies for 20 min at room temperature. After washing with PBS, cells were fixed and permeabilized according to the manufacturer's instructions (eBioscience, San Diego, CA, USA) for 45 min at 4 °C. Cells were washed twice and stained with CD4-PercP-Cy5.5 (BD Bioscience) 1:30 and intracellular IFN-y-Horizon V500 (BD Biosciences) 1:60, IL-4-PE-Cy7 (eBioscience) 1:240, IL-17A-BV421 (BioLegend, San Diego, CA, USA) 1:40 and Fox-P3-PE (BD bioscience) 1:10 in permeabilization buffer (eBioscience) for 45 min at 4 °C. We calculated the percentage of T-helper naive cells by subtracting the percentage of T-helper memory cells from the total population of T-helper cells.

Chapter 8

General discussion

MAIN CONCLUSIONS OF THIS THESIS

First-onset postpartum psychosis

> A substantial part of women with first-onset postpartum psychosis have "isolated postpartum psychosis": episodes of mania, psychosis, or severe psychotic depression limited to the postpartum period.

This thesis shows that a substantial part of women with first-onset postpartum psychosis (PP) have no recurrences outside the perinatal period (43.5% in our meta-analysis with a mean follow-up of 16 years and 67.9% in our own longitudinal prospective cohort study with a mean follow-up of 4 years). These women might have a vulnerability limited to the postpartum period and have "isolated postpartum psychosis": episodes of mania, psychosis, or severe psychotic depression limited to the postpartum period. For the remaining women, the first-onset PP is the incipient episode of a psychiatric disorder with a more disabling disease course and broader window of recurrence vulnerability (Chapter 2 and 3). Understanding who is at risk of a mood or psychotic disorder during follow-up, and whose vulnerability is limited to the postpartum period, is particularly important in guiding treatment decisions including long-term pharmacotherapy (Chapter 3). However, significant predictors for distinction between isolated postpartum psychosis and persistent psychiatric disorders, have not yet been found in our clinical cohort (Chapter 3). This in unfortunate, since the major differences in longitudinal outcomes between both disease courses ask for a distinct entity and associated treatment regimen (Chapter 2 and 3). Treatment of postpartum psychosis will be according to the clinical treatment algorithm, as described earlier by Bergink and colleagues (1). With an adequate treatment regimen, nearly all women with postpartum mood disorders achieve full remission (1). Moreover, treatment of depressive and/or manic symptoms will improve mother-to infant bonding in almost all women with PP in which impaired bonding is present (17.6%). This is important, as impaired mother-to-infant bonding can impact the child's emotional, cognitive, and behavioral long-term development. For a small group, treatment of symptoms is not enough, and special care and treatment focused on bonding may be required. Therefore, clinicians should assess if impaired bonding is still present after remission (Chapter 4).

Bipolar I disorder during the peripartum period

> Women with bipolar I disorder are at high risk of a bipolar episode after live childbirth, miscarriage and induced abortion, but not during pregnancy. The risk is especially high in the first four weeks postpartum.

The peripartum period has been identified as a high-risk period for women with bipolar I disorder. Women with bipolar I disorder have a particularly high risk for developing an episode during the postpartum period (30.1% of pregnancies), which is six times the risk during pregnancy (5.2% of pregnancies). The risk of a postpartum bipolar episode is highest after a live birth (34.4%) and lower after miscarriage (15.2%) and induced abortion (27.8%). Especially the early postpartum period (< 4 weeks) is a high-risk period for recurrence. During pregnancy or after childbirth, mania with or without psychotic features is the predominant affect, in contrast to other periods in life, where depression is most prevalent. This emphasizes the distinctive character of perinatal bipolar episodes compared to nonperinatal bipolar episodes (Chapter 5).

Women who have suffered from an episode during the first perinatal period are significantly less likely to have a second pregnancy (55.5%), compared to women with an uneventful first perinatal period (78.7%). And women who have experienced an episode related to their first perinatal period have an increased risk of an episode during a subsequent pregnancy (61.4%). In contrast, the risk is lower (20.5%), but not absent, after a first uneventful perinatal period. This pattern is further amplified over subsequent pregnancies (Chapter 5).

Lithium prophylaxis during pregnancy is associated with a lower episode risk during pregnancy and after delivery in women with bipolar I disorder. We found that the episode risk was 26.4% in lithium supported pregnancies compared to 46.7% in unsupported pregnancies (OR=0.41; 95% CI: 0.25-0.69; p=0.001). This association remained after adjusting for age of onset, total number of episodes, bipolar family history, and multiple pregnancies within unique women (Chapter 5). Nevertheless, the benefits of the protective effect of lithium prophylaxis during pregnancy should be weighed against the risk of fetal medication exposure, since earlier studies found an increased risk of congenital malformations during the first trimester, when women used lithium during pregnancy (2, 3). In addition to the teratogenicity, we also found that miscarriages occur more often in lithium-exposed pregnancies (20.8%), compared to unexposed pregnancies (10.9%). The odds ratio of miscarriage after lithium use during pregnancy was 2.94 (95% CI:

1.39-6.22; p<0.005), after adjusting for the age at conception and the clustering of pregnancies per woman (Chapter 6).

Our findings could have clinical implications, considering the teratogenicity during the first trimester in combination with the increased miscarriage risk compared to the relatively low risk of an episode during pregnancy. For patients with lower recurrence risk, clinicians might want to consider lowering the lithium dose or pause during the first trimester and restart prophylaxis after the first trimester. For those individuals at extremely high recurrence risk, decision making is even more complicated, but clinicians might want to consider continuing lithium throughout the entire pregnancy. In any scenario, prophylactic medication immediately after delivery is recommended given the high recurrence risk postpartum. Ideally, women with bipolar I disorder of reproductive age have access to specialized women's mental health care facilities in order to weigh both risk and benefits of medication, with a reproductive psychiatrist (Chapter 5 and 6).

Neurobiology of severe postpartum mood disorders

> Women with severe postpartum mood disorders are unable to mount a physiological T-cell immune activation in the postpartum period, which suggests a defect in the T-cell system.

The postpartum period in healthy women is a time of altered immune activity, with increase in T-cells compared to the non-postpartum period. Women with severe postpartum depression fail to mount a physiological T-cell activation in the postpartum period, which is consistent with earlier findings in patients with postpartum psychosis. This inability of postpartum depressed and postpartum psychotic women to mount a physiological T-cell immune activation in the postpartum period suggests a defect in the T-cell system (Chapter 7).

GENERAL DISCUSSION

The bipolar spectrum (4) is a spectrum of mood disorders with varying severity (5). According to the Diagnostic and Statistical Manual for Mental Disorders - 5th edition (DSM-V) (6), the bipolar spectrum includes three bipolar disorder types: bipolar I disorder (BDI), bipolar II disorder (BDII) and cyclothymia. All of these disorders have in common that they cause changes in a person's mood, energy, and ability to function. Nonetheless, every subtype also has its own characteristics (see Table 1). Patients with

bipolar I disorder have severe episodes of mania and alternating or intertwining episodes of depression. Sometimes psychotic symptoms occur during these severe alterations in mood (7). Patients with bipolar II disorder have severe depressive episodes as well, but instead of mania, they have episodes of hypomania. Hypomania is distinguished from mania by minimal impairment, if any, and by the fact that it is of shorter duration (8). In both bipolar disorder I and II, depressive episodes put a lot of burden on patients, since the risk of a depressive episode is 3 times the risk of a (hypo)manic episode (9, 10). In cyclothymia (sometimes unofficially called bipolar III disorder (BDIII)), a person has symptoms of (hypo)mania that alternates frequently with brief periods of depression. When present, though, the symptoms are not severe enough or do not last long enough to meet the criteria for BDI or BDII (8). In addition to these 3 previous categories, some patients clearly have severe mood symptoms, but these do not fulfill the criteria of BDI, BDII or BDIII and therefore fall in the category of bipolar disorder not otherwise specified (BD-NOS) (which is not stated in Table 1).

