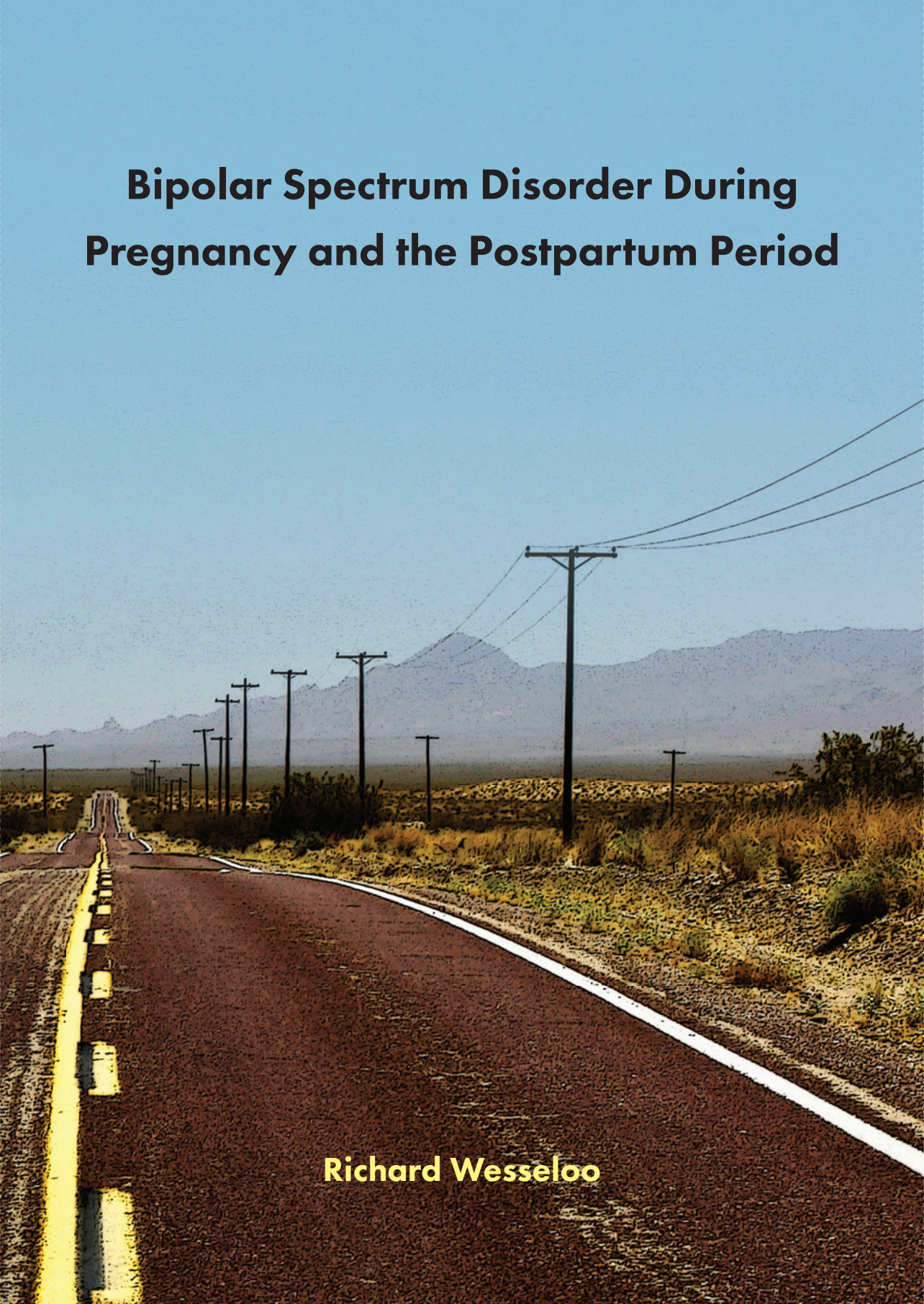
Bipolar Spectrum Disorder During Pregnancy and the Postpartum Period



Richard Wesseloo

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The studies described in this thesis were performed at the Department of Psychiatry, Erasmus Medical Center, Rotterdam, the Netherlands; the Department of Medical and Clinical Psychology, Tilburg University, Tilburg, the Netherlands; and the National Center for Register-Based Research, Aarhus University, Denmark.

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Chapter 1

Introduction

INTRODUCTION

During the postpartum period, women are at high risk for both first-onset and recurrent mood disorder episodes (1-3). This thesis focuses on the treatment and course of mood disorders during pregnancy and the postpartum period, with a main focus on bipolar disorder and postpartum psychosis (bipolar spectrum disorder). In the next paragraphs of this chapter we will provide a brief clinical overview of postpartum mood disorders, followed by the study populations, aims and outline of this thesis.

Postpartum blues

The most prevalent mood disturbance (incidence approximately 50%) during the postpartum period is postpartum blues (i.e. "maternity blues") (4). The onset is between 3 to 5 days postpartum and typical symptoms include: mood lability, tearfulness, irritability, anxiety and difficulty with clear thinking. Notably, feeling depressed is not a key symptom of postpartum blues (4). Postpartum blues is observed in a large number of countries and across different ethnicities (4, 5). Due to its self-limiting course (within a few hours – days) it is not considered as psychopathology (6). However, it is important to notice that postpartum blues is a risk factor for the occurrence of postpartum depression. In addition, it can be difficult to distinguish between postpartum blues and the initial presentation of postpartum psychosis (7, 8).

Postpartum depression

Postpartum depression (often incorrectly referred to as "postnatal depression") is a heterogeneous disorder with an incidence of approximately 10% (7, 9, 10). The onset is within one year postpartum, but in a substantial proportion of women the onset of postpartum depression is already before or during pregnancy (10). The depressive symptomatology can be mild and transient but also very severe and persistent, requiring a psychiatric admission (11). Postpartum depression is associated with a broad range of biological (e.g. age, chronic diseases), psychological (e.g. personality traits) and social (e.g. social economic status, social support) risk factors (7).The diagnostic criteria (adapted from the *Diagnostics and Statistics Manual of Mental Disorders, fifth edition* (DSM-5) (12)) are identical to depression outside the postpartum period and include at least five of the following symptoms (present for at least 2 weeks): either depressed mood or anhedonia, together with insomnia (or hypersomnia), weight loss (or weight gain), psychomotor agitation (or retardation), fatigue, feelings of guilt, diminished ability to think or concentrate, or recurrent thoughts of death. The *Edinburgh Postnatal Depression Scale* (EPDS) (13) is a validated and useful 10-item self-reporting questionnaire that is often used to identify women with a high probability of postpartum depression.

The most important clinical risk factor for postpartum depression is an episode of depression earlier in life and/or during pregnancy. However, a subgroup of women is at risk for a first-

onset episode of postpartum depression (7, 14). Among those women, biological risk factors probably play a more important role (15-17). During the diagnostic phase it is very important to beware of potential somatic causes of depressive symptomatology, such as auto-immune thyroid dysfunction. This disorder is defined by auto-immune inflammation of the thyroid and the presence of thyroid auto-antibodies (most commonly thyroid peroxidase antibodies (TPO-ab)) (18). It is also essential to assess the presence of social and/or environmental stressors such as lack of social support, life-events and financial problems. Treatment options of postpartum depression are psychotherapy, mother-baby therapy and treatment with antidepressants (7). The vast majority of women have a favorable prognosis. However, postpartum depression can also represent an incipient bipolar disorder mood episode (19, 20).

Bipolar disorder

Bipolar disorder (manic depressive illness) is a disabling and chronic psychiatric mood disorder with a lifetime prevalence of 1-3%. The onset is typically in early adulthood and the illness is characterized by recurrent episodes of depression and (hypo)mania (21, 22). The postpartum period is an important trigger for both first-onset and recurrent bipolar disorder mood episodes (1, 2).

The diagnostic criteria for bipolar depression are identical to the criteria for unipolar depression (see previous paragraph "postpartum depression") (12). Mania is defined with the following diagnostic criteria (adapted from the DSM-5 (12)): a distinct period of abnormally and persistently elevated, expansive or irritable mood and persistently increased activity of energy lasting at least one week, together with three (or four if the mood is only irritable) of the following symptoms: inflated self-esteem or grandiosity, decreased need for sleep, more talkative than usual/pressure to keep talking, flights of ideas or subjective experience that thoughts are racing, distractibility, increased in goal directed activity or excessive involvement in activities with potentially harmful consequences (12). Sometimes, patients also suffer from mood-congruent delusions (e.g. manic-psychotic episode).

In most cases, long-term maintenance treatment with medication is necessary to prevent future bipolar disorder mood episodes (22). Lithium is the most effective known mood stabilizer for the long-term prevention of recurrence in bipolar disorder (23). Other treatment options include valproate, carbamazepine, lamotrigine and second generation antipsychotics (olanzapine, quetiapine, risperidone) (23).

Maintenance treatment during pregnancy might be required, especially in women with recent and/or severe mood episodes. This is a concern because in utero exposure to medication is potentially harmful for the unborn child. Mood stabilizers that are used for the long-term treatment of bipolar disorder have different profiles regarding the risk for neonatal adverse effects. In utero exposure to lithium is probably associated with a slightly increased risk of congenital heart defects (24, 25). Use of valproate and carbamazepine should be avoided

during pregnancy because of the increased risk of neural tube defects and other adverse neonatal outcomes. Regarding second generation antipsychotics and lamotrigine, there seems to be no association with congenital malformations (26). In general, the potential long-term adverse effects of in utero exposure to moodstabilizing medication in children are poorly studied. However, discontinuation of moodstabilizing medication during pregnancy is associated with an increased risk of recurrence (27), which may also be potentially harmful for the unborn child (28). Accordingly, women with bipolar disorder and their clinicians should carefully weigh the risks and benefits of medication use during pregnancy. During the postpartum period, women with bipolar disorder are far more likely to suffer from severe recurrence than women with any other psychiatric diagnosis (2). Importantly, recurrence during pregnancy further increases the risk of a postpartum mood episode (29).

The first weeks after delivery women are particularly vulnerable for mania/psychosis, while depressive episodes typically occur later on in the postpartum period (30). Studies that specifically assessed to what extend use of moodstabilizing medication is effective in the prevention of recurrence during the peripartum period are scarce. This is probably a result of ethical and practical concerns that are related to research in women during their childbearing ages. From a clinical point of view this is very problematic, because it hampers evidence-based decision making during this vulnerable period.

Postpartum psychosis

Postpartum psychosis is the most severe form of psychiatric illness following childbirth with an estimated incidence of 0.3-0.6 per 1000 births in the general population and an onset within four weeks postpartum (1, 31, 32).

Interestingly, the majority of women with postpartum psychosis do not have a history of psychiatric illness (33). Contrary to what the term postpartum psychosis suggests, the disorder is in general considered to be a mood disorder within the bipolar disorder spectrum because affective symptoms (either depressive or (hypo)manic symptoms or a mixed state) are a hallmark of the disease. The most important risk factors are primiparity, a previously established diagnosis of bipolar disorder and/or a history of postpartum psychosis (1, 2, 30). In contrast to postpartum depression, there is no clear evidence that environmental/social risk factors play an important role in the onset of postpartum psychosis. The first symptoms typically present within two weeks postpartum and include insomnia, irritability and increased motor activity. Afterwards, women present with more severe mood symptoms (either depressive or (hypo)manic symptoms or a mixed state), suicide/infanticide thoughts and psychotic symptoms (delusions, hallucinations). In addition, some women have one or more of the following atypical/delirious-like symptoms: alterations in level of consciousness, disorientation, depersonalization and derealisation (33, 34). A psychiatric mother-baby admission is necessary for diagnostic evaluation (especially to assess potential somatic causes of postpartum psychosis), to reduce the risk of suicide/

infanticide, to optimize treatment and to enhance mother-baby interaction (34, 35).

Cases of severe psychiatric illness with an acute onset postpartum have already been described in the medical literature for centuries and nowadays the term postpartum psychosis is commonly used by both clinicians and researchers (5, 36). However, postpartum psychosis is not classified as a separate disorder in either the *International Classification of Diseases* (ICD) or DSM-5 (34, 36). The main reason for the absence of a separate disease status is the close link between postpartum psychosis and bipolar disorder. In a substantial proportion of women, first-onset postpartum psychosis is the incipient episode of a bipolar disorder disease course (3, 37). However, as stated by Bergink and colleagues (36) in a recent editorial, there are several arguments to maintain the diagnostic concept of postpartum psychosis: 1. It highlights childbirth as a highly specific and very significant trigger of psychiatric illness and the onset timing coincides with a period of several neurobiological changes. 2. Its distinct phenotype: although affective symptomatology is a hallmark of postpartum psychosis, the clinical presentation is often different than in bipolar disorder. For example, women with postpartum psychosis often have mood-incongruent delusions. 3. Its course: in contrast to women with bipolar disorder, a substantial group of women with postpartum psychosis is only vulnerable for the onset of psychiatric illness during the postpartum period.

Treatment of postpartum psychosis with a combination of antipsychotic medication and lithium is highly effective and at nine months postpartum the majority of women report good functional recovery (38, 39). As mentioned earlier, women with postpartum psychosis are at very high risk for mania or psychosis after a subsequent delivery. Fortunately, short-term prophylactic lithium use during the postpartum period is highly effective in the prevention of such episodes (29).

Study populations

Women that were included in studies described in this thesis were selected from the following clinical or population-based cohorts:

1. **The OPPER-study** (Onderzoeksprogramma Postpartum Psychose, Erasmus MC Rotterdam): a prospective clinical cohort study (2005 – present) including patients with a postpartum onset of severe depression, mania and/or psychosis who are admitted to the psychiatric mother-baby unit of Erasmus MC in Rotterdam. The OPPER-study focuses on the etiology, phenomenology, risk factors, treatment and course (follow-up) of postpartum psychosis.

2. **The NP3-study** (National Postpartum Psychosis Prevention study): a clinical cohort study. The aim of this study is to investigate the clinical outcome of pregnancies in women with a history of bipolar disorder and/or postpartum psychosis, with follow-up until 3.5 years

postpartum. The NP3-study primarily focuses on the risks and benefits of maintenance treatment during pregnancy and/or the postpartum period. The NP3-study consists of a retrospective cohort (2003 – 2013, Erasmus Medical Centre (Erasmus MC) Rotterdam and Leiden University Medical Centre (LUMC) and a prospective cohort with nationwide inclusion (2013 – present).

3. **The HAPPY-study** (Holistic Approach to Pregnancy and the first Postpartum Year, Tilburg University): a population based prospective cohort study (2013 – present) with follow-up of pregnant women throughout all trimesters of pregnancy and the first postpartum year. The HAPPY-study focuses on physiological and psychological determinants that may influence maternal and/or infant wellbeing during the peripartum period, with a specific focus on mental health (40).

4. **National Centre for Register Based Research** (Aarhus University, Denmark): all live-births and residents in Denmark are registered in The Danish Civil Registration System, which provides the unique opportunity to link individual data of several civil and medical registers (41). A major advantage of register based population based cohort studies is that the whole population is eligible for inclusion, thereby eliminating the risk of selection bias.

Outline and aims of this thesis

In **Part I** of this thesis we focus on the postpartum period as a trigger for first-onset or recurrent mood disorder episodes. In **chapter 2** we present a systematic review and meta-analysis. The aim of this study is to quantify the risk of postpartum recurrence/relapse among women with a history of bipolar disorder or postpartum psychosis. In addition, we summarize the current evidence regarding the efficacy of mood-stabilizing medication during pregnancy and the postpartum period. The aim of **chapter 3** is to provide an overview of the diagnostic considerations, treatment and prevention of postpartum psychosis. With regard to prevention, we specifically highlight the differences between women with bipolar disorder and an isolated history of postpartum psychosis. The objective of **chapter 4** is to identify subgroups of patients with postpartum psychosis based on symptom profiles, by using a patient centered analytic approach (OPPER-study). The aim of **chapter 5** is to assess the association between the presence of thyroid peroxidase antibodies (TPO-ab) in early pregnancy and the risk of first-onset postpartum depression (HAPPY-study).

Part II of this thesis focuses on dosing strategies and the efficacy of lithium use during pregnancy and the postpartum period among women with bipolar disorder. In **chapter 6**, we provide a general introduction on the history and clinical aspects of lithium therapy. The aim of **chapter 7** is to quantify the timing and onset of fluctuations in lithium blood levels, that are a

result of pregnancy-related physiological changes in renal function (NP3-study). In **chapter 8**, we compare the efficacy of lithium and lamotrigine use during pregnancy in the prevention of postpartum episodes (Danish National registers).

In **chapter 9** we present the main conclusions of this thesis and summarize the current evidence regarding the risks and benefits of maintenance treatment during the peripartum period in women with bipolar disorder. Finally, we provide directions for future research.