TABLE 1. Summary of DSM-V criteria for bipolar disorders#

	BD I	BD II	Cyclothymia
Main symptom criteria (mania)			
Elevated or irritable mood	+	Often irritable	+
Increased activity or energy	Goal-directed	+	+
Increased self-esteem	+	+	+
Decreased need for sleep	+	+	+
Pressured speech	+	+	+
Distractibility	+	+	+
Increased risk taking behaviour (especially for those with comorbid BPD)	+	+	
Main symptom criteria for depressive episodes			
(Same as MDD)		+	
Severity and duration of episodes			
(Hypo)Mania	Mania	Hypomania**	Sub-threshold Mania
Number of symptoms	3-4 symptoms	3-4 symptoms	≤ 3 symptoms
Duration of episode	> 7 days	4-7 days	< 4 days
Impact on functioning	Disrupts social and occupational functioning or results in hospitalization	Not severe enough to disrupt functioning or result in hospitalization	Symptoms of (hypo)mania/ depression cause significant distress or impairment in functioning
Depression	Depression	Depression	Sub-threshold Depression
Number of symptoms	> 5 symptoms	> 5 symptoms	≤ 5 symptoms
Duration	2 weeks	2 weeks	< 2 weeks
Frequency of episodes	≥ 1 manic episode	> 1 hypomanic + ≥ 1 depressive episode	Fluctuating subthreshold hypomanic and depressive symptoms for > 2 years (> 1 year for children/ adolescents)

** Hypomanic episodes are usually less severe and more likely to feature irritable mood than manic episodes. Presence of a manic episode alone is sufficient to meet criteria for BDI. Patients may also have experienced depressive or hypomanic episodes but this is not essential to qualify for a diagnosis of BDI.

Table from Malhi et al. (2015) (8)

There is clear evidence that postpartum psychosis is linked to the bipolar spectrum. Previous research and studies within this thesis suggested a fundamental link in 4 domains: (a) symptomatology, (b) diagnostic and longitudinal outcomes, (c) family history, and (d) recurrences in women with bipolar disorder (11).

Symptomatology

A majority of women (60.6%) with isolated postpartum psychosis suffer from mania (with and without psychotic features) (12), as do women with bipolar disorder (13). Mania is a distinct period of abnormally and persistently elevated, expansive or irritable

mood, lasting at least one week (or any duration if hospitalization is needed) (14). It is a characteristic of bipolar disorder disease and appearance of a single manic state makes a diagnosis of bipolar disorder sufficient according to the DSM-V (6). However, the minority of women with postpartum psychosis has a typical euphoric, manic symptomatology during admission (15). Instead, irritability might be an even more prominent hallmark of the disease (15). Delusions and hallucinations are also common features in women with postpartum psychosis (15). Moreover, patients with postpartum psychosis sometimes have a psychotic presentation without mood instability and even first rank schizophrenia like psychotic symptoms (12). Interestingly, these patients have either no episodes or affective recurrences during follow-up (12). Other important symptoms of postpartum psychosis are severe inattention, disorganization, disturbed consciousness and disorientation (15-25). These last two symptoms, combined with hallucinations, are also common in somatically ill patients with delirium. An undetected organic cause is suggested by the presence of these symptoms (18).

Diagnostic and longitudinal outcomes

Exploring the etiology, vulnerability to endocrine and immunological changes are present in both bipolar disorder and PP (26-28). But, for patients with postpartum psychosis this seems to be a selective vulnerability following childbirth, while for patients with bipolar disorder these neurobiological triggers are also present outside the postpartum period (26, 27). Detailed investigation of the immune system shows a shift in T-cell activation in BD I and PP when compared to healthy (postpartum) controls, indicating that T-cell dysregulation may be an important feature of mood disorders (26, 29-31). However, more research is needed to explore the possible etiological role of immune alterations in these devastating diseases.

Both patient populations are treated with mood stabilizing medication (preferably lithium) or antipsychotic medication (1, 32), but treatment response in PP might be faster (1) and probably with less residual symptoms, leading to more improved functioning at different domains (13, 33). Besides, in women with first-onset PP medication might be tapered off after 9 months under supervision of a specialized psychiatrist (1), while in patients with BD, this is only sometimes advised during pregnancy (32).

Recurrence

Bipolar disorder is characterized by recurrent mood episodes during the lifespan, with a lifetime recurrence risk of >90% (34-36). For women with postpartum psychosis the

magnitude of this risk was unknown for a long time, because of limited information on the longitudinal disease course (37). In our meta-analysis (37) and cohort study (12) we found that a considerable portion of women (range 32.1%-56.5%) with postpartum psychosis do indeed have recurrences outside the postpartum period during follow-up, leading to a diagnosis of bipolar mood disorder. Remarkably, a substantial part of women with a first-onset postpartum psychosis has no manic or psychotic recurrence outside the postpartum period after the index episode of first-onset postpartum psychosis (12, 37). These women have a favorable prognosis and their risk of recurrence appears limited to the period following subsequent delivery (27-29%) (37, 38), but not outside the postpartum period.

Family history

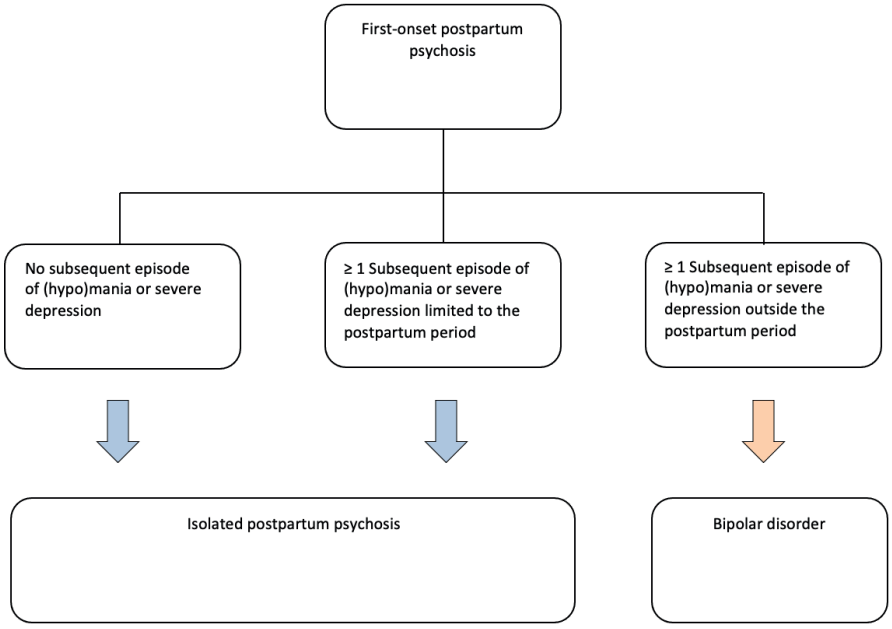
Both in patients with postpartum psychosis and bipolar disorder, a positive family history of bipolar disorder has been found (39, 40). Our cohort study also found higher percentages of a family history of bipolar disorder both in patients with isolated postpartum psychosis and patients with bipolar disorder, than within the general population (12). Although previous retrospective studies do find family history of psychiatric illness as a potential predictor for the disease course (23, 41, 42), we could not confirm this within our own cohort (12). Therefore, it remains unclear if the risk of an affective episode among first-degree relatives of patients with BD is similar, lower or higher compared to patients with PP.