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Chapter 2

Risk of postpartum relapse in bipolar disorder and postpartum psychosis: a systematic review and meta-analysis

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ABSTRACT

Objective: Women with a history of bipolar disorder, postpartum psychosis, or both are at high risk for postpartum relapse. The aim of this meta-analysis was to estimate the risk of postpartum relapse in these three patient groups.

Method: A systematic literature search was conducted in all public medical electronic databases, adhering to the PRISMA guidelines. Studies were included if they reported postpartum relapse in patients diagnosed with bipolar disorder and/or a history of postpartum psychosis or mania according to DSM or ICD criteria or the Research Diagnostic Criteria.

Results: Thirty-seven articles describing 5,700 deliveries in 4,023 patients were included in the quantitative analyses. The overall postpartum relapse risk was 35% (95% CI=29, 41). Patients with bipolar disorder were significantly less likely to experience severe episodes postpartum (17%, 95% CI=13, 21) than patients with a history of postpartum psychosis (29%, 95% CI=20, 41). Insufficient information was available to determine relapse rates for patients with bipolar disorder and a history of postpartum episodes. In women with bipolar disorder, postpartum relapse rates were significantly higher among those who were medication free during pregnancy (66%, 95% CI=57, 75) than those who used prophylactic medication (23%, 95% CI=14, 37).

Conclusions: One-third of women at high risk experience a postpartum relapse. In women with bipolar disorder, continuation of prophylactic medication during pregnancy appears highly protective for maintaining mood stability postpartum. In women with a history of isolated postpartum psychosis, initiation of prophylaxis immediately after delivery offers the opportunity to minimize the risk of relapse while avoiding in utero medication exposure.

INTRODUCTION

The onset of severe psychiatric illness immediately after childbirth has been described extensively. In the 19th century, case reports described women with severe mania or psychosis after every delivery, including some with as many as 13 pregnancies (1). Interestingly, these women had isolated episodes of postpartum psychosis or mania without psychiatric episodes outside the postpartum period. Later studies confirmed the vulnerability to psychosis and mania specifically in the postpartum period, including a high postpartum relapse risk after subsequent pregnancies (2, 3). Accordingly, a history of isolated postpartum psychosis is widely considered a strong risk factor for future severe postpartum episodes.

A second group at high risk for relapse in the postpartum period comprises women with a previous diagnosis of bipolar disorder. Patients with bipolar disorder are more likely to experience a puerperal psychiatric admission compared with patients with any other psychiatric diagnosis. Kendell et al. (4) were the first to quantify this risk in a population-based cohort. They described a relapse risk of 16% for puerperal admission in patients with bipolar disorder, compared with 3% for patients with schizophrenia and 2% for patients with depression. More recently, Munk-Olsen et al. (5) replicated this finding in a birth register study by comparing the relative risk for puerperal admissions during the first month postpartum with admissions 11–12 months postpartum. They found a higher relative risk for relapse during the early postpartum period for patients with bipolar disorder (relative risk=37.2, 95% CI=13.6, 102.0), compared with patients with schizophrenia (relative risk=4.6, 95% CI=2.5, 8.5) or other psychiatric disorders (relative risk=3.0, 95% CI=1.9, 4.7).

Women diagnosed with bipolar disorder are at high risk for postpartum episodes, including psychosis and mania. Moreover, first-onset psychosis or mania occurring in the postpartum period is sometimes found in retrospect to be the incipient episode of a lifelong diagnosis of bipolar disorder (6, 7). Importantly, however, retrospective long-term follow-up studies have shown that a substantial proportion of women with first-onset postpartum psychosis or mania do not have a bipolar illness course with manic and depressive episodes outside the postpartum period (6). Instead, these women have isolated postpartum psychosis: their risk of mania and psychosis appears to be limited to the postpartum period. Accordingly, increasing evidence suggests that isolated postpartum psychosis may represent a unique diagnostic entity, distinct from bipolar disorder (8). Previous studies have demonstrated important differences between isolated postpartum psychosis and bipolar disorder, in both acute treatment and medication prophylaxis (3, 8, 9). From a neurobiological perspective, it is likely that women with isolated postpartum psychosis have a selective vulnerability to the endocrine and immunological changes that follow childbirth, in contrast to women with bipolar disorder, for whom neurobiological triggers are also present outside the postpartum period (10, 11).

Estimation of relapse risks for women with isolated postpartum psychosis or bipolar disorder have been described in prospective, retrospective, and birth cohort studies. However,

the high variability of reported relapse rates across different studies has hampered efforts to obtain a precise quantification. For example, a Swedish birth register study described a postpartum relapse rate of 8.5% in patients with bipolar disorder, whereas an Italian retrospective cohort study found a prevalence rate of 75% in medication-free patients with bipolar disorder (12, 13). Similar difficulties in the interpretation of studies have arisen for patients with a history of postpartum episodes. For example, a 2012 prospective cohort study from the Netherlands reported a relapse rate of 14% in women with isolated postpartum psychosis, whereas a 2013 retrospective cohort study from the United Kingdom reported a relapse rate of 58% in patients with a history of postpartum psychosis (2, 3).

A weighted estimation of relapse risk is essential for clinicians and patients to perform a risk-benefit analysis and should ideally include an estimate of the duration of the high-risk period. On the basis of these evidence-based prognoses, patients can be empowered to develop an individualized peripartum plan with their clinicians, covering the period from conception to 1 year postpartum. Before conception, the magnitude of the estimated relapse risk often directly influences family planning. Previous studies have shown that women with first-onset postpartum mania or psychosis are less likely to have additional children. Moreover, women with bipolar disorder are known to have lower fecundity rates compared with the general population (14). The estimated risk of relapse is particularly relevant during pregnancy, in balancing the benefits of prophylactic medication with the risks of fetal medication exposure. In the postpartum period, decisions regarding pharmacotherapy and breastfeeding are strongly influenced by the estimated risk of relapse.

Clearly, the accuracy and reliability of the weighted estimation of relapse risk is a major determining factor underlying the benefit of this approach. Unfortunately, however, researchers and clinicians have limited knowledge about the relapse risk. An overestimation of relapse risk might lead to overly distressed future parents, excessive medication use, reduced rates of breastfeeding, or unnecessarily altered family planning. Underestimation of relapse risk might lead to ineffective relapse prevention strategies and delay referral for specialized perinatal care in which optimal coordination between obstetric and mental health care providers could otherwise be arranged (3). With even more severe consequences, underestimation of relapse risk would undoubtedly result in higher rates of quality of life impairment, acute inpatient hospitalization, and suicide (15).

In this study, we performed a systematic review and meta-analysis to examine the risk of postpartum relapse in women with a history of bipolar disorder, postpartum psychosis or mania, or both diagnoses. We compared the severity of episodes and the duration of postpartum follow-up and examined the association between relapse and prophylactic medication. We also identified methodological factors that account for heterogeneity across studies.

METHOD

Literature search

The initial systematic literature search was performed on Aug. 26, 2013, in all large electronic medical databases, using the search terms "bipolar," "postpartum," "psychosis," and "relapse" and "risk." The search was updated on Jan. 6 and Nov. 11, 2014 (see the data supplement that accompanies this article).

Selection of studies

The selection procedure was conducted according to the PRISMA and MOOSE guidelines (16, 17). Studies were eligible for inclusion if they were written in English and if patients were diagnosed with bipolar disorder and/or a history of a psychotic or manic episode following childbirth according to DSM criteria, ICD criteria, or the Research Diagnostic Criteria (RDC) (18). Information about psychiatric relapse within 12 months postpartum was obtained (proportion of patients and/or deliveries). We defined relapse as psychosis, mania or hypomania, depression (or a mixed episode), and/or psychiatric hospitalization. All longitudinal study designs (cohort studies, randomized controlled trials, and birth register studies) were suitable for inclusion.

Data extraction

Data were extracted by two independent observers (R.W. and A.M.K.) using a data extraction form. Observers were not blind to authors, institutions, or journals. In case of difference in assessment between the two observers, a decision was made with help from a third independent observer (V.B.). Relapse rates were extracted both for patients with a history of bipolar disorder and for those with a history of postpartum psychosis. Studies reporting incidence or prevalence rates were considered eligible for inclusion. As the numerator, relapse events, including psychosis, mania or hypomania, depression (or a mixed episode), and/or psychiatric hospitalization were counted. An event was defined as a severe relapse when an affective psychosis, mania, mixed episode, or relapse required hospitalization. As the denominator, we used the total number of deliveries (study outcome incidence rate) or patients (study outcome prevalence rate). For studies that included more than one delivery per patient, deliveries were considered independent events. In longitudinal studies of patients with a history of postpartum psychosis, only participants with subsequent deliveries were included. Studies that examined various diagnostic entities (e.g., bipolar disorder and schizophrenia) were included only if relapse outcomes were described for each diagnostic category. We screened all included studies for postpartum relapse rates with regard to prophylactic pharmacotherapy. We compared postpartum relapse rates between women with and without prophylactic medication use during pregnancy, the postpartum period, or both.

If a study reported relapse rates at more than one time point during the postpartum period, the data were pooled to calculate an overall relapse rate. All included studies were part of the qualitative synthesis. In those sets of articles for which overlapping cohorts were used, only the most complete or most recent data set was included in the meta-analysis (quantitative synthesis).

Quality Assessment

The reviewers independently assessed the quality of the included studies, according to the GRADE guidelines (19). Potential bias was assessed with regard to the following quality criteria (20): definition of inclusion (DSM, ICD, RDC), definition of relapse (DSM/RDC/ICD, hospitalization, clinical interview, or unknown), handling of missing data, and year of publication.

Procedure for meta-analyses

We used random-effects estimation and a 95% confidence interval to calculate an overall relapse rate. This provided the opportunity to compare relapse rates between patients with bipolar disorder and those with a history of postpartum psychosis and to assess the influence of pharmacotherapy on relapse. Random-effects analysis was used because it produces a more reliable estimate of the overall relapse rate than fixed-effects analysis in case of substantial heterogeneity (21). Univariate analyses were performed to assess the association of independent variables with the overall relapse rate. The association with categorical characteristics was assessed using random-effects estimation to calculate and compare the overall outcome per category. Q statistics and significance levels are reported. The association of continuous characteristics with outcome was assessed by performing mixed-effects meta-regression analyses using unrestricted maximum-likelihood estimation, with log relapse rate as the response variable. We added 0.0001 in case of zero cell observations. Beta values with 95% confidence intervals and significance levels are reported. Statistical analyses were performed using the Comprehensive Meta-Analysis program, version 2.2.034 (22).

Publication bias

Publication bias was visually assessed with a funnel plot and formally with the Egger test, to assess whether the relapse rate decreased with increasing sample size. Plots with a funnel shape are considered to occur only when publication bias is low or absent. Since nonsignificant studies are less likely to be published, studies in the bottom left-hand corner of the plot are often omitted (23).

Heterogeneity and sensitivity analyses

Cochran's Q test and I^2 statistics were used to quantify heterogeneity across studies. Heterogeneity was further explored by conducting sensitivity analyses. For this aim, we calculated the overall relapse rate using both fixed- and random-effects modeling and evaluated the impact of the modeling procedure on the overall relapse rate of all studies. We compared relapse rates based on the study quality criteria described in the Quality Assessment section above. In addition, we compared retrospective cohort, prospective cohort, and birth register studies; incidence rates and prevalence rates; one delivery per patient versus multiple deliveries per patient; qualitative versus quantitative synthesis; and duration of follow-up. For the analyses regarding the duration of follow-up, we categorized studies by the following thresholds: relapse within <4 weeks, <3 months, <6 months, and <12 months postpartum. Finally, we assessed the influence of the duration of follow-up as a continuous variable on relapse rate.

RESULTS

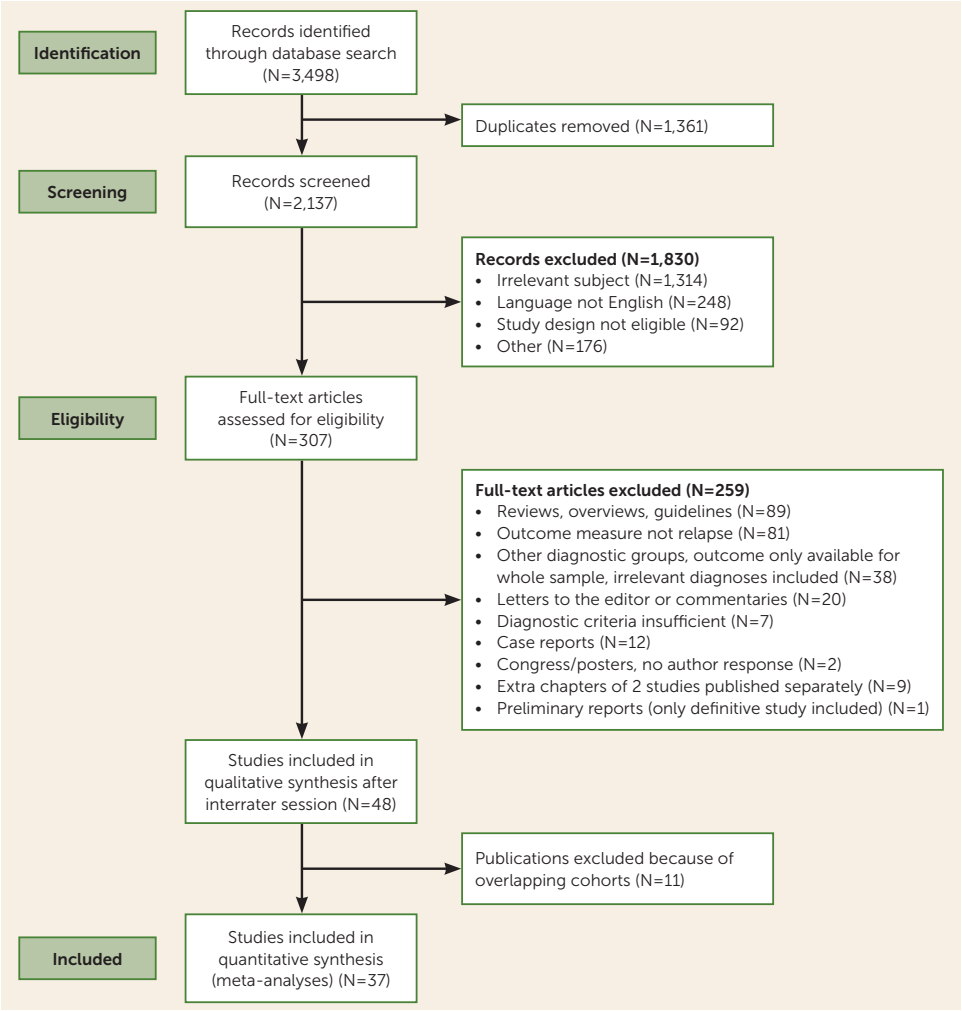
Selection of studies

The literature search produced a set of 3,498 articles. After de-duplication, the set was narrowed to 2,137 articles, which were then reviewed in an interrater session (R.W. and A.M.K.) based on title and abstract, resulting in an initial selection of 307 articles. After full-text assessment of the 307 articles, 48 were included in the qualitative synthesis. Screening for overlap in the investigated cohorts resulted in the exclusion of 11 studies. Therefore, 37 articles were included in the quantitative synthesis; publication dates were between March 1986 and October 2014 (articles published before March 1986 did not use DSM, ICD, or RDC criteria and were therefore not considered) (Figures 1 and 2). Interrater reliability was high (raw interrater agreement=94.7%, kappa=0.88, 95% CI=0.80, 0.96).

Study characteristics

In the quantitative selection (N=37 studies), the outcome of 5,700 deliveries in 4,023 patients was provided. We found an overall postpartum relapse risk of 35% (95% CI=29, 41). Twenty-four studies focused on patients with bipolar disorder, 12 studies focused on patients with a history of postpartum psychosis, and one study described independent groups of patients with bipolar disorder and a history of postpartum psychosis (Figures 2 and 3A). The largest study described the outcome of 1,828 deliveries in the United Kingdom (24). Other large studies were conducted at centers in the United States (1,120 deliveries) (25), Sweden (786 deliveries) (12), Italy (276 women) (13) and Denmark (208 deliveries) (5). Detailed characteristics of all studies are provided in Table S1 of the data supplement.