Both the results of previous studies as well as research described within this thesis shows the resemblance of first-onset postpartum psychosis and bipolar disorder, which makes us strongly believe postpartum psychosis is a bipolar spectrum disorder. Within the bipolar spectrum in the DSM-V, postpartum psychosis (including psychotic, manic, psychotic depressed, or mixed episodes) is not a distinct disease category (6, 15). Given that the majority of women with PP have prominent manic or mixed episode features (15), by the current DSM-V criteria these women should therefore be diagnosed with bipolar disorder at the time of their first-onset postpartum psychosis. However, our findings raise doubt about the validity of this approach (37). Considering the variation in presentation compared to other bipolar spectrum disorders, our research is contributing to the emerging consensus postpartum psychosis could be considered a separate type and may therefore be classified as a distinct diagnostic category within the bipolar spectrum (Figure 1). This distinction could be of clinical relevance given that the current practice of diagnosing all women with classical bipolar disorder following first-onset postpartum

psychosis has likely led to stigma and a substantial proportion of women receiving long-term pharmacotherapy while they might have been stable without medication as well.

We suggest that when a first episode of (hypo)mania occurs outside the peripartum period, a diagnosis of BD I or II will be established directly. But, it appears inaccurate to assign a diagnosis of bipolar I or II disorder at the time of a first-onset postpartum psychosis (37). A better approach could be to classify first-onset postpartum psychosis as a unique distinct entity within the bipolar spectrum. Only when nonpuerperal recurrence occurs during longitudinal follow-up, a diagnosis of bipolar I or II disorder would then be established (Figure 1). In this way, women will not be misclassified too early in their disease course (15).

FIGURE 1. Diagnostic system after first-onset postpartum psychosis#



#Figure based on Figure 3 from Gilden et al. (2020) (37)

We hope this thesis will add to a more evidence-based discussion about adding a distinct diagnosis of postpartum psychosis to bipolar spectrum disorders in the DSM, as it will reduce stigma in women with first-onset postpartum psychosis, but more importantly will

prevent them from taking long term prophylactic mood stabilizers in each scenario, while some women might not need these.

KNOWLEDGE GAPS AND DIRECTIONS FOR FUTURE RESEARCH

Onderzoeksprogramma Peripartum Psychiatrie Erasmus MC Rotterdam (OPPER)

OPPER is an ongoing prospective multicenter cohort study and focusses on the prevention, treatment and neurobiology of peripartum mood disorders. Women are eligible for this study if they (a) are between 18–45 years of age; (b) have a postpartum onset of psychosis, mania, or severe depression as assessed with the Structured Clinical Interview for DSM-IV Axis I disorders (SCID); and (c) are admitted to the Mother and Baby Unit (MBU). Exclusion criteria are: (a) prenatal onset of psychosis, mania or severe depression; (b) drug/alcohol dependence in the last 3 months; (c) intellectual disability (IQ < 80); (d) serious somatic illness; and (e) inability to read or write. The Medical Ethical Committee of the Erasmus Medical Center Rotterdam approved the study (MEC-2005226). Written informed consent is obtained from all participants.

During admission we collect demographic data and use validated questionnaires to assess symptoms of depression and/or (hypo)mania weekly. In addition, we use psychiatric/obstetric medical records to collect detailed information regarding psychiatric history (e.g., number of mood-episodes, family history), current use of maintenance treatment and/or other medication (including dose adjustments/blood levels), the occurrence of mood episodes during pregnancy and the postpartum period, somatic comorbidity and obstetric complications/neonatal complications (e.g., congenital malformations). We also collect blood cells and serum biomarkers in the acute state during admission. Women in this study receive pharmaceutical treatment according to medical guidelines. Patients with postpartum psychosis are treated with benzodiazepines, antipsychotics and/or lithium, while women with postpartum depression are treated with either tricyclic antidepressants or a selective serotonin reuptake inhibitor. In addition, non-pharmacological interventions to optimize mother–baby interaction take place as part of the regular program of the MBU. These interventions include guidance from nursing staff, video interaction guidance, baby massage and a support group for mothers.

The primary outcome of OPPER is recurrence, divided into 3 categories: (a) subsequent postpartum episodes, (b) subsequent episodes outside the postpartum period and (c) no subsequent episodes. Therefore, we perform follow-up measures at 9 months,

2, 3 and 4 years after remission. With face-to-face interviews and questionnaires, we assess the disease course of the mother. Besides we investigate the development of the child. During follow-up, we re-collect blood cells and serum biomarkers.

In 2017, we implemented a sub-study in which we execute longitudinal neuroimaging, only in women with first-onset postpartum psychosis during the acute phase and 9 months after complete remission. Additionally, a healthy control group of women from the normal population matched on demographics and postpartum interval at the time of neuroimaging is included in this sub-study.

The prospective recruitment of patients for the OPPER started in 2005 in Erasmus MC and was expanded to recruitment at the St. Antonius Ziekenhuis in Utrecht in 2017. To date, we were able to include approximately n=375 patients in OPPER. Over the past 15 years OPPER has evolved into the largest prospective cohort of patients with first-onset postpartum psychosis in the world, which is incredible given the low prevalence of women with a first-onset postpartum psychiatric disorder. Moreover, OPPER is the first study to implement and conduct longitudinal neuroimaging in patients with postpartum psychosis. In the coming years, we will enlarge the OPPER cohort. The collected data might be used to contribute to the following topics/objectives:

Individualized recurrence risk prediction

To better predict the disease course after an initial postpartum episode, prediction models are needed. This prediction is of profound clinical relevance given that the current practice of diagnosing all women with classical bipolar disorder during postpartum psychosis has likely led to stigma and a substantial proportion of women receiving long-term pharmacotherapy, while some women might not need these. Potential demographical and clinical determinants (e.g., psychiatric family history, number of previous mood episodes), can possibly be used to predict the risk of (peripartum) recurrence for individual patients. Previous studies (23, 41-43), including our own work (12), have tried to identify these determinants, but most studies were done retrospectively and all studies lack power, given that PP is a rare disorder (12, 23, 41-43). Since the incidence of postpartum psychosis is rather low, register based studies are probably the best fit to search for these determinants. In addition, genotyping through collected blood cells could add value to a prediction model, as bipolar disorder has a substantial genetic component (44). These data may be collected in prospective longitudinal studies in women with a bipolar spectrum disorder. Furthermore, it is important to investigate the utility of structural neuroanatomical signatures

in differentiation of subtypes within the bipolar spectrum, which could potentially add value as another objective diagnostic biomarker. While our own neuroimaging study is a step forward in this direction, obviously more studies with larger numbers are needed to give neuroimaging value within the model. In general, large numbers within multiple studies are needed to build solid prediction models based on patient characteristics and diagnostic markers. We envisage that in the future both play an important role in making clinically relevant predictions leading to better targeted therapies and improved patient care.

Efficacy of maintenance treatment during the peripartum period

Enlargement of the OPPER cohort and international collaboration will enable us to (further) investigate the efficacy and duration of maintenance treatment during pregnancy and the postpartum period. In women with an isolated history of postpartum psychosis, use of maintenance treatment during pregnancy can be avoided. Accordingly, in this group we will focus on the optimal duration of prophylactic treatment after a subsequent delivery. To determine the optimal duration, we must be able to distinguish between isolated postpartum psychosis and recurrent psychiatric disorders. Until we have accurate prediction models, information about time to recurrence after first-onset PP might guide diagnostic decision-making as well as conclusions on length of maintenance treatment after first-onset postpartum psychosis. In women with bipolar disorder long term mood stabilizing medication is recommended (45). Evidently, during pregnancy the benefits of the established protective effect of lithium prophylaxis should be weighed against the risk of fetal medication exposure (2, 3) and the risk of miscarriage (46). Considering the teratogenicity during the first trimester and the relatively low risk of an episode during pregnancy, clinicians could consider lowering the lithium dose or pause during the first trimester and restart prophylaxis after the first trimester. For those individuals at extremely high recurrence risk, clinicians could consider continuing lithium throughout the entire pregnancy. In any scenario, prophylactic medication immediately after delivery is recommended given the high recurrence risk postpartum. Accordingly, it could be meaningful to compare the effects of pausing lithium prophylaxis with continuation of lithium prophylaxis on recurrence during pregnancy in women with bipolar disorder. However, these kind of studies need to be performed with the greatest care, since recurrence during pregnancy will have severe consequences for both the mother and the unborn child.