FIGURE 1. Flowchart of the article selection process in a meta-analysis of risk of postpartum relapse in bipolar disorder and postpartum psychosis

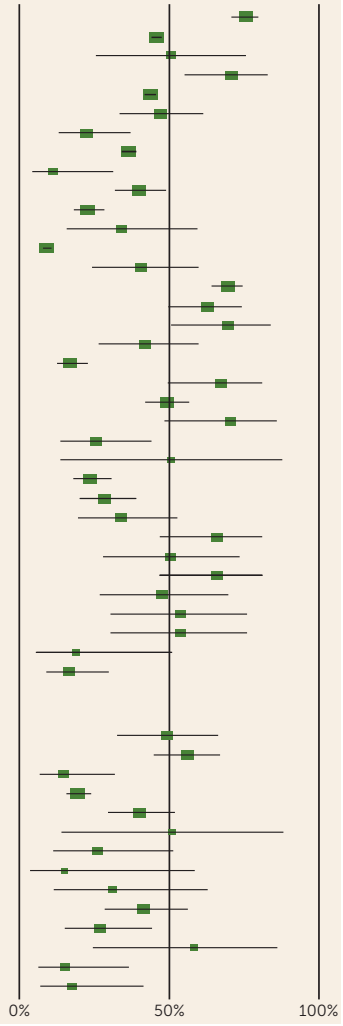


Postpartum relapse rates in patients with bipolar disorder

As shown in Figure 3A, patients with bipolar disorder had an overall relapse risk of 37% (95% CI=29, 45) (25 studies, 5,105 deliveries, 3,495 patients). Three large studies and one small study made a distinction between patients with bipolar I and II disorders (13, 24-26). Two studies included only patients with bipolar I disorder (27, 28) and one study enrolled only patients with bipolar II disorder (29). No significant difference in relapse rates was found between patients with bipolar I and II disorders (bipolar I disorder: N=2,190, 45% [95% CI=32, 58]; bipolar II disorder: N=1,249, 50% [95% CI=35, 65]; Q=0.25, df=1, p=0.62).

FIGURE 2. Postpartum relapse rate per study included in the qualitative and/or quantitative synthesis in a meta-analysis of risk of postpartum relapse in bipolar disorder and postpartum psychosis[a]

Study	Relapse rate (%)	Lower limit	Upper limit	Relapse / total (N / N)
Bipolar disorder				
2014 Maina	75	70	80	207 / 276
2014 Di Florio[1]	45	43	47	1052 / 2329
2014 Ardau	50	24	76	6 / 12
2013 Sharma	70	54	83	26 / 37
2013 Di Florio[1]	43	41	45	786 / 1828
2012 Doyle[1]	47	32	61	20 / 43
2012 Bergink	22	12	37	9 / 41
2011 Viguera[2]	36	33	39	403 / 1120
2010 Bilszta	11	3	31	3 / 23
2010 Colom	39	31	49	43 / 109
2009 Munk-Olsen	22	17	28	46 / 208
2008 Green	33	15	59	5 / 15
2007 Harlow	9	7	11	67 / 786
2006 Sharma	40	23	60	10 / 25
2006 Blackmore[1]	69	63	75	167 / 242
2005 Robertson[1]	62	49	74	34 / 54
2004 Wisner	69	49	84	18 / 26
2003 Kumar	41	25	60	12 / 29
2003 Akdeniz	16	11	23	26 / 160
2002 Freeman	67	48	81	20 / 30
2001 Jones[1]	49	41	57	74 / 152
2000 Viguera[2]	70	47	86	14 / 20
2000 Grof	25	12	44	7 / 28
1999 Pfuhlmann	50	12	88	2 / 4
1998 Blehar	23	17	31	32 / 139
1995 Hunt	28	19	39	22 / 79
1995 Cohen	33	18	53	9 / 27
1993 Kumar[3]	65	46	81	17 / 26
1992 Van Gent	50	27	73	8 / 16
1992 Marks[3]	65	46	81	17 / 26
1992 Austin	47	26	70	8 / 17
1991 Wieck[3]	53	29	76	8 / 15
1989 Wieck[3]	53	29	76	8 / 15
1988 Platz[4]	18	5	51	2 / 11
1987 Kendell[4]	16	8	30	7 / 44
History of postpartum psychosis				
2014 Kapfhammer	48	31	66	14 / 29
2013 Blackmore	55	43	67	37 / 67
2012 Bergink	14	5	31	4 / 29
1999 Terp[5]	18	14	24	49 / 266
1999 Kirpinar	39	28	51	25 / 64
1998 Bagedahl	50	12	88	2 / 4
1995 Videbech[5]	25	10	51	4 / 16
1995 Sichel	14	2	58	1 / 7
1995 Meakin	30	10	62	3 / 10
1994 Schopf	40	27	56	17 / 42
1993 Rohde	26	13	44	8 / 31
1992 Benvenuti	57	23	86	4 / 7
1991 Stewart	14	5	36	3 / 21
1986 McNeil	17	5	41	3 / 18



[a]References are listed in the data supplement. Studies included in the quantitative meta-analysis are shown in boldface. Superscripted numerals adjacent to author names indicate multiple publications based on the same cohort.

Postpartum relapse rates in patients with a history of postpartum psychosis or mania

Patients with a history of postpartum psychosis had an overall relapse risk of 31% (95% CI=22, 42) (13 studies, 595 deliveries, 528 patients) (Figure 3A). Eleven of the 13 studies included only patients with first-onset psychosis, and the other two studies provided no information regarding psychiatric history prior to the onset of their postpartum psychosis. Of the 11 studies that included only patients with first-onset postpartum psychosis, the longitudinal illness course was reported in seven studies.

In three of these seven longitudinal follow-up studies patients with isolated postpartum psychosis were described (54 deliveries, 54 patients) (3, 30, 31). The remaining four studies (144 deliveries, 144 patients) reported that a proportion of patients had nonpuerperal episodes during follow-up. There was no significant difference in postpartum relapse rate between patients with bipolar disorder and patients with a history of postpartum psychosis (Q=0.71, df=1, p=0.40). Heterogeneity was substantial in both diagnostic groups.

FIGURE 3. Overall postpartum relapse rate for each diagnostic group in a meta-analysis of risk of postpartum relapse in bipolar disorder and postpartum psychosis

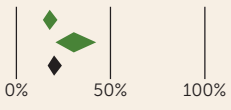
A. Overall relapse[a] rate postpartum per diagnostic group

Diagnostic group	Relapse rate (%)	Lower limit	Upper limit	Total N
Bipolar disorder[b]	37	29	45	5,105
History of postpartum psychosis[c]	31	22	42	595
Overall	35	29	41	5,700

I^2 for bipolar disorder=95%, I^2 for postpartum psychosis=78%, df=1, Q=0.71, p=0.400

B. Overall severe relapse[d] rate postpartum per diagnostic group

Diagnostic group	Relapse rate (%)	Lower limit	Upper limit	Total N
Bipolar disorder[e]	17	13	21	5,078
History of postpartum psychosis[f]	29	20	41	531
Overall	19	15	23	5,609



I^2 for bipolar disorder=82%, I^2 for postpartum psychosis=78%, df=1, Q=5.77, p=0.016

[a] Definitions of relapse: psychosis, mania or hypomania, depression (or a mixed episode), and/or psychiatric hospitalization.
[b] Studies, k=25; deliveries, N=5,105; patients, N=3,495.
[c] Studies, k=13; deliveries, N=595; patients, N=528.
[d] Definitions of severe relapse: psychosis, mania, mixed episode, and/or psychiatric hospitalization.
[e] Studies, k=24; deliveries, N=5,078; patients, N=3,468.
[f] Studies, k=12; deliveries, N=531; patients, N=464.

Postpartum relapse rates in patients with bipolar disorder and previous postpartum episodes

Nine studies provided information on the prior history of postpartum episodes (9/25, 36%). Two birth register studies included only primiparous patients, who by definition did not have a history of postpartum episodes (5, 11). Three studies provided detailed information on patients with bipolar disorder and a prior history of postpartum episodes. The relapse rate was 87% in one study (45/52 patients) (13) and 50% in each of the other two studies (2/4 patients, (32) 4/8 patients (3)). In the remaining four studies, 41–73% of patients with bipolar disorder had a history of postpartum episodes (33-36). Together, there is currently insufficient available information on relapse risk for women with bipolar disorder to permit stratification by their history of previous postpartum episodes.

In a subanalysis, the risk of a severe postpartum episode (affective psychosis, mania, mixed episode, or relapse requiring hospitalization) was significantly higher in patients with a history of postpartum psychosis (29%, 95% CI=20, 41) compared with patients with bipolar disorder (17%, 95% CI=13, 21; Q=5.77, df=1, p=0.016) (Figure 3B). Two studies were excluded because of insufficient information regarding the clinical severity of the postpartum episodes (33, 37).

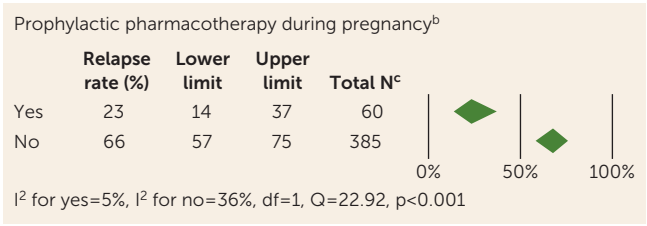
Prophylactic pharmacotherapy during the peripartum period in bipolar disorder

In the quantitative synthesis, a total of five studies provided sufficient information to assess the association between postpartum relapse and prophylactic pharmacotherapy during *both* pregnancy and the postpartum period (3, 35, 36, 38, 39). In addition, three studies provided information on pharmacotherapy during pregnancy (13, 26, 40), and three studies described pharmacotherapy during the postpartum period (33, 34, 41). Overall, patients with bipolar disorder using prophylactic pharmacotherapy during pregnancy had a significantly lower relapse rate (N=60; 23%, 95% CI=14, 37) compared with medication-free patients (N=385; 66%, 95% CI=57, 75; Q=22.92, p<0.001) (Figure 4). Moreover, patients with bipolar disorder using prophylactic pharmacotherapy during the postpartum period had a lower relapse rate (N=98; 29%, 95% CI=16, 47) compared with those who remained medication free (N=107; 65%, 95% CI=55, 73; Q=10.91, p=0.001). Of all 98 women reported as having used medication postpartum, 38 women initiated prophylactic medication during pregnancy (3, 36). Twenty-two patients were medication free during pregnancy and initiated prophylaxis immediately postpartum (3, 35, 36) (see Table S1 in the data supplement). Information regarding the timing of medication initiation was unavailable for 38 women.

Prophylactic pharmacotherapy during the peripartum period in patients with a history of postpartum psychosis or mania

Five studies (5/13, 39%) provided information on pharmacotherapy during the peripartum period. During pregnancy, all patients in these five studies were medication free. Of these studies, three provided information on prophylactic medication use during the postpartum period. One study reported a relapse rate of 30% in 10 medication-free patients (3/10) (42). The second study reported a relapse rate of 14% in 21 patients with lithium prophylaxis (3/21) (43). In the third study, none of the patients using lithium prophylaxis relapsed (0/20), compared with a relapse rate of 44% (4/9) for medication-free patients (3).

FIGURE 4. Overall postpartum relapse rates in patients with bipolar disorder stratified by prophylactic pharmacotherapy during pregnancy[a]



[a] Definitions of relapse: psychosis, mania or hypomania, depression (or a mixed episode), and/or psychiatric hospitalization.
[b] Medications included antipsychotics and mood stabilizers.
[c] Total N indicates the number of patients included in the analysis.

Publication bias

There was no association between year of publication and relapse rates (β=0.02, 95% CI=–0.01, 0.05, Q=1.55, p=0.21). The studies reporting the lowest (9%) and highest (75%) relapse rates (12, 13) were both published relatively recently (2007 and 2014, respectively). A visual inspection of the funnel plot revealed that the plot was asymmetric, with a slightly larger proportion of the medium sized trials clustering to the left of the mean, but no indication of decreasing event rates with increasing sample size (see Figure S1 in the data supplement). The Egger test did not suggest the presence of publication bias (intercept =–0.57, 95% CI=–2.37, 1.24, p=0.53).

Heterogeneity and sensitivity analyses

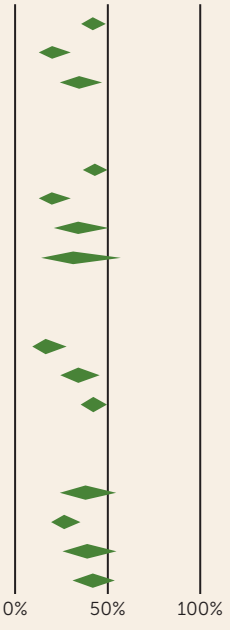
We compared both the inclusion criteria (DSM, ICD, or RDC) and the criteria for relapse (DSM/ICD/RDC, hospitalization, clinical interview, or unreported). Studies that included patients by DSM diagnoses showed higher relapse rates (41%, 95% CI=34, 48) compared with those using ICD diagnoses (19%, 95% CI=12, 29) or RDC criteria (33%, 95% CI=23,

46) (Q=11.74, df=2, p=0.003). Studies that defined their relapse criteria on the basis of DSM, ICD, or RDC criteria showed a higher overall relapse rate (42%, 95% CI=35, 49) compared with studies that used distinct criteria (hospitalization: 19%, 95% CI=12, 29; clinical interview: 33%, 95% CI=20, 50; unreported criteria: 30%, 95% CI=13, 56) (Q=13.07, df=3, p=0.004). No significant difference was found in overall relapse rates, depending on whether or not studies reported their procedures for handling missing data (respectively, 35%, 95% CI=27, 45, and 34%, 95% CI=25, 44; Q=0.05, df=1, p=0.82).

Birth register studies reported lower relapse rates (15%, 95% CI=8, 27) compared with prospective and retrospective cohort studies (33%, 95% CI=23, 45 and 41%, 95% CI=34, 49, respectively; Q=12.42, df=1, p=0.002), primarily because of relatively high relapse rates in the retrospective cohort studies. Twenty-eight studies reported incidence rates (3,297 patients), and the remaining nine studies reported prevalence rates (726 patients). No significant difference was found between studies that reported incidence rates (32%, 95% CI=26, 40) and those that reported prevalence rates (43%, 95% CI=28, 60; Q=1.32, df=1, p=0.25).

FIGURE 5. Relevant sensitivity analyses in a meta-analysis of risk of postpartum relapse in bipolar disorder and postpartum psychosis

	Relapse rate (%)	Lower limit	Upper limit	Total N[a]
Inclusion criteria				
DSM	41	34	48	4,149
ICD	19	12	29	1,323
RDC	33	23	46	228
(df=2, Q=11.74, p=0.003)				
Relapse criteria				
DSM/ICD/RDC	42	35	49	3,976
Hospitalization	19	12	29	1,323
Clinical interview	33	20	50	354
Unreported criteria	30	13	56	47
(df=3, Q=13.07, p=0.004)				
Study design				
Birth register study	15	8	27	1,260
Prospective cohort	33	23	45	402
Retrospective cohort	41	34	49	4,038
(df=2, Q=12.42, p=0.002)				
Duration of follow-up[b]				
1 month	37	23	53	1,091
3 months	26	18	34	1,685
6 months	38	24	54	1,250
12 months	41	30	53	2,143
(df=3, Q=5.57, p=0.134)				



[a] Total N indicates the number of deliveries included in the analysis.

[b] Four studies reported relapse at several time points and were included in two or three categories.

In 10 studies, there were more deliveries than patients. Together these studies described the outcome of 3,613 deliveries in 1,936 patients. There was no significant difference in relapse rates when comparing these 10 studies (33% 95% CI=26, 41) with the 27 studies that limited inclusion to one delivery per patient (35%, 95% CI=25, 47; Q=0.16, df=1, p=0.69).

No significant difference was found between the qualitative and quantitative synthesis (Q=0.82, df=1, p=0.37). The duration of postpartum follow-up ranged from 1 month to 12 months across studies (see Table S1 in the data supplement). However, the majority (89%) of studies defined a threshold between 4 weeks and 6 months postpartum. Regression analysis revealed no significant association between relapse risk and duration of follow-up (β=0.02, 95% CI=-0.06, 0.09; Q=0.23, p=0.63). Furthermore, no difference was found between studies that used different thresholds for the duration of follow-up (Q=5.57, p=0.13). Results of the relevant sensitivity analyses are shown in Figure 5.

DISCUSSION

Our meta-analysis demonstrated that patients with either a history of affective psychosis in the postpartum period or bipolar disorder are at high risk for postpartum relapse. We included 37 articles describing the outcome of 5,700 deliveries in 4,023 patients, and found an overall relapse risk of 35% (95% CI=29,41).

Postpartum relapse rates in patients with bipolar disorder

In women with bipolar disorder, we found an overall relapse risk of 37%. In 17% of the cases, patients suffered from affective psychosis, mania, mixed episodes, or relapses requiring hospitalization, defined as severe episodes. Accordingly, the remaining patients had nonpsychotic affective episodes (mostly depressive and a limited number of hypomanic episodes).

In our subanalysis, we were able to include seven studies, describing the outcome of 2,190 deliveries to patients with bipolar I disorder and 1,249 deliveries to patients with bipolar II disorder. Remarkably, we were unable to detect a differential relapse risk between patients with bipolar I and II disorders. A previous study (24) found a higher relapse risk in patients with bipolar I disorder compared with patients with bipolar II disorder in the United Kingdom. However, as acknowledged by the authors, they observed few hypomanic episodes, possibly because of inherent difficulties in retrospectively documenting hypomanic episodes and therefore biasing the results toward a lower observed relapse risk in patients with bipolar II disorder.