Etiology of postpartum psychosis

The peripartum period is a time of known immune dysregulation and one of the few periods in life when there is an obvious biological trigger (parturition) that can be linked to psychiatric symptoms (31). However, it remains unclear why the vulnerability in this specific period is so high. Despite extensive effort in mood disorder studies on sex steroid hormones (47-49) and the HPA-axis (50-56), no consistent endocrinological etiology for PP has been demonstrated. Studies on alternative etiological mechanisms, both in bipolar disorder (57-63) as in postpartum psychosis (26, 27, 64) do exist as well. However, despite all effort, the immune-related trigger has also not yet been identified. Interestingly, studies that link endocrine alterations to those of the immune system in postpartum mood disorders are lacking (31). An improved understanding of the etiology will hopefully provide identification of modifiable exposure variables or risk factors. Therefore, we suggest expansion of immune- and endocrine-related studies, so immune- and endocrinological changes during pregnancy and postpartum can be studied in more detail.

Child development after exposure to parental psychiatric mood disorders

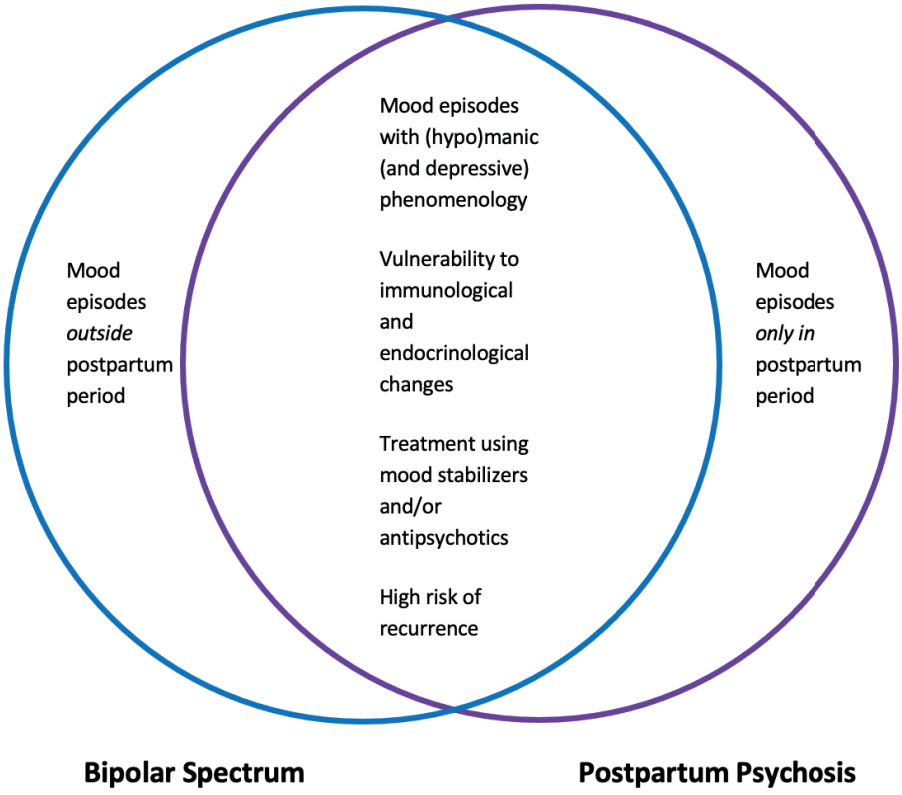
Parents of children with a mother with a bipolar spectrum disorder are concerned about the effect of the disease and/or medication use during pregnancy on the development of their children. Since the risk during the peripartum period in women with bipolar spectrum disorders is higher than during other periods in life (38, 65-67), a high-risk period of illness recurrence coincides with the period when mother-infant interaction patterns are evolving (68). As described in our own work (69), studies have shown associations between impaired mother-to-infant bonding and child behavior problems in early childhood (70), and an increased child's risk of developing psychopathology in adulthood (69, 71). Therefore, bonding is an important factor to predict the child's emotional, cognitive, and behavioral long-term development (69). In our own cohort we found that bonding problems during admission for women with postpartum psychosis were not as evident as for women with postpartum depression (69). However, long-term effects on the emotional and social development of the child remained unknown. Therefore, follow-up measurements at 2 and 3 years postpartum in our OPPER cohort might be used to investigate potential negative long-term effects of parental mood disorder on child development. It is important to focus on cognitive, language, motor, and social-emotional

development and problematic behavior. Children born to mothers with a bipolar spectrum disorder without in utero exposure to medication and children that are participating in the HAPPY-follow study (72) can be used as control groups. In addition to the effect of the disease and it's treatment, bipolar disorder is strongly genetically determined, so children of patients with bipolar disorder (bipolar offspring) constitute an at-risk population (73). However, heritability in postpartum psychosis remains unclear until now. Given that this is a disorder with low prevalence, enlargement of the OPPER cohort and international collaboration will enable us to (further) investigate heritability and to identify a valid risk profile for offspring of mothers with PP. Possibly early intervention is indicated to enhance normal development and prevent onset of mood disorders in identified high-risk children.

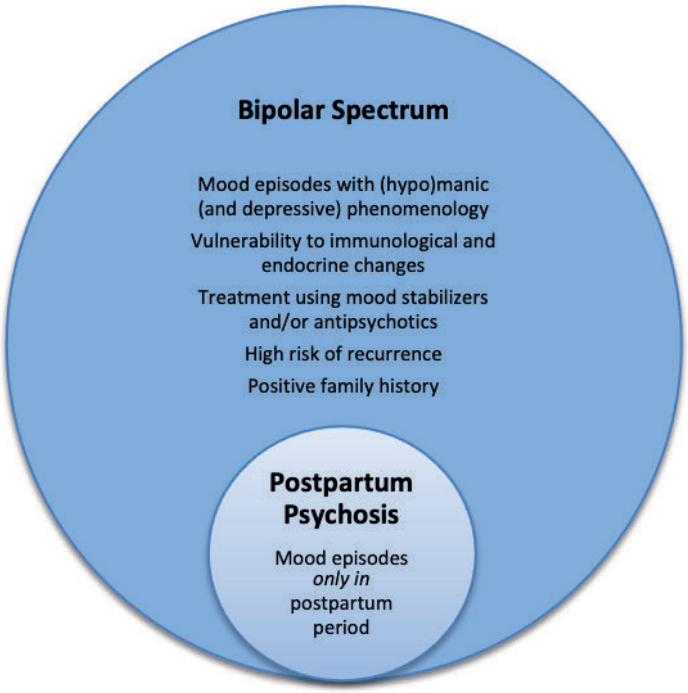
MODELS FOR THE RELATIONSHIP BETWEEN POST-PARTUM PSYCHOSIS AND BIPOLAR DISORDER

In this thesis, we have discussed the fundamental link of postpartum psychosis to the bipolar spectrum based on previous studies and research within this thesis. Thinking about the possible etiology and biology, but also treatment regimen and prognosis, different models could be envisioned for its classification (Figure 2). Hopefully, future research will address the unanswered questions about postpartum psychosis, and its unique entity within the bipolar spectrum. This will make a significant impact on our understanding of this condition, leading to the best possible care for these specific patients, both now and in the future.