Most studies did not provide information on previous postpartum episodes. The widespread clinical impression is that women with bipolar disorder and previous postpartum episodes might fall within the highest risk category. Unfortunately, we could not estimate the risks for this specific group. Moreover, since we were not able to stratify patients with bipolar disorder by a history of postpartum episodes, it is unclear whether bipolar disorder and a history of postpartum relapse contribute linearly or nonlinearly to the relapse risk for bipolar patients.

Postpartum relapse rates in patients with a history of postpartum psychosis or mania

Few studies have focused on patients with a history of psychosis in the postpartum period, likely because of both the low prevalence and uncertainties regarding its diagnostic status. We included 13 studies (595 deliveries, 528 patients), for which the overall relapse risk was 31%. Notably, only three studies included patients exclusively with isolated postpartum psychosis (54 deliveries, 54 patients). In the remaining 10 studies, a proportion of patients might have had bipolar episodes before the onset of postpartum psychosis (two studies) or after postpartum psychosis (eight studies), although this information was not reported.

The overall relapse rate of patients with a history of postpartum psychosis was not significantly different from the relapse risk observed in patients with bipolar disorder, but patients with a history of postpartum psychosis were more likely to have severe postpartum relapse episodes compared with patients with bipolar disorder. We observed that studies reported few nonsevere postpartum relapse episodes in patients with a history of postpartum psychosis, which could be due to selection and/or information bias. For example, studies in women with a history of postpartum psychosis might have been designed with an inclusion bias favoring patients with severe manic or psychotic relapse but not depression or hypomania. Accordingly, the 31% overall relapse rate we found could be an underestimation.

Prophylactic pharmacotherapy is highly effective for relapse prevention

Most studies of prophylactic pharmacotherapy for bipolar disorder and postpartum psychosis have focused on lithium. In contrast, data regarding the prophylactic efficacy of lamotrigine, olanzapine, quetiapine, and risperidone are scarce (see Table S1 in the data supplement). In women with bipolar disorder, we were able to stratify postpartum relapse rates by pharmacotherapy during pregnancy in 445 women. Women without prophylactic pharmacotherapy during pregnancy had a postpartum relapse rate of 66%, compared with 23% for women with prophylaxis (Figure 4). Medication prophylaxis during pregnancy in women with bipolar disorder appears important not only to maintain mood stability during pregnancy (44), but also for postpartum relapse prevention. However, the benefits of prophylactic pharmacotherapy during pregnancy should be weighed against the potential adverse effects of in utero medication exposure.

Available data were insufficient to allow us to evaluate the efficacy of pharmacotherapy when it is initiated immediately after delivery as a prophylaxis strategy in women with bipolar disorder. Together, our findings suggest a protective effect of lithium throughout pregnancy and the postpartum period.

Two studies (60 patients) described the efficacy of prophylactic pharmacotherapy in women with a history of postpartum psychosis (3, 43). Both studies reported that initiation of prophylactic lithium immediately postpartum after a medication-free pregnancy—and thus eliminating the risk of in utero medication exposure—is highly effective for relapse prevention.

Clinical predictors of relapse

Another possible predictor of relapse is parity. Previous studies showed that primiparity is a risk factor for relapse in the early postpartum period (45, 46). Di Florio et al. (46) found that this effect was not due to women with a history of postpartum episodes being less likely to have additional children. In addition, Munk-Olsen et al. (45) found a higher risk for a first-time psychiatric episode after a second delivery with increasing time between the births of the first and second children. In the present meta-analysis, we were not able to stratify for parity. Therefore, the interpretation of an overall relapse risk requires some caution, especially when comparing patients with bipolar disorder who could be either primiparous or multiparous, with patients with a history of postpartum psychosis who are by definition not primiparous. Notably, as mentioned by Di Florio et al. (46), it is possible that the association between primiparity and relapse is confounded by the higher proportion of multiparous patients using prophylactic pharmacotherapy.

Several additional predictors for postpartum relapse have been described previously, including relapse during pregnancy (3, 47), psychiatric history (13, 48), family history (49), and obstetric complications (50, 51). The assessment of the weight of each of these factors enables clinicians to establish individualized prevention plans for the high-risk postpartum period. Unfortunately, these variables have been understudied and therefore could not be included in this meta-analysis as effect modifiers or confounders.

Heterogeneity across studies

There was considerable heterogeneity across studies, both in their design and in their inclusion and relapse criteria. In contrast to population-based studies, selection bias may have occurred in both prospective and retrospective cohort studies. Our sensitivity analyses demonstrated that retrospective studies reported significantly higher relapse rates compared with birth register and prospective studies. Notably, an important source of selection bias in retrospective cohort studies is nonsystematic sample recruitment. For example, the largest study we examined involved the retrospective analysis of a U.K. cohort of patients with bipolar disorder from which 74% of the patients were recruited via sources such as public media and patient organizations (24). As acknowledged by the authors, this may have led to an overestimation of relapse risk. In addition, retrospective studies have considerable potential for information bias because of long intervals between the relapse episode and data collection. Conversely, prospective studies are inherently biased toward underestimation of relapse risk because of selection bias, since patients with a poor prognosis are less likely to visit an outpatient clinic during pregnancy or to participate in a clinical study.

Birth register studies are more likely to provide estimates of relapse rates that are free of selection and information bias. Moreover, they have superior external validity because they are based on nationwide registers. However, a limitation of birth register studies is the precision

of the available diagnostic information, in particular, the likely absence of data regarding less severe episodes that do not require contact with mental health care specialists, since available information is only based on women who actively sought care. Given that relapse was defined in all birth register studies using the criteria of an inpatient psychiatric admission, it is not surprising that the relapse rates were lower in birth register studies compared with cohort studies.

The majority of patients were included based on DSM or ICD criteria. The substantial difference in relapse rates between patients diagnosed using DSM versus ICD criteria is most likely the result of underlying study designs, rather than the criteria themselves. Almost all studies using ICD criteria were birth register studies (5, 12), while DSM criteria were used in the largest cohort studies (24, 25).

Among the studies included in this meta-analysis, the duration of postpartum follow-up was highly variable, ranging from 4 weeks to 1 year, with the majority of studies having a follow-up interval in the range of 3-6 months. We did not find a statistically significant contribution of follow-up duration to relapse rate, which is consistent with the uniquely high relapse risk in the early postpartum period. In particular, the highest risk period for patients with bipolar disorder and/or a history of postpartum psychosis occurs within the first 3 months postpartum (5, 24).

Research implications

Over the past three decades, postpartum relapse rates in women with a history of bipolar disorder or postpartum psychosis have remained consistently high. Ongoing efforts to elucidate the risk and protective factors for these severe postpartum episodes hold considerable potential for substantially lowering the risk of postpartum relapse. Based on our data, we were not able to quantify the risk of relapse for women with both bipolar disorder and a history of postpartum episodes. Whether these risk factors combine linearly or interact nonlinearly remains to be determined. Future studies should be designed to quantify the relapse risk for potentially distinct subgroups of women with a history of isolated postpartum psychosis or mania, bipolar disorder, and both bipolar disorder and (severe) postpartum episodes. This classification should be based on information on parity and all previous postpartum and nonpostpartum episodes. Notably, birth register studies might be of substantial importance in obtaining these outcomes given their population-wide and naturalistic implementation without selection or information bias.

In addition, there is an urgent need for more detailed data on the efficacy of prophylactic pharmacotherapy, including type, dosing, timing and duration of medication use. Randomized controlled trials are likely to be very difficult to implement. Therefore, large-scale naturalistic prospective cohort studies may be the most practical approach to obtaining these data. Ideally, both maternal and neonatal outcomes should be included, given that postpartum psychiatric episodes are likely to influence the long-term outcome not only of the mother but also of her children.

Clinical implications

In no other situation in psychiatry is it possible to define the moment of illness onset as precisely as in postpartum relapse, which offers the unique possibility of an individualized postpartum relapse prevention plan drafted in collaboration between women and their health care providers. Minimally, relapse prevention planning should include 1) medication prophylaxis during pregnancy and after delivery; 2) an obstetric birth plan, including preference regarding the mode of delivery; 3) progressive intervention strategies beginning from the earliest possible signs of prodromal symptoms for relapse; 4) neonatal medical evaluation for children with in utero medication exposure; 5) preference for baby feeding; 6) strategies to assist women in obtaining adequate sleep, maintain a stable circadian rhythm, limit their stress, support maternal-newborn bonding, and enjoy their newborn experience.

Conclusions

In this meta-analysis, we found an overall postpartum relapse risk of 37% in women with bipolar disorder and 31% in women with a history of postpartum psychosis. The distinction between women with bipolar disorder and those with a history of postpartum psychosis is of substantial clinical relevance, as patients with bipolar disorder were significantly less likely to experience severe episodes postpartum (17%) compared with patients with a history of postpartum psychosis (29%). Moreover, for women with bipolar disorder, continuation of prophylactic medication during pregnancy appears to be critically important for maintaining mood stability after delivery. In contrast, for women with a history of isolated postpartum psychosis, the initiation of prophylaxis immediately after delivery appears to be highly effective for relapse prevention and eliminates the risk of in utero medication exposure. Women have multiple contacts with health services during pregnancy, which provide a compelling opportunity for prevention of postpartum psychiatric episodes. Postpartum relapse prevention plans should be drafted for all women at high risk.

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DATA SUPPLEMENT

Search, selection, and data extraction procedures

A systematic electronic literature search was performed by a medical information specialist on August 26th 2013 supplemented with the search updates on January 6th and November 11th 2014, in all large medical electronic databases: Embase, MEDLINE, Cochrane, Web-Of-Science, PsycINFO and Google Scholar. The following search terms were used: "risk", "relapse", "recurrent", "recur*", "bipolar disorder", "bipolar", "bipolar*", "manic", "mania", "pregnancy", "pregnant", "puerperium", "pregnan*" "puerper*", "puerperal disorder", "post natal", "postnatal", "postnatal care", "perinatal period", "perinatal care", "puerperal psychosis", "post partum", "postpartum", "psychosis", "puerperal psychosis", "psycho*" and "English". Exclusion search terms were: "conference", "abstract", "conference paper", "conference review", "editorial", "erratum", "case study", and "case report". On January 6th and November 11th 2014, search updates were performed to locate publications after the initial search. Furthermore, relevant textbooks and bibliographies of reviews and retrieved papers were searched to identify any additional papers.

All papers were handled and screened for duplicates with the citation manager EndNote (1). At first, papers eligible for inclusion were screened in an inter-rater session. Two reviewers (RW and AMK) independently screened all titles and abstracts for eligibility, after which full text articles were assessed. Mismatches between these reviewers were discussed with an independent psychiatrist (VB). Inter-rater agreement was calculated, by which a kappa of 0.61-0.80 reflected substantial, and a kappa of 0.81-1.00 nearly perfect, agreement (2). When data was reported in an inconclusive format, the full text of the paper was screened for additional clarification. If necessary, authors were contacted to request additional data. If more papers published about the same cohort, the most complete/recent publication was included in the quantitative synthesis.

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TABLE S1. Overview characteristics included studies qualitative synthesis (N=48)

Study[a]	Patients included (n)	Event rate[b,c]	Outcome	Diagnosis[d]	Study Design I[e]	Study Design II	Duration follow up in months	Inclusion criteria	Relapse criteria	Missing data reported	Medication use during pregnancy	Medication use postpartum	Cohort	Time Frame
Akdinez 2003 (1)	72	26/160	incidence	BD	R	cohort	1	DSM IV	Clinical interview	yes	n.a.	n.a.	Istanbul, TR	n.a.
Ardau 2014 (2)	12	6/12	incidence	BD I+II	R	case series	6	DSM IV	DSM IV	no	58.3% (7/12) lithium	n.a.	Cagliari, IT	1976 - 2012
Austin 1992 (3)	17	8/17	incidence	BD	R	cohort	3	RDC 1978	RDC 1978	no	41.2% (7/17) lithium	53% (9/17) lithium	Edinburgh, UK	1978 - 1988
Bagedahl 1998 (4)	2	2/4	incidence	PP	P	cohort	12	DSM IV	Hospital-ization	yes	n.a.	n.a.	Stockholm, SE	1976 - 1992
Benvenuti 1992 (5)	7	4/7	prevalence	PP	R	cohort	2	DSM III R	DSM III	yes	n.a.	n.a.	Florence, IT	1973 - 1987
Bergink BD 2012[f] (6)	41	9/41	incidence	BD	P	cohort	3	DSM IV	DSM IV	yes	75.6% (31/41) mostly lithium	88% (36/41) mostly lithium	Rotterdam, NL	2003 - 2010
Bergink PP 2012[f] (6)	29	4/29	incidence	PP	P	cohort	3	DSM IV	DSM IV	yes	0%	69% (20/29) mostly lithium	Rotterdam, NL	2003 - 2010
Bilszta 2010 (7)	23	3/23	incidence	BD	P	cohort	2 & 6	DSM IV	Clinical interview	yes	65% (15/23) various	n.a.	Melbourne, AU	n.a.
Blackmore 2006 (8)[g]	129	167/242	incidence	BD	R	cohort	1	DSM IV	DSM IV	yes	n.a.	n.a.	Birmingham, UK	n.a.
Blackmore 2013 (9)	57	37/67	incidence	PP	R	cohort	1	DSM IV/ ICD 10	DSM IV	yes	0%	n.a.	Birmingham,UK	n.a.
Blehar 1998 (10)	139	32/139	prevalence	BD I	R	cohort	1	DSM III R	Clinical interview	yes	n.a.	n.a.	Multiple sites, US	n.a.
Cohen 1995 (11)	27	9/27	incidence	BD	R	cohort	3	DSM III R	Clinical interview	yes	n.a.	51.9% 14/27) mostly lithium	Boston, US	n.a.
Colom 2010 (12)	109	43/109	prevalence	BD	R	cohort	1	DSM IV	DSM IV	Yes	n.a.	n.a.	Barcelona, Spain	12 years
Di Florio 2013 (13)	864	786/1828	incidence	BD I+II	R	cohort	12	DSM IV	DSM IV	yes	n.a.	n.a.	Birmingham, UK	1991 - 2010
Di Florio 2014 (14)	1212	1052/2329[h]	incidence	BD I+II	R	cohort	6	DSM IV	DSM IV	yes	n.a.	n.a.	Birmingham, UK	1991 - 2010

TABLE S1. Overview characteristics included studies qualitative synthesis (N=48) *(Continued)*

Study[a]	Patients included (n)	Event rate[b,c]	Outcome	Diag-nosis[d]	Study Design I[e]	Study Design II	Duration follow up in months	Inclusion criteria	Relapse criteria	Missing data reported	Medication use during pregnancy	Medication use postpartum	Cohort	Time Frame
Doyle 2012 (15)	43	20/43	incidence	BD	R	cohort	1	DSM IV	DSM IV	yes	62% (26/42) various	n.a.	Birmingham, UK	2000 -2009
Freeman 2002 (16)	30	20/30	prevalence	BD	R	cohort	1	DSM IV	Clinical interview	no	6.7% (2/30) valproate	3.3% (1/30) unknown	Arizona, US	n.a.
Green 2008 (17)	15	5/15	incidence	BD	P	cohort	12	ICD 10	Hospital-ization	yes	n.a.	n.a.	London, UK	2002 - 2004
Grof 2000 (18)	28	7/28	prevalence	BD I	R	cohort	9	RDC 1978	RDC 1978	no	16% (4/25)[i]	n.a.	Multiple sites AU,CZ,DK,DE,SE	n.a.
Harlow 2007(19)	786	67/786	incidence	BD	B	birth register	3	ICD 8,9,10	Hospital-ization	yes	n.a.	n.a.	Birth register, SE	1987 - 2001
Hunt 1995 (20)	36	22/79	incidence	BD	R	cohort	3	RDC 1978	RDC 1978	yes	n.a.	n.a.	London, UK	1985 - 1987
Jones 2001 (21)	152	62,86/ 152[b]	prevalence	BD	R	cohort	1 & 6	DSM IV	DSM IV	yes	n.a.	n.a.	Birmingham, UK	1991 - 2010
Kapf-hammer 2014 (22)	23	14/29	incidence	PP	R	cohort	1	DSM IV	DSM IV	yes	n.a.	n.a.	Munich, Germany	1975 - 1995
Kendell 1987 (23)	33	7/44	incidence	BD	P	cohort	3	ICD 8,9	Hospital-ization	yes	n.a.	n.a.	Edinburgh, UK	1970 - 1981
Kirpinar 1999 (24)	64	25/64	prevalence	PP	R	cohort	3	DSM IV	Clinical interview	yes	n.a.	n.a.	Erzurum, TR	1973 - 1994
Kumar 1993 (25)	26	17/26	incidence	BD	P	cohort	3 & 6	RDC 1978	RDC 1978	yes	0%	0%	London, UK	n.a.
Kumar 2003 (26)	29	12/29	incidence	BD	P	clinical trial	3	RDC 1978	RDC 1978	yes	0%	100% estrogen[i]	London, UK	n.a.
Maina 2014 (27)	276	207/276	prevalence	BD I+II	R	cohort	1	DSM IV	DSM IV	yes	0%	n.a.	Turin, IT	1995 - 2009
Marks 1992 (28)	26	17/26	incidence	BD	P	cohort	6	RDC 1978	RDC 1978	yes	0%	0%	London, UK	n.a.
McNeil 1986 (29)	18	3/18	incidence	PP	P	case control	6	RDC 1978	RDC 1978	yes	n.a.	n.a.	Southern Sweden, SE	1973 - 1977
Meakin 1995 (30)	10	3/10	incidence	PP	P	cohort	1	RDC 1978	Unknown	yes	0%	0%	Leeds, UK	n.a.