FIGURE 2. Models for classification of postpartum psychosis within the bipolar spectrum



a. Model I – classification based on different biology



b. Model II – classification based on overlapping biology

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Summary

PART I. FIRST-ONSET POSTPARTUM PSYCHOSIS

Women with a history of first-onset postpartum psychosis are at high risk for recurrences. However, there is high variability in reported recurrence rates across studies. An evidence-based overview of the occurrence of subsequent episodes after first-onset postpartum psychosis is therefore important, particularly with regard to risk-benefit analyses of maintenance pharmacotherapy. An overestimation of recurrence risk might lead to unfounded concerns for health care providers, patients, and their families, resulting in excessive medication use, unnecessary prevention strategies, or altered family planning. Conversely, underestimation of recurrence risk might lead to insufficient attention from health care professionals and insufficient maintenance treatment, potentially leading to impaired quality of life and increased risk for hospitalization or suicide. Therefore, the aim of the systematic review and meta-analysis described in **chapter 2** was to quantify the risk of recurrence in women with a history of first-onset postpartum psychosis. We conducted a systematic literature search in all public medical electronic databases and included 6 articles describing recurrence (defined as any subsequent psychiatric episode after first-onset postpartum psychosis) in 645 patients in the quantitative analyses. We observed a substantial part of women with first-onset postpartum psychosis (43.5%) did not have a recurrence outside the postpartum period during a mean follow-up period of 16 years. The remaining women had at least one subsequent non-puerperal episode during longitudinal follow-up. For these women, delivery was the incipient episode of a psychiatric disorder with a more disabling disease course and broader window of recurrence vulnerability. This finding is of substantial clinical relevance as 'isolated postpartum psychosis' (episodes of mania, psychosis, or severe psychotic depression limited to the postpartum period) might therefore be considered a distinct category with a more favorable prognosis and no need for lifelong prevention or treatment.

Most studies included in the previously described meta-analysis were performed in the 1970s and 1980s, limiting the generalizability of the results. There is a need to investigate recurrence rate and study longitudinal follow-up in more current treatment settings. Therefore we assessed recurrence risk in our own OPPER cohort in **chapter 3.** We investigated the long-term outcomes of 106 patients with postpartum psychosis over a four-year follow-up. We found that for an even higher number of women (67.9%) the risk of illness was limited to the period after childbirth. The differences between this study and our meta-analysis may be due to the differences in the follow-up period, which was four years in this study but ranged from 11 to 26 years in the meta-analysis. It is conceivable that recurrence rates increase with longer follow-up periods. The relatively

lower recurrence rates may also be attributed to good care during follow-up, including continued medication use, and specialized health care for these women in the current treatment setting.

We further aimed to identify potential clinical markers of a psychiatric disorder with mood or psychotic episodes outside of the postpartum period in this longitudinal prospective study. Although we did find that the vast majority of non-postpartum episodes during follow-up occurred within the bipolar spectrum, we unfortunately could not find clinical predictors of 'isolated postpartum psychosis' versus a vulnerability for postpartum psychosis as an expression of a subsequent affective disorder with non-postpartum episodes.

In **chapter 4** we present the effect of first-onset postpartum psychosis on mother-to-infant bonding. Development of mother-to-infant bonding is important, as impaired bonding can impact the child's emotional, cognitive, and behavioral long-term development. While in most situations adequate bonding develops gradually after birth, bonding can be impaired when the mother suffers from a psychiatric disorder. Numerous studies have described the association between postpartum depression and impaired bonding, but there is hardly any research on mother-to-infant bonding in postpartum psychosis. As the underlying nature and the clinical picture of postpartum depression and postpartum psychosis differs substantially, it is uncertain whether bonding in these groups is comparable. In addition, earlier studies did not investigate how the relationship between postpartum depression/postpartum psychosis and impaired bonding is affected by the treatment of the depressive and manic symptoms. Acquiring this data could provide insights into driving factors behind impaired bonding and underline the importance of particular treatment regimens. In this inpatient study on a Mother and Baby Unit at the Erasmus University Medical Center (2005-2013), we examined the differences in mother-to-infant bonding between women with postpartum psychosis and women with severe postpartum depression. In this prospective cohort study, we included 155 women with a severe postpartum mood disorder, of which 91 were diagnosed with postpartum psychosis and 64 were diagnosed with postpartum depression. We found that impaired mother-to-infant bonding is a major problem in inpatient women with severe postpartum depression (57.1%), while less than 1 out 5 women with postpartum psychosis reported impaired bonding (17.6%). A decrease of depressive and manic symptoms was significantly associated to improved mother-to-infant bonding over the course of Mother and Baby Unit admission. Treatment of the depressive and/or manic symptoms will therefore improve bonding in almost all women. For a small group (5.7%), treatment of symptoms was not sufficient and special

care and treatment focused on bonding might be required. Therefore clinicians should assess mother-to-infant bonding in mothers with postpartum psychosis and postpartum depression both during the acute episode and after remission.

PART II. BIPOLAR I DISORDER DURING THE PERIPARTUM PERIOD

There is strong, clear, and consistent evidence of a specific relationship between childbirth and the risk of a bipolar episode. In contrast to the postpartum period, information about the recurrence risk during pregnancy is limited and the wide variation in the reported rates hampered previous efforts to do a meta-analysis. In addition, very few studies have investigated the risk of a bipolar episode after miscarriage and induced abortion. This is remarkable since both miscarriage and induced abortion are common pregnancy outcomes. The aim of **chapter 5** was to provide an overview of recurrence risk during pregnancy and after live childbirth, miscarriage and induced abortion in women with bipolar I disorder. Participants were 436 women with bipolar I disorder from the Dutch Bipolar Cohort study. These women had in total 919 pregnancies of which 762 resulted in a live childbirth, 118 ended in a miscarriage and 39 ended in induced abortion. Women reported on the occurrence of manic or depressed episodes during the perinatal period. Information about medication use was obtained by questionnaires. The episode risk was 5.2% during pregnancy, and 30.1% in the postpartum period, with a peak in the early postpartum period. The risk of an episode was highest after a live birth (34.4%), and lower after miscarriage (15.2%) and induced abortion (27.8%). Women with an episode during pregnancy or postpartum were less likely to have a second child compared to women with an uneventful first pregnancy (OR=0.34; 95% CI: 0.22-0.51; $p<0.001$); if they had a second child their risk of an episode was significantly elevated with a subsequent pregnancy (OR=6.17; 95% CI: 3.64-10.45; $p<0.001$).

In addition, we explored the preventive effect of lithium use during pregnancy on bipolar episode risk. Information on the use of lithium during pregnancy could be extracted for 462 pregnancies in 272 women with a diagnosis of bipolar I disorder *before* conception. In total, 18.8% (87/462) of pregnancies were supported by lithium prophylaxis. The episode risk was significantly lower in lithium supported pregnancies (26.4%; 23/87) compared to unsupported pregnancies (46.7%; 175/375) (OR=0.41; 95% CI: 0.25-0.69; p=0.001). This association remained after adjusting for age of onset, total number of episodes, bipolar family history, and multiple pregnancies within unique women (OR=0.47; 95% CI: 0.26-0.83; p=0.009).

While lithium has the largest evidence base for efficacy in the peripartum period among all mood stabilizers and we did find a protective effect of lithium use during pregnancy on recurrence risk in women with bipolar I disorder, this should always be weighed against the risk of fetal lithium exposure. Recent studies have provided new data on the teratogenicity of lithium, especially during the first trimester, with lithium-exposure during pregnancy leading to an increased risk of major malformations (including cardiac malformations). Lithium use during pregnancy has also been associated with a higher risk of miscarriage. In **chapter 6** we investigated this latter association in n=241 women with a diagnosis of bipolar I disorder from the Dutch Bipolar Cohort study. These women had 443 pregnancies, of which 56 ended in a miscarriage (12.6%; 56/443). The remaining pregnancies ended in a live birth (87.4%; 387/443). Miscarriages occurred in 20.8% of the lithium-exposed pregnancies (16/77), compared with 10.9% of the unexposed pregnancies (40/366) (OR=2.14; 95% CI: 1.13–4.06; p=0.018). After adjusting for the age at conception and the clustering of pregnancies per woman, the odds ratio of miscarriage after lithium use during pregnancy was 2.94 (95% CI: 1.39–6.22; p<0.005). Our findings suggest that, in addition to or via its teratogenic effect, lithium may increase the risk of miscarriage. These possible risks associated with lithium use during pregnancy, need to be carefully weighed against the risk of maternal recurrence. Ideally, women with bipolar I disorder of reproductive age have access to specialized women's mental health care facilities in order to weigh both risk and benefits of medication, with a health care provider specialized in reproductive psychiatry.

PART III. NEUROBIOLOGY OF SEVERE POSTPARTUM MOOD DISORDERS

The perinatal period is a time of known immune dysregulation and one of the few periods in life when there is an obvious biological trigger (parturition) that can be linked to psychiatric symptoms. However, it remains unclear why the vulnerability in this specific period is so high. Most studies of immune dysregulation in perinatal mood and anxiety disorders have focused on peripheral cytokines, but literature from non-perinatal mood disorders also implicates T-cell defects. Earlier research in women with postpartum psychosis showed a defect in the physiological T-cell activation during the postpartum period, and we sought to expand the available evidence on T-cell functioning in women with postpartum depression as well, as described in **chapter 7**. We enrolled n=21 women with postpartum depression matched to n=39 healthy postpartum controls, and

n=114 healthy non-postpartum women, in order to control for confounding factors related to the normal postpartum period. Blood was collected in sodium-heparin EDTA tubes and was analyzed using flow cytometry. We found that mean counts of T-cells (all CD3+ T-cells), T-helper cells (CD3+CD4+ T-cells), and T-cytotoxic cells (CD3+CD8+ T-cells) were significantly increased in healthy postpartum women compared to healthy non-postpartum controls ($p<0.001$, $p=0.007$, and $p=0.002$, respectively), but not in women with postpartum depression. The increases in healthy postpartum women were driven by increases in T_H1 cells and T regulatory cells, increases that were nonexistent or attenuated in women with postpartum depression. Mean counts of CD4+ T-helper memory cells were also increased in healthy postpartum women ($p=0.009$), but slightly decreased in women with postpartum depression ($p=0.066$), when compared to healthy non-postpartum controls. Our study confirms that the postpartum period in healthy women is a time of enhanced T-cell activity. Women with postpartum depression failed to show the physiological enhanced T-cell activity, with possible implications for fetal tolerance and vulnerability to infection and autoimmunity. Future research is needed to further elucidate underlying pathogenic disease mechanisms and potential clinical consequences.

In **chapter 8** we present the main conclusions of this thesis and summarize the current knowledge regarding the relationship between first-onset postpartum psychosis and bipolar disorder. We conclude that first-onset postpartum psychosis might be classified as a distinct diagnostic category within the bipolar spectrum. We discuss implications of current findings and give recommendations for future research, which should advance in considering first-onset postpartum psychosis as a separate entity to postpartum bipolar recurrences. This will make a significant impact on our understanding of the disease classification, leading to appropriate treatment and management of these conditions.

Nederlandse samenvatting

DEEL I. FIRST-ONSET POSTPARTUM PSYCHOSE

Vrouwen met een voorgeschiedenis van *first-onset* postpartum psychose hebben een hoog risico op het krijgen van recidieven. Echter in de literatuur worden grote verschillen in het risico op een recidief beschreven. Een *evidence-based* overzicht van het optreden van terugval na *first-onset* postpartum psychose is belangrijk, met name om de voor- en nadelen van onderhoudsmedicatie te kunnen afwegen. Een overschatting van het risico op terugval kan leiden tot ongegronde zorgen bij zorgverleners, patiënten en hun families, resulterend in overmatig medicatiegebruik, onnodige preventiestrategieën of verandering in gezinsplanning. Omgekeerd kan een onderschatting van het risico op terugval leiden tot onvoldoende aandacht van zorgverleners en onvoldoende onderhoudsbehandeling, wat mogelijk kan resulteren in een verminderde kwaliteit van leven en een verhoogd risico op ziekenhuisopname of zelfmoord. Het doel van de systematische review en meta-analyse beschreven in **hoofdstuk 2** was daarom om het risico op recidief te kwantificeren bij vrouwen met een voorgeschiedenis van *first-onset* postpartum psychose. We voerden een systematisch literatuuronderzoek uit in alle openbare medische elektronische databases en includeerden 6 artikelen in de kwantitatieve analyse, waarin het risico op een recidief (gedefinieerd als elke volgende psychiatrische episode na een *first-onset* postpartum psychose) beschreven wordt bij 645 patiënten. We zagen dat een substantieel deel van de vrouwen met een *first-onset* postpartum psychose (43.5%) geen recidief kreeg buiten de postpartum periode gedurende een gemiddelde follow-up periode van 16 jaar. De overige vrouwen hadden tijdens longitudinale follow-up ten minste één terugval buiten de peripartum periode. Voor deze vrouwen was de bevalling de start van een psychiatrische stoornis met een meer invaliderend ziekteverloop en een grotere kwetsbaarheid voor terugval. Deze bevinding heeft substantiële klinische relevantie aangezien 'geïsoleerde postpartum psychose' (episoden van manie, psychose of ernstige psychotische depressie beperkt tot de postpartum periode) daardoor als een aparte categorie kan worden beschouwd met een gunstiger prognose zonder noodzaak tot levenslange preventie of behandeling.

De meeste studies die in de eerder beschreven meta-analyse zijn geïncludeerd, zijn uitgevoerd in de jaren zeventig en tachtig. Hierdoor is de generaliseerbaarheid van de resultaten beperkt. Het is belangrijk om het risico op recidieven en de longitudinale follow-up te bestuderen in meer actuele behandelsettings. Daarom hebben we het risico op terugval in ons eigen OPPER cohort onderzocht in **hoofdstuk 3**. We analyseerden de lange termijn uitkomsten van 106 patiënten met een voorgeschiedenis van postpartum

psychose. Bij het merendeel van de vrouwen (67.9%) bleef het risico op terugval beperkt tot de periode direct na de bevalling. Het verschil tussen het percentage vrouwen met een geïsoleerde postpartum psychose in deze studie in vergelijking met het percentage vrouwen in onze meta-analyse (43.5%) kan te wijten zijn aan de verschillen in de follow-up periode. Die was in ons OPPER cohort vier jaar, maar varieerde in de meta-analyse van 11 tot 26 jaar. Het is denkbaar dat het percentage recidieven toeneemt naarmate de follow-up langer duurt. Het relatief lagere recidiefpercentage kan ook worden toegeschreven aan goede zorg tijdens de follow-up, waaronder voortzetting van medicatiegebruik en gespecialiseerde gezondheidszorg voor deze vrouwen in de huidige behandelsetting.