TABLE S1. Overview characteristics included studies qualitative synthesis (N=48) *(Continued)*

Study[a]	Patients included (n)	Event rate[b,c]	Outcome	Diag-nosis[d]	Study Design I[e]	Study Design II	Duration follow up in months	Inclusion criteria	Relapse criteria	Missing data reported	Medication use during pregnancy	Medication use postpartum	Cohort	Time Frame
Munk-Olsen 2009 (31)	208	37,46, 57/ 208[b]	incidence	BD	B	birth register	1,3, & 12	ICD 8, 10	Hospital-ization	no	n.a.	n.a.	Birth register, DK	1973 - 2005
Pfuhlmann 1999 (32)	4	2/4	incidence	BD	R	cohort	6	ICD 10	Clinical interview	no	n.a.	n.a.	Wurzburg, DE	1981 - 1990
Platz 1988 (33)	n.a.	2/11	incidence	BD	P	cohort	3	RDC 1978	Hospital-ization	yes	n.a.	n.a.	Edinburgh, UK	1971 - 1977
Robertson 2005 (34)	54	31,36/ 54[c,h]	incidence	BD	R	cohort	1, 6	DSM IV	DSM IV	yes	n.a.	n.a.	Birmingham, UK	n.a.
Rohde 1993 (35)	31	8/31	prevalence	PP	P	cohort	1	DSM III, DSM III R	Clinical interview	yes	n.a.	n.a.	Cologne and Bonn, DE	1950 - 1979
Schopf 1994 (36)	42	17/42	prevalence	PP	R	cohort	3	DSM III R	Clinical interview	no	n.a.	n.a.	Lausanne/ Zurich, CH	1949 - 1990
Sharma 2013 (37)	37	26/37	incidence	BD II	P	cohort	12	DSM IV	DSM IV	yes	46% (17/37) various[i]	86% (32/37) various[i]	Ontario, CA	n.a.
Sharma 2006 (38)	25	10/25	incidence	BD	P	clinical trial	1	DSM IV	DSM IV	yes	n.a.	68% (17/25) olanzapine	Ontario, CA	n.a.
Sichel 1995 (39)	7	1/7	incidence	PP	P	cohort	1,3, & 12	DSM III R	DSM III	yes	0%	100% estrogen[i]	Boston, USA	n.a.
Stewart 1991 (40)	21	3/21	Incidence	PP	P	clinical trial	6	RDC 1978	Unknown	no	0% (0/21) lithium[k]	100% lithium	Toronto, CA Rotterdam, NL Edinburgh, UK	n.a.
Terp 1999 (41)	217	49/266	incidence	PP	B	birth register	3	ICD 8	Hospital-ization	no	n.a.	n.a.	Birth register, DK	1973 - 1993
Van Gent 1992 (42)	11	6,10/16[b]	incidence	BD	P	cohort	3 & 12	DSM III	Unknown	yes	n.a.	69% (11/16) mostly lithium	Utrecht, NL	1982 -1989
Videbech 1995 (43)	16	4/16	prevalence	PP	B	birth register	12	ICD 8	Hospital-ization	yes	n.a.	n.a.	Birth register, DK	1973 - 1980
Viguera 2011 (44)	621	403/1120	Incidence	BD I+II	R	cohort	6	DSM IV	DSM IV	no	n.a.	n.a.	Boston, VS Sardinia/ Rome, IT	1980 - 2010

TABLE S1. Overview characteristics included studies qualitative synthesis (N=48) *(Continued)*

Study[a]	Patients included (n)	Event rate[b,c]	Outcome	Diagnosis[d]	Study Design I[e]	Study Design II	Duration follow up in months	Inclusion criteria	Relapse criteria	Missing data reported	Medication use during pregnancy	Medication use postpartum	Cohort	Time Frame
Viguera 2000 (45)	20	14/20	incidence	BD	R	cohort	6	DSM IV	DSM IV	no	45% (9/20) lithium	n.a.	Boston, VS Sardinia, IT	n.a.
Wieck 1991 (46)	15	8/15	incidence	BD	P	cohort	3	RDC 1978	RDC 1978	yes	n.a.	n.a.	London, UK	n.a.
Wieck 1989 (47)	15	8/15	incidence	BD	P	cohort	3	RDC 1978	RDC 1978	yes	n.a.	n.a.	London, UK	n.a.
Wisner 2004 (48)	26	18/26	incidence	BD	P	clinical trial	5	DSM IV	DSM IV	yes	0%	58% (15/26) valproate	Pittsburgh, VS	1996-1997

[a] Studies included in the quantitative meta-analysis are shown in bold;

[b] In case studies included more deliveries than patients the event rates are shown underlined.

[c] In case more event rates per study are shown, studies included more than one postpartum follow-up time points.

[d] BD = bipolar disorder; PP = history of postpartum psychosis

[e] R= retrospective; P = prospective; B= birth register study

[f] Study shown twice (BD and PP patient sample).

[g] Sample selected on a history of postpartum relapse (study not included in quantitative synthesis).

[h] In a small subset of patients the onset (pregnancy or postpartum) of relapse episodes was unknown (study not included in quantitative synthesis).

[l] Data on medication was not stratified for relapse. Therefore, these studies were not included in the pharmacotherapy analyses.

[i] Since estrogen is not commonly used as prophylactic medication, these studies were not included in the pharmacotherapy analyses.

[k] In 5 patients prophylactic therapy was started at the end of the third trimester.

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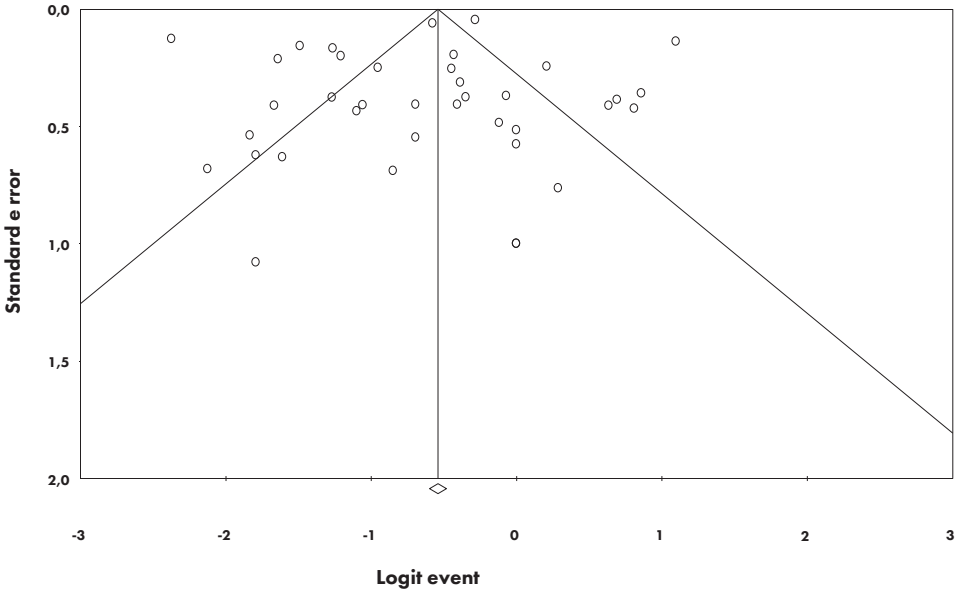
FIGURE S1. Funnel plot of standard error by logit event rate in quantitative synthesis



Chapter 3

Postpartumpsychose in de klinische praktijk: diagnostiek, behandeling en preventie

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ABSTRACT

Background: Postpartum psychosis is a severe psychiatric disease which occurs in the early postpartum period after 1 - 2 per 1000 deliveries. Patients with a history of postpartum psychosis and/or bipolar disorder are at extreme high risk of relapse postpartum.

Aim: To discuss diagnostic considerations, treatment and the prevention of postpartum psychosis, and to give clinical recommendations.

Methods: Literature search with PubMed and relevant textbooks.

Results: Inpatient psychiatric admission enables the clinician to ensure the safety of mother and baby, perform physical and neurological examination, and laboratory analysis to exclude known organic causes for acute psychosis. Antipsychotic and lithium and ECT are effective treatment options. Women with postpartum psychosis compared to those with bipolar disorder had a substantial difference in their clinical outcomes and prophylaxis requirements.

Conclusion: Inpatient screening for somatic (co)morbidity is essential in patients with postpartum psychosis. With adequate treatment, almost all patients achieve complete remission and the prognosis is optimistic. Initiation of prophylaxis immediately postpartum in women with a history of postpartum psychosis with lithium was highly effective for preventing postpartum relapse.

SAMENVATTING

Achtergrond: Postpartumpsychose is een ernstig ziektebeeld dat ontstaat binnen vier weken post partum na 1 à 2 op de 1000 bevallingen. Patiënten met in de voorgeschiedenis een postpartumpsychose en/of een bipolaire stoornis hebben een sterk verhoogd risico op het ontstaan van een postpartumpsychose.

Doel: Bespreken van diagnostiek, behandeling en preventie van postpartumpsychose. Per onderwerp aanbevelingen doen voor de klinische praktijk.

Methode: Literatuuronderzoek met PubMed, relevante boeken en naslagwerken.

Resultaten: Bij vermoeden van een postpartumpsychose kan met een psychiatrische opname eventueel gevaar voor moeder en kind worden afgewend en is uitgebreide diagnostiek mogelijk ter uitsluiting van somatische (co)morbiditeit. Antipsychotica, lithium en elektroconvulsietherapie zijn effectieve behandelopties. Het medicamenteuze beleid ter preventie van een recidief van postpartumpsychose verschilt bij patiënten met in de voorgeschiedenis een postpartumpsychose en patiënten met een bipolaire stoornis.

Conclusie: Een postpartumpsychose vereist een psychiatrische opname waarbij specifieke aandacht dient uit te gaan naar de aanwezigheid van somatische (co)morbiditeit. Door adequate medicamenteuze behandeling herstellen vrijwel alle patiënten met een postpartumpsychose volledig en is de prognose gunstig. Een recidief van een postpartumpsychose is goed te voorkomen met lithiumprofylaxe post partum.

INLEIDING

De postpartumperiode gaat gepaard met een sterk verhoogd risico op het ontstaan van ernstige psychiatrische ziekte. Bij vrouwen met een blanco psychiatrische voorgeschiedenis ontstaat na 1 à 2 op de 1000 bevallingen een postpartumpsychose (1). Bij patiënten met een bipolaire stoornis of een postpartumpsychose in de voorgeschiedenis loopt dit risico op tot 23-44% (2, 3). Naast eerder doorgemaakte psychiatrische ziekte in de kraamtijd is primipariteit de belangrijkste beschreven risicofactor voor het ontstaan van een postpartumpsychose (1, 4).

Een postpartumpsychose kan zich snel en onvoorspelbaar ontwikkelen en ontstaat binnen vier weken na de bevalling. Echter, meestal manifesteren de symptomen zich al in eerste week na de bevalling. Na enkele symptoomvrije dagen ontstaan er bijvoorbeeld slaapstoornissen, prikkelbaarheid, ontremming en achterdocht. Vervolgens worden vaak na ongeveer een week ernstiger psychiatrische verschijnselen waargenomen, bijvoorbeeld verwardheid, hallucinaties, wanen, gestoorde realiteitsbeleving, symptomen van manie of depressie en soms ook desoriëntatie en een wisselend bewustzijn (4, 5).

Diagnostiek en behandeling vinden om veel redenen bij voorkeur plaats tijdens een moeder-kindopname (6), tweede keus is een opname op een psychiatrische afdeling van een algemeen ziekenhuis. Op deze manier wordt eventueel gevaar voortkomend uit suïcidale gedachten of gedachten gericht op infanticide afgewend en kan adequate somatische en psychiatrische diagnostiek plaatsvinden. In sommige gevallen is het aanvragen van een Bopz-maatregel hiervoor noodzakelijk. Naast farmacologische behandeling, zijn het herstellen van de slaaphygiëne, verbeteren van de moeder-kind interactie en het betrekken van het steunsysteem belangrijke onderdelen van de behandeling.

In dit artikel bespreken wij de diagnostiek, behandeling en preventie van postpartumpsychose aan de hand van recente literatuur. Er worden aanbevelingen gedaan voor de klinische praktijk.

METHODE

Met PubMed zochten wij naar relevante artikelen, waarbij de volgende zoektermen werden gebruikt: 'post partum, peripartum, postpartum psychosis, bipolar disorder, diagnosis, treatment, prevention'. Daarnaast werd informatie verkregen met relevante handboeken en naslagwerken.

RESULTATEN

Diagnostiek

Postpartumpsychose wordt niet als opzichzelfstaande diagnose beschreven in *Diagnostic and Statistical Manual of Mental Disorders*. Het gevolg hiervan is dat er in publicaties vaak

slecht gedefinieerde termen en inconsistente classificaties worden gebruikt. Historisch gezien is postpartumpsychose echter wel vaak als aparte entiteit beschreven met termen zoals 'puerperal insanity' en 'puerperal psychosis'. Hiermee werd al in de klassieke oudheid verwezen naar het plotseling, onverwacht ontstaan van ernstige psychiatrische ziekte in het kraambed (7).

Patiënten met een doorgemaakte postpartumpsychose of een bipolaire stoornis hebben het hoogste risico op een postpartumpsychose (2, 8). De meeste patiënten die een postpartumpsychose doormaken hebben echter een blanco psychiatrische voorgeschiedenis. Bij deze groep is de postpartumpsychose soms de eerste manifestatie van een onderliggende stoornis in het bipolaire spectrum. Retrospectief onderzoek suggereert dat dit bij 35-65% van die vrouwen het geval is (9). Hieruit vloeit voort dat bij een substantieel deel van de patiënten die een postpartumpsychose doormaken, uiteindelijk geen bipolaire stoornis wordt gediagnosticeerd. De kwetsbaarheid voor ernstige psychiatrische ziekte beperkt zich in dit geval tot de kraamtijd. Het verdient daarom onze voorkeur om bij patiënten die een eerste postpartumpsychose hebben doorgemaakt nog geen bipolaire stoornis te diagnosticeren. De diagnose "psychose of manie (stemmingsstoornis) niet anderszins omschreven (NAO), begin post partum", is in dit geval een betere diagnostische classificatie. Uiteraard dient de diagnose wel te worden aangepast naar 'bipolaire stoornis' wanneer er een ernstige stemmingsepisode buiten het kraambed optreedt.

Postpartumpsychose wordt over het algemeen beschouwd als een stemmingsstoornis en niet als een primair psychotische stoornis. De term postpartumpsychose kan daardoor enige verwarring geven. Stemmingssymptomen (depressie, manie of een combinatie van beide) behoren namelijk tot de kernsymptomen van postpartumpsychose. Daarnaast is er qua familiaire belasting en het beloop overlap met de bipolaire stoornis (10).

Bij vermoeden van een postpartumpsychose dient de huisarts of psychiater uit de eerste lijn de patiënt te verwijzen voor een psychiatrische opname (11). Het belangrijkste argument hiervoor is dat het gevaar van suïcide en infanticide kan worden afgewend. In het Engelse rapport 'Why mothers die' is beschreven dat er tussen 2000 en 2002 bij 9 van de 26 suïcides post partum sprake was van een psychotische episode. In 5 gevallen was er sprake van een ernstige depressieve episode en in 4 gevallen was er in deze groep naast suïcide ook sprake van infanticide (12).

Behalve om het gevaar af te wenden biedt een opname de beste mogelijkheden voor snelle diagnostiek en behandeling, hetgeen van belang is omdat het klinisch beeld van uur tot uur en van dag tot dag vaak sterk kan wisselen. Tijdens opname dienen zo snel mogelijk algemeen lichamelijk onderzoek en bloedonderzoek te worden uitgevoerd om een onderliggende somatische oorzaak uit te sluiten. Differentiaaldiagnostisch moet worden gedacht aan infecties, eclampsie, postpartumthyreoïditis (13), paraneoplastische encefalitis (14), primaire hypoparathyreoïdie (15), vitamine deficiënties (met name van vitamine B_1, B_{12} en foliumzuur), cerebrovasculaire accidenten en een drugsgeïnduceerde psychose (11). Tevens zijn er gevalsbeschrijvingen gepubliceerd over het ontstaan van postpartumpsychose door ureumcyclusstoornissen (16) en citrullinemie type I (17).