Verder wilden we in deze longitudinale prospectieve studie potentiële klinische markers van een psychiatrische stoornis met stemmings- of psychotische episodes buiten de postpartum periode identificeren. Hoewel we vonden dat de overgrote meerderheid van de episodes buiten de kraamtijd tijdens follow-up plaatsvond binnen het bipolaire spectrum, konden we helaas geen klinische voorspellers vinden van 'geïsoleerde postpartum psychose' versus een kwetsbaarheid voor postpartum psychose als uiting van een daaropvolgende affectieve stoornis met episodes buiten de kraamtijd.

In **hoofdstuk 4** presenteren we het effect van *first-onset* postpartum psychose op de hechting tussen moeder en kind. De ontwikkeling van een veilige moeder-kind hechting is belangrijk, aangezien een verstoorde hechting van invloed kan zijn op de emotionele, cognitieve en gedragsmatige ontwikkeling van het kind op de lange termijn. Terwijl in de meeste situaties een adequate hechting zich geleidelijk ontwikkelt na de geboorte, kan de hechting verstoord raken wanneer de moeder lijdt aan een psychiatrische stoornis. Talrijke studies hebben het verband tussen postpartum depressie en onveilige hechting beschreven, maar er is nauwelijks onderzoek gedaan naar moeder-kind hechting bij vrouwen met een postpartum psychose. Omdat de onderliggende aard en het klinische beeld van postpartum depressie en postpartum psychose aanzienlijk verschilt, is het onzeker of de moeder-kind hechting in deze groepen vergelijkbaar is. Bovendien is in eerdere studies niet onderzocht hoe de relatie tussen postpartum depressie/postpartum psychose en onveilige hechting wordt beïnvloed door de behandeling van depressieve en manische symptomen. Het verkrijgen van deze gegevens kan inzicht verschaffen in de drijvende factoren achter een onveilige hechting en het belang van bepaalde behandelstrategieën onderstrepen. In deze klinische prospectieve cohort studie op een moeder baby unit in het Erasmus Universitair Medisch Centrum (2005-2013), onderzochten we de verschillen in moeder-kind hechting tussen vrouwen met een postpartum psychose en vrouwen met

een ernstige postpartum depressie. We includeerden 155 vrouwen met een ernstige postpartum stemmingsstoornis, van wie 91 gediagnosticeerd werden met een postpartum psychose en 64 met een postpartum depressie. We ontdekten dat een verstoorde moeder-kind hechting een groot probleem is bij vrouwen met een ernstige postpartum depressie (57.1%), terwijl minder dan 1 op de 5 vrouwen met een postpartum psychose een verminderde hechting rapporteerde (17.6%). Een afname van depressieve en manische symptomen was significant geassocieerd met een verbetering van de moeder-kind hechting tijdens de opname op de moeder baby unit. Behandeling van de depressieve en/of manische symptomen zal daarom bij bijna alle vrouwen de moeder-kind hechting verbeteren. Voor een kleine groep (5.7%) was de behandeling van depressieve en/of manische symptomen niet voldoende en zou speciale zorg en behandeling gericht op hechting nodig kunnen zijn. Daarom moeten zorgverleners de moeder-kind hechting zowel tijdens de acute psychiatrische episode als na remissie beoordelen bij moeders met een postpartum psychose of postpartum depressie.

DEEL II. BIPOLAIRE I STOORNIS TIJDENS DE PERI-PARTUM PERIODE

Er is overduidelijk en consistent bewijs voor een verhoogd risico op een bipolaire episode na de bevalling. Er is echter weinig literatuur over het risico op een bipolaire episode tijdens de zwangerschap en de grote variatie in de gerapporteerde percentages belemmerde eerdere pogingen om een meta-analyse te doen. Bovendien hebben slechts weinig studies dit risico onderzocht na een miskraam of een geïnduceerde abortus. Dit is opmerkelijk omdat zowel een miskraam als een geïnduceerde abortus veel voorkomende zwangerschapsuitkomsten zijn. Het doel van **hoofdstuk 5** was om een overzicht te geven van het risico op een stemmingsepisode tijdens de zwangerschap en na de bevalling van een levendgeborene, een miskraam en een geïnduceerde abortus bij vrouwen met een bipolaire I stoornis. Deelnemers waren 436 vrouwen met een bipolaire I stoornis uit de Nederlandse Bipolar Genetics studie. Deze vrouwen hadden in totaal 919 zwangerschappen, waarvan er 762 resulteerden in een levendgeborene, 118 eindigden in een miskraam en 39 eindigden in een abortus. Vrouwen rapporteerden over het optreden van manische of depressieve episodes tijdens de perinatale periode. Informatie over medicatiegebruik werd verkregen door middel van vragenlijsten. Het risico op een episode was 5.2% tijdens de zwangerschap en 30.1% in de postpartum periode met een piek in de vroege postpartum periode. Het episode-risico was het hoogst na

een levendgeborene (34.4%) en lager na een miskraam (15.2%) en een geïnduceerde abortus (27.8%). Vrouwen met een episode tijdens de eerste zwangerschap of postpartum periode kregen minder vaak een tweede kind in vergelijking met vrouwen die geen episode hadden tijdens deze periode (OR=0.34; 95% CI: 0.22-0.51; p<0.001); als ze wel een tweede kind kregen, was hun risico op een episode significant verhoogd bij een volgende zwangerschap (OR=6.17; 95% CI: 3.64-10.45; p<0.001).

Daarnaast hebben we het preventieve effect van lithiumgebruik tijdens de zwangerschap op het risico op bipolaire episodes onderzocht. Informatie over het gebruik van lithium tijdens de zwangerschap kon worden verkregen voor 462 zwangerschappen bij 272 vrouwen waarvan de diagnose bipolaire I stoornis *voor* de conceptie gesteld was. In totaal werd 18.8% (87/462) van de zwangerschappen medicamenteus ondersteund door lithiumprofylaxe. Het episode risico was significant lager bij door lithium ondersteunde zwangerschappen (26.4%; 23/87) in vergelijking met niet-ondersteunde zwangerschappen (46.7%; 175/375) (OR=0.41; 95% CI: 0.25-0.69; p=0.001). Deze associatie bleef bestaan na correctie voor confounders: leeftijd waarop de ziekte begon, het totaal aantal episodes, een positieve bipolaire familiegeschiedenis en meerdere zwangerschappen bij unieke vrouwen (OR=0.47; 95% CI: 0.26-0.83; p=0.009).

Hoewel lithium in de peripartum periode het best onderzochte en meest effectieve middel is onder alle stemmingsstabilisatoren en ook wij een beschermend effect van lithiumgebruik tijdens de zwangerschap op het risico op terugval hebben gevonden bij vrouwen met een bipolaire I stoornis, moet dit altijd worden afgewogen tegen het risico van foetale blootstelling aan lithium. Recente onderzoeken rapporteren over de teratogeniciteit van lithium, met name tijdens het eerste trimester. Blootstelling aan lithium tijdens de zwangerschap leidt tot een verhoogd risico op ernstige misvormingen, inclusief hartafwijkingen. Lithiumgebruik tijdens de zwangerschap is ook in verband gebracht met een hoger risico op een miskraam. In **hoofdstuk 6** onderzochten we deze laatste associatie bij n=241 vrouwen met de diagnose bipolaire I stoornis uit de Nederlandse Bipolaire Genetics studie. Deze vrouwen hadden 443 zwangerschappen, waarvan 56 in een miskraam eindigden (12.6%; 56/443). De overige zwangerschappen eindigden in een levendgeborene (87.4%; 87/443). Miskramen traden op bij 20.8% van de aan lithium blootgestelde zwangerschappen (16/77), in vergelijking met 10.9% van de niet-blootgestelde zwangerschappen (40/366) (OR=2.14; 95% CI: 1.13-4.06; p=0.018). Na correctie voor confounders (de leeftijd bij de conceptie en de clustering van zwangerschappen per vrouw), was de odds ratio van een miskraam na lithiumgebruik

tijdens de zwangerschap 2.94 (95% CI: 1.39–6.22; p<0.005). Onze bevindingen suggereren dat lithium, naast - of via - het teratogene effect, het risico op een miskraam kan verhogen. De mogelijke risico's die samenhangen met het gebruik van lithium tijdens de zwangerschap, moeten zorgvuldig worden afgewogen tegen het risico op een recidief bij de moeder. Idealiter hebben vrouwen met een bipolaire I stoornis in de vruchtbare leeftijd toegang tot gespecialiseerde instellingen voor geestelijke gezondheidszorg gericht op vrouwen, om zowel de risico's als de voordelen van medicatie af te wegen met een zorgverlener die gespecialiseerd is in reproductieve psychiatrie.