De kraamtijd is een periode waarin auto-immuunschildklierziekten relatief vaak voorkomen (postpartumthryreoïditis ook wel auto-immuun- of hashimoto-thryreoïditis genoemd). Bij vrouwen met postpartumpsychose is er enige aanwijzing voor een verhoogde prevalentie van auto-immuunschildklierziekte vergeleken met een controlegroep kraamvrouwen uit de algemene bevolking (13). Het is daarom zinvol om naast de schildklierfunctie (thyroïdstimulerend hormoon; TSH) ook thyroïdperoxidase (TPO)-antistoffen te bepalen. Als deze verhoogd zijn dient de schildklierfunctie frequent gecontroleerd te worden, zeker als gestart wordt met lithium. Het is zinvol de screening 6 maanden post partum te herhalen omdat schildklierproblemen ook later nog kunnen optreden.

Als er sprake is van cognitieve symptomen, een delierachtig beeld of neurologische symptomen dient men bedacht te zijn op de aanwezigheid van een NMDA-encefalitis (NMDA: N-methyl-D-asparaginezuur) (18). Screening op NMDA-antistoffen in serum of liquor is dan geïndiceerd. Verder dient bij een atypische presentatie en/of afwijkingen bij lichamelijk en neurologisch onderzoek laagdrempelig verder onderzoek plaats te vinden middels beeldvorming. Een overzicht met aanbevelingen wat betreft de diagnostiek is opgenomen in Tabel 1.

TABEL 1. Diagnostiek van postpartumpsychose

- Het vermoeden van een postpartumpsychose vormt een opname-indicatie, indien mogelijk een moeder-kindopname.
- Doe navraag naar aanwezigheid van suïcide- of infanticidegedachten.
- Stel na een eerste postpartumpsychose de diagnose 'psychose of manie (stemmingsstoornis) NAO, begin post partum' en nog niet de diagnose 'bipolaire I-stoornis'.
- Voer een uitgebreide somatische screening uit, bestaande uit:
  1. Volledig lichamelijk en neurologisch onderzoek.
  2. Urineonderzoek (sediment, op indicatie urinescreening op drugs).
  3. Aanvullend bloedonderzoek: infectieparameters (leukocytengetal, CRP), elektrolyten (inclusief calcium), lever- en nierfunctie, creatinine, ureum,thyroïdstimulerend hormoon (TSH), thyroïdperoxidase(TPO-)antistoffen (schildklierparameters 6 maanden post partum herhalen) en op indicatie de vitaminestatus (B1, B12 en foliumzuur).
  4. Op indicatie aanvullend onderzoek middels beeldvorming en autoantistofbepalingen in serum en/of liquor (waaronder NMDA-autoantistoffen).

Behandeling

Medicatie is de hoeksteen in de behandeling van een postpartumpsychose. Daarnaast zijn structuur, slaaphygiëne, optimalisering van de moeder-kindinteractie en aandacht voor de partner en de familie van de patiënte van groot belang.

Medicatie en ECT

Weinig is bekend over de medicamenteuze behandeling van postpartumpsychose. Er zijn in totaal 11 gevalsbeschrijvingen verschenen en 9 naturalistische studies gedaan waarvan er slechts 3 meer dan 10 patiënten includeerden (19). Er bestaan dan ook geen specifieke richtlijnen voor de medicamenteuze behandeling van postpartumpsychose. Vanwege de relatie tussen postpartumpsychose en bipolaire stoornis, kan de richtlijn voor de behandeling van acute manie aangehouden worden in de acute fase van een postpartumpsychose. Bij patiënten bij wie reeds een bipolaire stoornis is gediagnosticeerd, is het uiteraard ook van belang om informatie in te winnen over de farmacologische respons ten tijde van eerdere ziekte-episodes.

De meeste patiënten met een postpartumpsychose hebben echter een blanco psychiatrische voorgeschiedenis. In het Erasmus MC worden deze patiënten al langere tijd succesvol behandeld volgens een vast farmacologisch algoritme. Allereerst wordt gestart met benzodiazepinen. Bij een klein deel van de patiënten leidt herstel van het slaap-waak ritme alleen al tot herstel. Tijdens de behandeling met alleen benzodiazepinen kan verdere diagnostiek plaatsvinden. Wanneer de psychiatrische symptomen na enkele dagen niet afnemen wordt gestart met een antipsychoticum. Haloperidol (2-5 mg per dag) is daarbij het middel van eerste keus vanwege de beschreven snelle antimanische effecten (20). Daarnaast kent haloperidol relatief weinig interacties, is er veel ervaring met de lange termijn effecten en is het middel in alle toedieningsvormen beschikbaar. Er is helaas nog geen onderzoek gepubliceerd dat specifiek is gericht op het behandeleffect van andere antipsychotica dan haloperidol bij patiënten met een eerste postpartumpsychose.

Indien behandeling met antipsychotica niet leidt tot sterke klinische verbetering wordt na twee weken lithium toegevoegd (bloedspiegel tussen de 0.8 – 1.2 mmol/l). Overigens worden benzodiazepinen gedurende de behandeling zo snel als mogelijk geleidelijk afgebouwd. Met dit farmacotherapeutisch behandelalgoritme bereikte 98% van de patiënten complete remissie (21). Als patiënten niet reageren op medicatie of wanneer er sprake is van ernstige katatonie, is electroconvulsietherapie (ECT) aangewezen (22).

In de literatuur is er weinig bekend over de medicamenteuze behandeling van postpartumpsychose met depressieve kenmerken, ook wel postpartumdepressie met psychotische kenmerken genoemd. Een depressie met psychotische kenmerken buiten de kraamtijd wordt volgens de richtlijnen depressie behandeld. Uit de klinische praktijk komt echter naar voren dat gebruik van antidepressiva bij patiënten in de post partum periode kan leiden tot een verslechtering van het psychiatrische beeld (23, 24). Wij raden daarom gebruik van antidepressiva af bij patiënten met een postpartumdepressie met psychotische kenmerken. We adviseren deze groep patiënten te behandelen met een antipsychoticum en lithium (23). Een andere behandeloptie is ECT (22).

Na complete remissie van psychotische en affectieve symptomen wordt de medicatie gecontinueerd waarbij remissie is opgetreden: bij patiënten die goed herstelden op een antipsychoticum alleen, werd het antipsychoticum als onderhoudsbehandeling gecontinueerd. Bij patiënten behandeld met een antipsychoticum en lithium (omdat zij onvoldoende herstelden op een antipsychoticum alleen) werd het antipsychoticum middels afbouw gestaakt en lithium als onderhoudsbehandeling gegeven.

Het is niet bekend hoelang medicatie (antipsychoticum en/of lithium) na de actieve ziekte episode dient te worden gecontinueerd. In het Erasmus MC wordt gemiddeld negen maanden na de actieve ziekte-episode begonnen met geleidelijke afbouw van psychofarmaca, indien patiënte stabiel is en geen bipolaire stoornis gediagnosticeerd is. Uit ons onderzoek komt naar voren dat een onderhoudsbehandeling met lithium beter beschermt tegen terugval dan een antipsychoticum. We adviseren daarom onderhoudsbehandeling met lithium gedurende minimaal een half jaar (21).

Borstvoeding

Het geven van borstvoeding wordt in het algemeen ontraden bij vrouwen die opgenomen zijn met een postpartumpsychose. Door het psychotische beeld zijn zij vaak niet in staat op een veilige en adequate wijze hun kind te voeden. Borstvoeding en nachtelijke verzorging van de baby verstoren het slaap-waakritme, hetgeen niet bevorderlijk is voor het herstel of de toestand zelfs kan doen verslechteren. Daarnaast worden psychofarmaca uitgescheiden in de moedermelk (25). Aangeraden wordt geen dopamineagonisten (bromocriptine) voor te schrijven om de melkproductie te remmen omdat dit psychotische verschijnselen kan induceren (7). Als gevolg van het staken van borstvoeding is het extra van belang te letten op de eventuele aanwezigheid van mastitis. Pijnklachten door stuwing kunnen worden behandeld met paracetamol tot 4000 mg/dag.

Aanvullende begeleiding

Naast medicamenteuze behandeling, dient structuur geboden te worden middels een rust- en activiteitenschema. Op moeder-baby units slapen moeders en baby's gescheiden van elkaar en zijn de activiteiten hoofdzakelijk gecentreerd rondom het (zo nodig onder begeleiding) verzorgen van de baby en het moederschap. Er dient specifieke aandacht te zijn voor de optimalisering van de moeder-kindinteractie (26). Het is belangrijk de partner te betrekken bij de opname met ondersteuning, psycho-educatie en in de loop van de opname een of meerdere systeemgesprekken. Een overzicht met aanbevelingen wat betreft de behandeling is opgenomen in Tabel 2.

TABEL 2. Behandeling postpartumpsychose

1. Overweeg enkele dagen monotherapie met benzodiazepinen. Op deze manier kan het effect van slaaphygiëne worden geëvalueerd en kan diagnostiek plaatsvinden.
2. Start bij geen/onvoldoende afname van psychiatrische symptomen meteen antipsychoticum (haloperidol 2-5 mg of een atypisch antipsychoticum).
3. Voeg lithium toe, streefspiegel 0,8-1,2 mmol/l bij persisterende symptomen, maar ook als terugvalpreventie.
4. Overweeg bij onvoldoende respons op medicamenteuze behandeling elektro-convulsietherapie (ECT). Overweeg bij ernstige katatonie om ECT als eerste behandeling in te zetten.
   - Het voorschrijven van antidepressiva wordt sterk afgeraden, ook als depressieve symptomen op de voorgrond staan (psychotische depressie).
   - Ondersteuning middels dagstructuur en slaaphygiëne zijn van groot belang.
   - Tijdens de opname heeft het de voorkeur borstvoeding te staken in verband met het herstel van slaap-waakritme en de uitscheiding van psychofarmaca in de moedermelk.
   - Let op de eventuele aanwezigheid van mastitis.
   - Start niet met lactatieremmers.
   - Besteed voldoende aandacht aan optimalisering van de moeder-kindinteractie.
   - Ongeveer negen maanden na de actieve ziekte-episode kan ervoor worden gekozen medicatie voorzichtig af te bouwen als patiënte stabiel is en er geen bipolaire stoornis is gediagnosticeerd.

Preventie

Sinds halverwege de vorige eeuw worden al (voornamelijk observationele) studies gepubliceerd die het hoge risico (25-50%) op een recidief van een postpartumpsychose beschrijven na een volgende bevalling (27, 28). Daarnaast zijn studies met grote patiëntenaantallen gepubliceerd die een hoog risico op een nieuwe ziekte episode post partum beschrijven bij patiënten met een bipolaire stoornis. Ongeveer 1 op de 4 vrouwen met een bipolaire stoornis die voor het eerst zwanger worden, maakt een ernstige episode post partum door (3, 8).

Bij patiënten met een eerdere postpartumpsychose en bij bipolaire patiënten is slaapgebrek mogelijk een belangrijke risicofactor voor terugval post partum (29).

Tot op heden is er weinig onderzoek verricht naar de effectiviteit van profylactische behandeling. Retrospectief onderzoek in kleine patiëntengroepen is gedaan met lithium, valproïnezuur en olanzapine. Lithiumprofylaxe resulteerde in lagere recidiefpercentages, valproïnezuur was niet effectief en er is meer onderzoek nodig naar profylaxe met olanzapine om hierover conclusies te kunnen trekken (19).

In het Erasmus MC werden 70 vrouwen met een hoog risico op postpartumpsychose behandeld in een programma ter preventie van een recidief postpartumpsychose (2). Daarmee bleven 29 vrouwen die een postpartumpsychose hadden doorgemaakt (maar nooit een manie of psychose buiten de kraamtijd) stabiel tijdens hun zwangerschap, zonder medicatie. Vrouwen die meteen na de bevalling startten met lithium of antipsychotica kregen geen van

allen een recidief van postpartumpsychose. Bij 44% van de vrouwen die geen preventieve medicatie gebruikten, was wel sprake van psychiatrische terugval. De profylactische medicatie werd tot drie maanden post partum gecontinueerd. Vrouwen met een postpartumpsychose in de voorgeschiedenis (en geen psychose of manie op andere tijden) kunnen dus het beste onmiddellijk na de bevalling starten met profylactische behandeling (eerste keus is lithium) om terugval te voorkomen. Blootstelling van de foetus aan psychofarmaca kan bij deze patiënten dus worden voorkomen.

Vrouwen met een bipolaire stoornis bleken helaas soms wel instabiel tijdens de zwangerschap, voornamelijk de vrouwen die geen medicatie gebruikten. Na de bevalling kregen juist de vrouwen met een bipolaire stoornis die instabiel waren tijdens de zwangerschap vaker een postpartumpsychose. Onze bevindingen komen overeen met eerder onderzoek waaruit blijkt dat staken van lithium tijdens de zwangerschap gepaard gaat met een verhoogd risico op terugval (30). Tevens blijkt dat terugval tijdens de zwangerschap een belangrijke risicofactor is voor het ontstaan van een ziekte-episode post partum (31).

Samenvattend heeft het bij patiënten met een bipolaire stoornis de voorkeur om profylactische medicatie tijdens de zwangerschap te continueren, om de moeder stabiel te houden. Echter, het gebruik van psychofarmaca (en de keuze welke) dient te worden afgewogen tegen de risico's voor het ongeboren kind.

Wat betreft de stemmingsstabilisatoren is lithium vanwege de laagste kans op teratogeniteit eerste keus (32). We adviseren valproïnezuur te staken vanwege het hoge risico op neuralebuisdefecten (33). Het kan overwogen worden lamotrigine te continueren als patiënten stabiel zijn bij gebruik van deze medicatie. Wat betreft antipsychotica is haloperidol het middel van eerste keus. Tot slot kan in het algemeen worden gesteld: vermijd polyfarmacie en zoek naar de laagst effectieve dosering.

Het gebruik van psychofarmaca tijdens de zwangerschap gaat gepaard met een hoog risico (20-30%) op ontwenningsverschijnselen bij de pasgeborene. Om deze reden wordt klinische observatie van de pasgeborene gedurende de eerste 48 uur post partum geadviseerd (34). Er is geen evidentie voor de meerwaarde van profylactische behandeling tijdens de zwangerschap bij medicatievrije patiënten met een bipolaire stoornis die al langere tijd psychiatrisch stabiel zijn. Bij deze patiënten is er zeker een duidelijke indicatie om direct post partum te starten met lithiumprofylaxe. In de klinische praktijk adviseren we vaak om in de loop van het derde trimester te starten ter voorkoming van terugval door stress en slaapgebrek rondom de bevalling en zodat patiënten post partum sneller een adequate bloedspiegel bereiken. Een overzicht met aanbevelingen wat betreft de preventie is opgenomen in Tabel 3.

De met de patiënt gemaakte afspraken kunnen op een gestructureerde manier worden vastgelegd in een behandelplan ter preventie van postpartumpsychose (zie een voorbeeld in Tabel 4). Op deze manier is relevante informatie voor alle betrokkenen duidelijk en makkelijk toegankelijk.

TABEL 3. Preventie van postpartumpsychose

Patiënten met in de voorgeschiedenis een postpartumpsychose:

- Vrouwen met een postpartumpsychose in de voorgeschiedenis (en geen psychose of manie op andere tijden) kunnen het beste onmiddellijk na de bevalling starten met profylactische behandeling om terugval te voorkomen.
- De meeste evidentie is er voor het starten met lithium. Bepaal de bloedspiegel op dag 2, 5 en 12 post partum en houd een streefspiegel aan van 0,8-1,2 mmol/l. Bepaal op dag 12 tevens thyroïdstimulerend hormoon (TSH) en TPO-antistoffen.
- Er is ook enige evidentie dat het profylactisch gebruik van een antipsychoticum effectief is.
- Continueer profylactische medicatie in ieder geval tot drie maanden post partum.

Patiënten met een bipolaire stoornis:

- Continueer medicatie tijdens zwangerschap en in de post partum periode om het risico op terugval zo laag mogelijk te houden. Echter, weeg het gebruik van deze medicatie (en de keuze welke) af tegen de risico's voor het ongeboren kind.
- Vermijd polyfarmacie en zoek de laagst mogelijke effectieve dosering.
- Staak valproïnezuur *of switch naar lithium* in verband met het hoge risico op teratogeniteit.
- Wanneer patiënten met een bipolaire stoornis stabiel zijn zonder medicatie voor de zwangerschap, is er geen duidelijke indicatie om in het begin van de zwangerschap zonder psychiatrische klachten alsnog met medicatie te starten. Start bij deze groep in het laatste trimester of direct post partum met profylaxe.
- De meeste evidentie is er voor het starten met lithium. We adviseren de spiegel te bepalen op dag 2, 5 en 12 post partum en houd een streefspiegel aan van 0,8-1,2 mmol/l. Bepaal op dag 12 tevens TSH en TPO antistoffen.

CONCLUSIE

Postpartumpsychose is een ernstig ziektebeeld waarbij er een risico bestaat op suïcide of infanticide. Een psychiatrische opname is daarom geïndiceerd, bij voorkeur op een moeder-babyafdeling. Bij de diagnostiek is het van belang onderscheid te maken tussen patiënten met alleen een postpartumpsychose en patiënten met een bipolaire stoornis. Bij een substantieel deel van de patiënten met een voorgeschiedenis met alleen een post partum psychose blijft de kwetsbaarheid voor een (manisch) psychotische ontregeling beperkt tot de post partum periode. Daarmee is hun prognose gunstiger dan die van patiënten met een bipolaire stoornis. Daarnaast is het van belang somatische oorzaken van psychose of manie uit te sluiten en bedacht te zijn op de aanwezigheid van somatische comorbiditeit. Medicatie is het belangrijkste onderdeel van de behandeling. Benzodiazepinen, antipsychotica en lithium hebben een plek bij de acute behandeling. Er zijn aanwijzingen dat lithium, in tegenstelling tot een antipsychoticum, effectief is als onderhoudsbehandeling de eerste 9 maanden post partum. Patiënten met in de voorgeschiedenis een postpartumpsychose en/of een bipolaire stoornis hebben een hoog risico op psychiatrische terugval postpartum na een volgende

zwangerschap. Bij een volgende zwangerschap biedt het starten van profylaxe direct na de bevalling voldoende bescherming tegen psychiatrische terugval bij patiënten met een postpartumpsychose in de voorgeschiedenis. Blootstelling van de foetus aan psychofarmaca kan bij deze patiënten worden voorkómen. Patiënten met een bipolaire stoornis staken bij voorkeur niet de onderhoudsbehandeling tijdens de zwangerschap. Met goede psychiatrische zorg herstellen patiënten met een postpartumpsychose over het algemeen snel en is de prognose gunstig.

TABEL 4. Voorbeeld van een behandelplan ter preventie van een postpartum psychose

Naam:
Gravida; Para;
Aterme datum:

Psychiatrische diagnose:

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

Somatische diagnose:
Obstetrische voorgeschiedenis:
Vermeld eventuele bijzonderheden tijdens eerdere bevallingen.

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

Medicatie tijdens de zwangerschap:
Huidige medicatie inclusief startdatum, spiegels en mogelijke gevolgen ongeboren kind.

Bevalling:
Vermeld of er een inleiding of sectio is gepland, gemaakte afspraken met betrekking tot pijnstilling en waar de bevalling gaat plaatsvinden. Vermeld ook de naam van de gynaecoloog.

Borstvoeding:
Patiënte geeft wel/geen borstvoeding. Lactatieremmers zijn gecontra-indiceerd.
Verpleegkundige/ partner neemt de nachtvoeding over.

Medicatie na de bevalling:
De eerste avond na de bevalling wordt om .... lithium / antipsychotica / andere medicatie verhoogd/ gestart in een dosering van ...
In het geval van lithium:
de spiegel wordt bepaald op dag 2, 5 en 12 post partum. De streefspiegel is tussen 0,8-1,0 mmol/l. Op dag 12 tevens thyroïdstimulerend hormoon (TSH) en vrij thyroxine (fT4) en TPO-antistoffen bepalen. Slaapmedicatie (middel en dosering) wordt standaard/ op indicatie aangeboden voor de nacht en evt. verhoogd bij slaapproblemen. Indien medicatie gebruikt werd tijdens de zwangerschap: De baby zal direct na de bevalling door de kinderarts worden onderzocht i.v.m. psychofarmacagebruik en gedurende ...uur geobserveerd worden op ontwenningsverschijnselen. (Bij lithium:
in navelstrengbloed zal de lithiumspiegel, TSH, fT4 en thyroïdstimulerend immunoglobuline (TSI) bepaald worden).

Signaleringsplan:

Nazorg:
Hoe lang medicatie te continueren?

Psychiater Mw..... (naam patiënte, en handtekening)

Kopie:
- Huisarts Behandelend gynaecoloog
- Patiënte zelf Behandelaren in de ggz

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Chapter 4

Phenotypical characteristics of postpartum psychosis: a clinical cohort study

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ABSTRACT

Objectives: Postpartum psychosis (PP) is known for its clear onset but its phenotype has never been clearly described in a cohort. The aim of this study was to describe PP symptomatology, and to identify subgroups of patients based on symptom profiles.

Methods: We prospectively assessed a wide range of symptoms in cases of PP in a cohort of women (N=130) admitted to the Mother-Baby inpatient unit. Using a person-centered analytic approach, we distinguished mutually exclusive subgroups of women. Subgroups were related to demographic and clinical characteristics.

Results: The most prevalent symptoms of PP were irritability (73%), abnormal thought content (72%), and anxiety (71%). Suicidal and infanticidal ideation was present in 19% and 8% of patients, respectively. Delusions and hallucinations often had a negative content. Latent class analysis revealed three symptom profiles, a manic (34%), depressive (41%) or atypical (25%) profile, respectively. The manic profile is characterized by manic symptoms and agitation, the depressive profile by depressive and anxiety symptoms and the atypical profile by disturbance of consciousness and disorientation. In women with a depressive profile, treatment was started 2 weeks later (p=0.049) and more often voluntarily, than in manic and atypical women (p=0.037).

Conclusions: We distinguished subgroups of PP patients with a manic, depressive, and atypical profile. Disturbance of consciousness, disorientation, and depersonalization/derealisation were less prevalent than previously suggested in the literature. Instead, the depressive profile was the most prevalent, but the depressive profile can easily remain undetected, which could lead to treatment delay and risk of suicide/infanticide. Within the manic profile, irritability was highly prevalent and occurred more often than elevated mood.

INTRODUCTION

Since antiquity, young women have been described with a first onset acute severe psychiatric illness after childbirth. Over time, several names have been given to this postpartum disease such as "mania lactea", "amentia", "puerperal insanity", "puerperal psychosis", "puerperal mania", "dreamlike delirium" and finally "postpartum psychosis" (PP). Since the 19th century PP has been widely appreciated as a severe disease, requiring acute intervention. Moreover, epidemiologic studies consistently report a greatly increased risk in psychiatric inpatient admissions within 6 weeks after childbirth compared to any other period in a woman's life (1, 2). Many of these first onset severe postpartum episodes are, in retrospect, the initial presentation of bipolar disorder. Therefore, there is general consensus that PP falls within the bipolar spectrum. Importantly however, not all postpartum episodes serve as starting point for bipolar disorder; some women have isolated PP with severe episodes only after childbirth. For this reason, in 2016, the international classification of rare diseases "orphanet" has recognized PP as a distinct and rare disease within the bipolar spectrum with an incidence of 0.5/1000 (3).

Several authors have described the atypical phenotypic characteristics of PP, e.g. delirium like symptoms, misrecognition of people, depersonalization, non-auditory hallucinations and bizarre delusions (4-7). These enigmatic symptoms have captivated the minds of clinicians and researchers but the occurrence of these symptoms has never been quantified. In an effort to further define the phenotype of this disorder, we provide detailed phenotypic information on symptomatology in 130 women consecutively admitted with PP. In addition, our study was designed to determine homogeneous subgroups of patients based on coherent symptom patterns.

METHOD

Participants

The study was approved by the Medical Ethical Committee of the Erasmus Medical Center, Rotterdam. Participants in this study were recruited from the Onderzoeksprogramma Postpartum Psychose Erasmus MC Rotterdam (OPPER-cohort), as described previously (8). The study was conducted and results are reported according to the STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE) guidelines (9). Briefly, OPPER is a prospective study of women with an onset of psychotic and/or manic symptoms within 6 weeks postpartum, who did not experience manic or psychotic symptoms during pregnancy. Between August 2005 and January 2015, all women admitted to the Mother-Baby inpatient unit of the Department of Psychiatry of the Erasmus Medical Center were screened for inclusion. The Mother-Baby unit treats female patients with severe psychopathology in the postpartum period (0–6 months after parturition). A total of 285 women were screened, of whom 130 (46%) met

the inclusion criteria, and were subsequently included in the OPPER-cohort. All participants provided written informed consent after receiving a complete description of the study.

Assessment of psychiatric symptoms

Psychiatric symptoms were assessed by highly trained mental health professionals through standardized questionnaires and clinical diagnostic interview, all of which have been previously used within perinatal populations and in studies of PP. A total of 58 symptoms were assessed through questionnaires, diagnostic interview and review of medical records (see Supplementary Table 1 for a detailed description of symptoms and assessment).

Diagnostic interview and questionnaires

The Structured Interview for DSM-IV Axis I Disorders (SCID) was administered during admission. The Young Mania Rating Scale (YMRS), Edinburgh Postpartum Depression Scale (EPDS), and Hamilton Rating Scale for Depression (HAM-D) were administered weekly. For the purpose of these analyses, symptoms assessed using the YMRS, EPDS and HAM-D were scored as being present at their most severe occurrence.

Manic symptoms were assessed using the YMRS. With regards to depressive symptomatology, most symptoms were elicited from the EPDS, since the EPDS is developed for women in the postpartum period specifically (10). Remaining depressive symptoms were assessed using selected items from the HAM-D (early morning awakening, loss of libido, loss of appetite, psychomotor agitation and retardation) and SCID (diurnal worsening of mood).

The presence of psychotic and catatonic symptoms were elicited from the SCID. Finally, medical records were reviewed for seven additional symptoms previously described in the PP literature, which were not included in the YMRS, EPDS, HAM-D or SCID: disturbance of consciousness/perplexity, inattention, disorientation, depersonalization/derealisation, delusions related to pregnancy and childbirth, obsessive thoughts related to the child, and thoughts of infanticide.

The presence of symptoms was independently rated by two experienced psychiatry residents (MV and RW). Mean interrater reliability was substantial (κ=.69±0.39) (11). Kappas ranged from 0.39 to 1.00 for individual symptoms with the exception of 'obsessive thoughts concerning the child' for which the kappa was poor (κ= -0.05±0.05) due to the low prevalence of the symptom.

Statistical analysis

The data were analyzed using latent class analysis (LCA), a subtype of finite mixture modeling that is person-centered (as opposed to variable-centered) and is used to discover or confirm homogenous subtypes (or classes) of people from a multivariate dataset (for a non-technical

overview see Charak et al. (12), and seminal references (13-15)). Whereas more traditional types of cluster analysis, such as discriminant analysis, describe the relationship among observed variables, LCA models also include unobserved variables. Persons are assigned to a certain class according to membership probabilities which are estimated directly from the model. LCA is powerful technique; it can handle (any combination of) continuous, categorical, or count data, and can handle a violation of the assumptions of homogeneity, linearity and normality of the data. In clinical samples, non-conformity of the data is often reality. As such, LCA is less vulnerable to bias (15). These techniques are increasingly being used in psychiatric phenomenology (16, 17) as they aim to increase homogeneity within a class and maximize heterogeneity between classes of individuals who have similar patterns of symptoms. The model fit and final class resolution should be distinct and conceptually and clinically meaningful (12-14). The term LCA is typically used when the variables studied are categorical and latent profile analysis (LPA) is used when the variables studied are continuous, which was the case in this study.

First, symptoms were grouped into clusters based on clinical domains and a confirmatory factor analysis (CFA) was used to evaluate the factor structure thus formed; goodness of fit was assessed using the Comparative Fit Index (CFI), Tucker-Lewis Index (TLI) (values >0.90 indicate good fit), root mean square error of approximation (RMSEA)(values <0.08 indicate acceptable fit) and weighted root mean square residuals (WRMR) (<1.0 indicates good fit) (18). Details of the CFA modelling procedure and fit are reported in Supplement 2.

Next, we calculated aggregated factor scores, i.e. the proportion of symptoms present for each factor, and used these as input for the LPA using robust maximum likelihood estimation (MLR). Goodness of fit was assessed using Akaike's and (adjusted) Bayesian Information criteria (AIC and (adjusted) BIC, respectively). Lower values indicate a better fit. The distinctiveness of the profiles is evaluated using entropy, where a higher proportion indicates a clearer distinction between profiles (>80% desirable), log likelihood, Vuong–Lo–Mendell–Rubin likelihood ratio (VLMR) test, and bootstrap likelihood ratio (BLR) test. The VLMR and BLR tests examine whether a model with k profiles fits significantly better than a model with *k*–1 profiles (12-14). The best fitting CFA and LCA models were chosen based on goodness-of-fit measures, in combination with clinical experience, and interpretability of the derived factors and classes. Finally, potential associations between obtained profiles and variables were formally tested using chi-square for categorical variables, ANOVA for continuous variables, and the Kaplan–Meier test for time-dependent variables.

In total 3.7% of data were missing with 39 cases having missing data. For our statistical analyses, missing values were substituted by their series median after assessing for randomness. This was done by creating a missing-indicator variable and relating it to the other values in our dataset.

RESULTS

Demographics

The sample comprised 130 women, admitted with PP between August 2005 and January 2015. The mean age of these women was 31.4 years (SD= 4.8). The majority were of Dutch descent (N=116; 89%) and had a college education (N=105; 81%). 76% of the women (N=99) were primiparous. Thirty women (n=30) had experienced mania or psychosis outside the perinatal period. Of these women, 22 had a history of affective psychosis and eight women a history of brief non-affective psychosis. One of these women had also experienced a postpartum episode following a previous delivery. Most women (n=100) had not experienced mania or psychosis outside the postpartum period (isolated PP). Of these 100 women, 25 women were multiparous of whom 15 women had had a previous severe postpartum episode. Median admission duration was 56 days (95% CI 50-62 days). In total 63 women (48%) were admitted involuntary (civil detention). The most prevalent legal grounds for civil detention were related to the safety of the newborn, i.e. the risk of neglecting the baby (45/63, 71%) and the risk of causing the baby serious harm or committing infanticide (31/63, 49%). In 30 women (30/63, 48%), self-neglect was cited as a legal ground; suicide risk or risk of causing serious self-harm was mentioned in 28 (28/63, 44%) detained women. One woman had attempted suicide prior to admission.

Prevalence of symptoms

In Figure 1 we present the prevalence of the assessed psychiatric symptoms. Each symptom was either present or absent during admission.

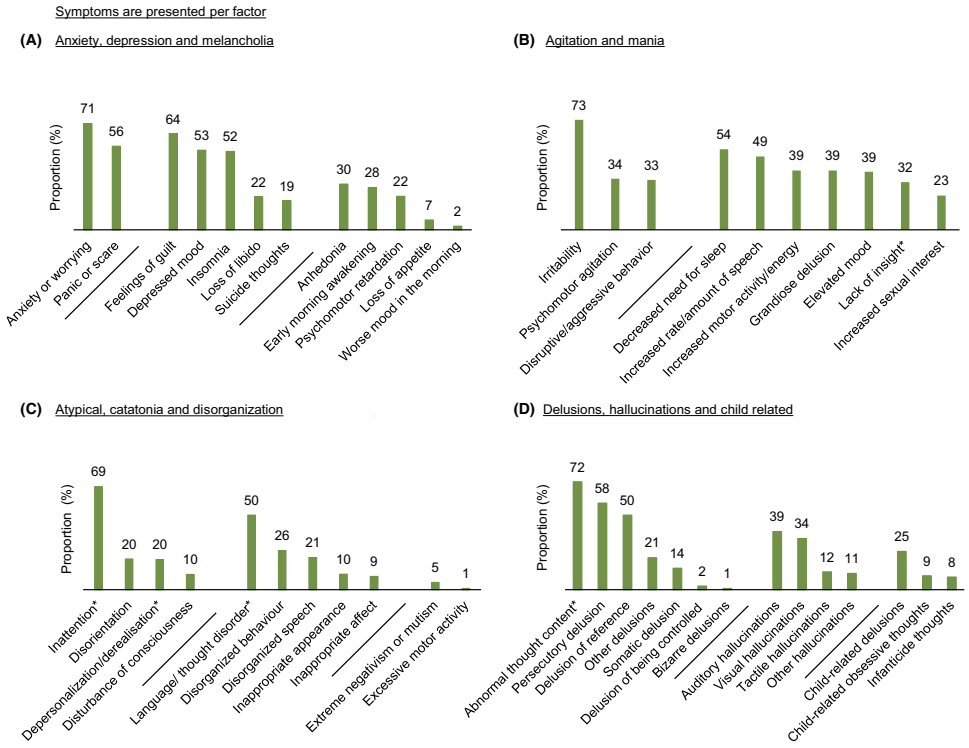
Depressive and anxiety symptoms were present in the majority of patients. Suicidal thoughts were present in approximately one out of five patients. Classical melancholic symptoms were not highly prevalent.

Within the manic spectrum, irritability was highly prevalent (73%) and occurred more often than elevated mood (39%). Decreased need for sleep and increased rate of speech were present in half of the patients.