DEEL III. NEUROBIOLOGIE VAN ERNSTIGE POST-PARTUM STEMMINGSSTOORNISSEN

De perinatale periode is een van de weinige perioden in het leven waarin de kwetsbaarheid voor psychiatrische symptomen kan worden geassocieerd met een duidelijke biologische trigger, zoals immunologische en hormonale veranderingen. Het blijft echter onduidelijk waarom de kwetsbaarheid precies in deze periode zo groot is. De meeste onderzoeken naar immuundysregulatie bij perinatale stemmings- en angststoornissen hebben zich gericht op perifere cytokines, maar literatuur over niet-perinatale stemmingsstoornissen impliceert ook T-cel defecten. Eerder onderzoek bij vrouwen met een postpartum psychose toonde een defect in de fysiologische T-cel activering tijdens de postpartum periode aan. Wij hebben geprobeerd het beschikbare bewijs over het functioneren van T-cellen uit te breiden naar vrouwen met een postpartum depressie, zoals beschreven in **hoofdstuk 7**. We includeerden daartoe n=21 vrouwen met een postpartum depressie gematched met n=39 gezonde postpartum controles, en n=114 gezonde niet-postpartum vrouwen om te controleren op confounders gerelateerd aan de normale postpartum periode. Bloed werd verzameld in natrium-heparine EDTA-buizen en werd geanalyseerd met behulp van flowcytometrie. We vonden dat de gemiddelde tellingen van T-cellen (alle CD3+ T-cellen), T-helper cellen (CD3+CD4+ T-cellen) en T-cytotoxische cellen (CD3+CD8+ T-cellen) significant verhoogd waren bij gezonde postpartum vrouwen vergeleken met gezonde niet-postpartum controles (respectievelijk p<0.001, p=0.007 en p=0.002), maar niet bij vrouwen met een postpartum depressie. De stijgingen bij gezonde postpartum vrouwen werden veroorzaakt door stijgingen in T_H1-cellen en T-regulerende cellen, stijgingen die niet bestonden of afzwakten bij vrouwen met een postpartum depressie. Het gemiddelde aantal CD4+ T-helper geheugencellen was ook verhoogd bij gezonde postpartum vrouwen (p=0.009), maar licht gedaald

bij vrouwen met een postpartum depressie (p=0.066) in vergelijking met gezonde niet-postpartum controles. Onze studie bevestigt dat de postpartum periode bij gezonde vrouwen een periode is van verhoogde T-cel activiteit. Vrouwen met een postpartum depressie vertoonden geen fysiologisch verhoogde T-cel activiteit met mogelijke implicaties voor foetale tolerantie en kwetsbaarheid voor infecties en auto-immuniteit. Toekomstig onderzoek is nodig om de onderliggende pathogene ziektemechanismen en mogelijke klinische gevolgen verder te verhelderen.

In **hoofdstuk 8** presenteren we de belangrijkste conclusies van dit proefschrift en vatten we de huidige kennis samen over de relatie tussen *first-onset* postpartum psychose en een bipolaire stoornis. We concluderen dat *first-onset* postpartum psychose geclassificeerd kan worden als een aparte diagnostische categorie binnen het bipolaire spectrum. We bespreken implicaties van de huidige bevindingen en geven aanbevelingen voor toekomstig onderzoek naar *first-onset* postpartum psychose als een afzonderlijke entiteit ten opzichte van episodes in het kader van een bipolaire stoornis. Dit zou een aanzienlijke impact kunnen hebben op de classificatie van deze ziekte en mogelijk leiden tot een beter passende preventie en behandeling.

PhD portfolio

Name PhD student:	Janneke Gilden
Erasmus MC Department:	Psychiatry
Research School:	NIHES
PhD period:	June 2016 – November 2021
Promotors:	W.J.G. Hoogendijk, V. Bergink
Supervisor:	A.M. Kamperman

PHD TRAINING AND ACTIVITIES	**Year**	**ECTS**
Master of Science in Clinical Epidemiology	2017 – 2020	70

Common Core:

- Principles of Research in Medicine and Epidemiology (ESP01)
- Study Design (CC01)
- Biostatistical Methods I: Basic Principles (CC02)
- Biostatistical Methods II: Classical Regression Models (EP03)
- M Research (M-RES)
- Introduction to Medical Writing (SC02)

Specialisation:

- Clinical Translation to Epidemiology (CE01)
- Clinical Epidemiology (CE02)
- Principles in Causal Inference (EP01)
- Methods of Public Health Research (ESP11)
- Clinical Trials (ESP14)
- Health Economics (ESP25)
- The Practice of Epidemiologic Analysis (ESP65)
- Fundamentals of Medical Decision Making (ESP70)

Elective courses:

- Women's Health (EP19)
- Cohort Studies (ESP39)
- Case-control Studies (ESP40)
- Introduction to Global Public Health (ESP41)
- History of Epidemiologic Ideas (ESP53)
- Value Based Healthcare, from theory to implementation (ESP76)
- Advanced topics in Decision-making in Medicine (EWP02)
- Advanced Topics in Clinical Trials (EWP10)

PHD TRAINING AND ACTIVITIES (CONTINUED)	Year	ECTS
Other courses		
- Good Clinical Practice re-registration (BROK)	2019	1.5
- Hamilton Depression Rating Scale (HDRS)	2017	
- BKO-workshop "Teach the teacher I"	2016	2.0
- BKO-workshop "Omgaan met groepen"	2016	
- MRI scan authorization	2016	
- Safety course MRI	2016	
- Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)	2016	
- Positive and Negative Syndrome Scale (PANSS)	2016	
- Open Clinica	2015	
- Research Integrity	2015	0.3
- Good Clinical Practice (BROK)	2014	1.5
- Systematic literature retrieval in PubMed	2014	0.4
- Systematic literature retrieval in other databases	2014	0.2
- EndNote	2014	0.2
Supervision and teaching		
- Master thesis Anne K. Smit (MSc)	2018	
- Minor in psychiatry (BSc)	2016	
- Minor in psychiatry (BSc)	2015	
Conference presentations		
- European Conference on Schizophrenia Research	2015	

Publications

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Gilden J, Kamperman AM, Munk-Olsen T, Hoogendijk WJG, Kushner SA, Bergink V
Long-term outcomes of postpartum psychosis: a systematic review and meta-analysis
Journal of Clinical Psychiatry 2020 Mar 10;81(2):19r12906.

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Accepted by International Journal of Bipolar Disorders

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Gilden J*,Osborne LM*, Kamperman AM, Hoogendijk WJG, Spicer J, Drexhage HA, Bergink V
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Holterhues M, **Gilden J,** Bergink V. Psychiatrische stoornissen tijdens de zwangerschap en postpartum periode. Handboek Psychopathologie bij vrouwen en mannen. Van 0 tot 100+.
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