Disorganized behavior occurred in one out of four patients. Disorientation was present in 20% of women, and disturbance of consciousness in 10%. Catatonic symptoms were observed in 5% of women (five women with mutism, and one with excessive motor activity, other catatonic symptoms were not observed). In total 72% of women had abnormal thought content. Most prevalent were persecutory delusions, and delusions of reference. In total 49 women (39%) reported auditory hallucinations, of whom 12 women (9%) heard commentary voices and eight women (6%) voices conversing with each other. Visual hallucinations were present in one out of three patients.

Pregnancy- and childbirth-related delusions were present in a quarter of the women. In particular, twelve women thought that their child was dead or would die, six women were convinced that the child was not theirs and five women believed that they were pregnant. Grandiose or spiritual delusions related to the child were rare: only one woman thought that her child had a special talent and two women were convinced that a deceased relative was reincarnated in the child. Obsessive thoughts concerning the child (mostly anxiety of harming the child) were present in 12 women (9%). Infanticide thoughts (for example, dropping the baby when holding it or choking the child) were reported by ten women (8%). Four of them also had suicidal thoughts.

FIGURE 1. Prevalence of psychiatric symptoms in women (n=130) with postpartum psychosis during admission presented per symptom factor



Eleven symptom factors are: anxiety, depression, melancholia, agitation, mania, atypical, catatonia, disorganization, delusions, hallucinations, and child-related symptoms. Symptoms with a zero prevalence (i.e. thought withdrawal, erotomanic delusion, stupor, peculiarities of movement, and echolalia/echopraxia) are not included in the figure. Other delusions, auditory hallucinations and other hallucinations represent symptom categories (see supporting information Supplementary Table 1). *indicates symptoms that are not included in subsequent latent class analysis (see supporting information Supplementary Table 2).

Symptoms are presented in accordance to the factor structure resulting from the CFA modeling procedure. A series of alternative models have been tested. The best fit in both clinical and statistical terms was found for a model consisting of 11 symptom factors: anxiety, depression, melancholia, agitation, mania, atypical (disturbance of consciousness and disorientation), disorganization, catatonia, delusions, hallucinations, and child-related symptoms. The model showed an acceptable fit with the data (χ^2=970; df=764; p<0.001; CFI=.84; TLI=.81; RMSEA =0.046 (95%CI: 0.036-0.054); WRMR=1.21). See Supplement 2 for details on CFA modelling procedure and fit.

Symptom profiles

Table 1 presents the results of the LCA. Although AIC, BIC, and adjusted BIC values indicated better fit of two profiles, the VLMR- test and BLR test suggested that three profiles fit the data better than two profiles. Four profiles resulted in an overall worsening of the fit measures. Based on goodness-of-fit indices and clinical meaningfulness we concluded that our best model contained three distinct latent profiles (log likelihood= 135; AIC= −176; BIC =−41; adjusted BIC = −189; entropy=86%). We labeled these profiles the manic, depressive and atypical symptom profiles (see figure 2).

TABLE 1. Latent profile analysis procedure and model fit

Number of latent profiles included in the model	2	3	4	5
Loglikelihood	96	135	152	150
AIC	-122	-176	-187	-158
BIC	-22	-41	-17	45
Adjusted BIC	-132	-189	-204	-179
Entropy	98%	86%	85%	84%
VL MR test[a]	P=0.284	P=0.062	P=0.446	P=0.768
BLR test[a]	P<0.001	P<0.001	P=0.013	P>0.999

[a]A significant result indicates that a model with k profiles fits better than a model with k − 1 profiles.
AIC, Akaike's information criterion; BIC, Bayesian information criterion; BLR, bootstrap likelihood ratio; VLMR, Vuong–Lo–Mendell–Rubin likelihood ratio.

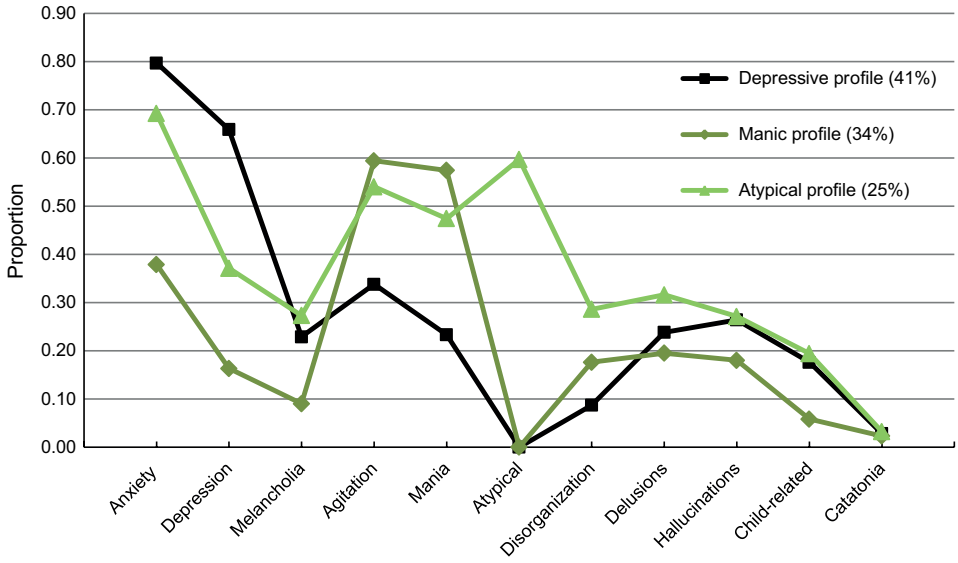
Profile 1: the manic profile. A total of 34% (n=44) of the women had this profile. The manic profile is characterized by a high prevalence of manic symptoms combined with symptoms of agitation (proportions were .57 and .59, respectively), and a relatively low prevalence of anxiety and depression (proportions were .38 and .16, respectively).

Profile 2: the depressive profile. A total of 41% (n=54) of the women had this profile. The depressive profile is characterized by a high prevalence of depressive and anxiety symptomatology (proportions were .66, and .80, respectively), and a relatively low

prevalence of symptoms of agitation and mania (proportions were .34 and .23, respectively). The depressive profile is in many respects the opposite of the manic profile.

Profile 3: the atypical profile. A total of 25% (n=32) of the women had this profile. Disturbance of consciousness and disorientation (factor atypical) were exclusively found in the atypical profile (the proportion was .60), alongside a high prevalence of anxiety (.69), depression (.37), agitation (.54) and mania (.47). Either disturbance of consciousness or disorientation (factor atypical) was present in all women with this profile, and 18% (six out of 32 women) had both symptoms present.

FIGURE 2. Symptom profiles based on latent class analysis



Included symptoms per factor are as follows. Anxiety: anxiety or worrying, and panic or scare. Depression: feelings of guilt, depressed mood, insomnia, loss of libido, and suicide thoughts. Melancholia: anhedonia, early morning awakening, psychomotor retardation, loss of appetite, and worse mood in the morning. Agitation: irritability, psychomotor agitation, and disruptive/aggressive behavior. Mania: decreased need for sleep, increased rate/amount of speech, increased motor activity or energy, grandiose delusion, elevated mood, and increased sexual interest. Atypical: disorientation and disturbance of consciousness. Disorganization: disorganized behavior, disorganized speech, inappropriate appearance, and inappropriate affect. Delusions: persecutory, delusions of reference, other (religious, guilt or jealous), somatic, being controlled, and bizarre delusions. Hallucinations: auditory (including commentary voices, and two or more voices), visual, tactile, and other (tactile and olfactory). Child-related: delusions, obsessive thoughts, and infanticide thoughts. Catatonia: extreme negativism or mutism, and excessive motor activity

Table 2 describes the demographic and clinical characteristics related to the three profiles and statistically assesses differences between them. The three subgroups of women with the profiles did not differ in terms of demographic characteristics, however, more women with the manic profile had been diagnosed with a bipolar disorder prior to their first pregnancy.

TABLE 2. Description and statistical comparison of demographic and clinical characteristics of the patients with each profile

	Manic profile	Depressive profile	Atypical profile	Test	p-value
N (%)	44 (34)	54 (41)	32 (25)		
Demographics					
Age, years [mean (sd)]	32.6 (5.2)	30.6 (4.3)	31.1 (5.1)	F(130,2)=2.15	0.12
Native Dutch [n (%)]	39 (89)	49 (91)	28 (88)	$\chi^2(2)=0.24$	0.89
College education [n (%)]	38 (88)	42 (79)	25 (78)	$\chi^2(2)=1.78$	0.41
Primiparous [n (%)]	35 (80)	39 (72)	25 (78)	$\chi^2(2)=0.81$	0.69
Complication during childbirth [n (%)]	17 (42)	16 (30)	14 (44)	χ^2 (2)=2.23	0.33
Clinical					
Positive family history of mood disorder[a] [n (%)]	22 (54)	31 (59)	15 (47)	$\chi^2(2)=0.59$	0.74
Positive family history of postpartum depression or psychosis[b] [n (%)]	7 (18)	16 (30)	6 (20)	$\chi^2(2)=2.14$	0.34
No previous episode [n (%)]	28 (64)	44 (82)	28 (87)	$\chi^2(2)=7.03$	0.032
Mania or psychosis prior to pregnancy [n (%)]	16 (36)	10 (18)	4 (13)		
Involuntary admission [n (%)]	25 (57)	19 (35)	19 (59)	$\chi^2(2)=6.57$	0.037
Time between onset of first symptoms and admission, days [median (95% CI)]	11 (9-13)	23 (17-29)	9 (5-13)	Log Rank $\chi^2(2)=6.05$	0.049
Time to remission[c], days [median (95%CI)]	26 (19-33)	30 (19-41)	30 (18-42)	Log Rank $\chi^2(2)=5.48$	0.065
Admission duration, days [median (95%CI)]	53 (46-60)	57 (52-62)	54 (39-69)	Log Rank $\chi^2(2)=2.97$	0.23

[a]Defined as a first- or second-degree relative known to have unipolar depression or bipolar disorder.
[b]Defined as a first- or second-degree relative known to have postpartum depression or postpartum psychosis.
[c]Defined as the absence of psychotic, manic, and depressive symptoms for at least 1 week[8].
CI, confidence interval; SD, standard deviation.

Of these 30 women, 16 (54%) were classified is having the manic profile, 10 (33%) as having the depressive profile, and four (13%) as having the atypical profile. The women in the profile subgroups did not significantly differ with respect to the treatment outcome (remission rates ranged from 82 to 94%), but women in the manic profile subgroup reached symptom remission approximately 4 days earlier after initiating treatment. Women with the depressive profile received treatment significantly later than women with the other two profiles; the average time from symptom onset to treatment was 23 days, almost 2 weeks longer than for women with a manic or atypical profile. Hospitalization of the majority of the women with the depressive profile took place voluntarily, while women in the mania and atypical profile subgroups were more often admitted through civil detention. In line with the symptomatology of the profiles, risk for suicide or serious self-harm was more frequent in women with the depressive profile, i.e. 58% of women with the depressive profile presented these risks vs 32% of women with the manic profile and 47% of women with the atypical profile. Women with the atypical profile were more often committed to prevent self-neglect, i.e. 63% of those with the atypical profile vs 36% of those with the manic profile, and 47% of those with the depressive profile. However, none of these differences reached significance.

DISCUSSION

PP is one of the few disorders in psychiatry for which the primary etiological event is known (i.e. childbirth), which is an important phenotypic characteristic of the disorder. The characteristic acute postpartum onset and clinical presentation have been exquisitely described by experts in the field, but prospective, well-characterized symptom assessment in a larger cohort has been lacking. Here we have performed a detailed assessment of symptomatology during the acute phase and we have identified three symptom profiles using latent cluster analysis. The first profile is best characterized as a manic (34%), the second as a depressive (41%) and the third as an atypical symptom profile (25%).

Affective symptoms

Our results confirm the affective nature of the disease because manic, depressive and other affective symptoms are highly prevalent. For both the manic and atypical symptom profiles, dysphoric manic symptoms and agitation were more prevalent than euphoric mania. This has been reported previously in women with a history of bipolar disorder with a postpartum relapse (19, 20). The low prevalence of "classical euphoric mania" could be a gender characteristic because mixed episodes are more common in women compared to men (21, 22). In addition, this could be seen as a specific characteristic of the postpartum period. Remarkably, anxiety was highly prevalent in all three symptom profiles, especially in depressive profile. We suspect that affective symptoms such as anxiety, irritability and agitation are particularly prevalent

in postpartum psychiatric episodes compared to non-postpartum episodes (4, 23), and it is tempting to speculate that these symptoms are related to the endocrine and physiological changes that occur after delivery (24, 25).

Delusions and hallucinations

Delusions and hallucinations were present in a majority of the patients, which is in line with a high prevalence of psychotic symptoms in first manic episodes outside the postpartum period (26). The most prevalent delusions were paranoid delusions and delusions of reference. More specific to this disease was the occurrence of childbirth related delusions in 24% of women with PP. Occasionally these were delusions of grandiosity ('my child is the new messiah') but mostly the content of these pregnancy- and childbirth-related delusions was negative. Interestingly, the prevalence of childbirth related delusions was much higher in India, where 78% of women with PP reported these kind of delusions (27). The lower prevalence in our study may be due to cultural differences and is quite similar to the prevalence found in a British study (28). It is quite possible that mothers keep their psychotic thoughts regarding their child or childbirth well hidden.

Schneiderian first-rank symptoms were rare, as described previously (5, 6). Lastly, we report a prevalence of visual hallucinations of 34%, which is in concordance with a retrospective case series from The Netherlands (4). Visual hallucinations are uncommon in bipolar episodes outside the postpartum period (29).

Symptoms typical for postpartum psychosis?

Previous studies have described disturbance of consciousness, disorientation, severe inattention and depersonalization/derealization as important symptoms of PP (4-7, 19, 30-34). Notably, there might be a bias towards reporting these symptoms in case reports, case series or retrospective studies, because these symptoms are remarkable and extraordinary.

In our latent class analysis, disorientation, disturbance of consciousness, and disorganization clustered together into a single profile. More specifically, all patients with this profile (n=32) had at least one of the two symptoms: disturbance of consciousness and/or disorientation. These symptoms were exclusively present in this profile. Disturbance of consciousness, disorientation but also visual hallucinations are common characteristics of delirium in somatically ill patients. The presence of these symptoms suggests an undetected organic cause (6). Despite a thorough somatic screening of all patients, we could identify this organic cause [N-methyl D-aspartate (NMDA) receptor encephalitis] in two women only (35). Remarkably, only one of these had this atypical profile, the other had a manic profile.

Risk of suicide and infanticide

Prior to admission, potential risks of suicide and infanticide were important justifications for both voluntary and involuntary patient admissions. Importantly, almost half of our cohort consisted of women with involuntary admission. The initial legal grounds for the involuntary admission were civil detention to prevent acute danger for the safety of the patients or others (including risk of suicide, homicide, causing serious harm to herself/ others or neglecting selfcare or care of the baby). One woman committed a life threatening suicide attempt prior to admission. During admission, 19% of women reported suicidal thoughts. Higher rates of suicidal thoughts and attempts in women with postpartum mental illness have been found in previous studies (4, 6, 32). The cultural and socio-economic background of our patient cohort might have contributed to this finding (36).

Ten women (8%) reported thoughts of infanticide during admission. In an Indian study in 50 women with severe postpartum mental illness, nearly half of the patients reported infanticide ideas. Main risk factors were depression and psychotic symptoms (37). In a study in the USA, homicidal ideation and behavior were present in respectively 33 and 14% (6), and a British study found a prevalence of 9% (28). Taken together, these findings indicate that clinicians should always inquire, harming her infant or harming other children.

Strengths and limitations

One of the strengths in this study is the use of data from the largest clinical cohort of women diagnosed with PP (34). Data were collected prospectively, over the course of admission. In doing so, we were able to avoid recall bias in symptom reporting. A potential limitation is the use of the EPDS. With regards to depressive symptomatology, we chose self-reported EPDS items over clinician rated symptoms since the EPDS has been developed for women in the postpartum period specifically (10, 38). Obtaining self-reported depressive symptomatology via EPDS might have led to subjective reporting, which could have hindered the identification of more severe depressive symptoms, including suicidal thoughts. A subset of symptoms was elicited from the medical records. Reliability regarding the presence of these symptoms was therefore dependent on the quality of reporting by the treating clinician. From our weekly assessments, we have scored the presence of symptoms at their most severe occurrence. In doing so, we were able to capture a broad array of symptoms present during admission (7, 39), but we could not capture the rapid fluctuations of symptomatology within patients (the so called "kaleidoscopic" picture). Because of our sample size, latent class analyses were conducted using aggregated symptoms, i.e. the proportion of symptoms present for each symptom factor. This form of data reduction enabled us to distinguish clinically relevant symptom profiles, but also forced us to make assumptions about the relationship among symptoms. Finally, in our analyses, patients might have been misclassified to the latent symptom profiles, resulting in an underestimation of the relationship between illness course and symptom profile.

Conclusions

PP is a severe disorder; its inclusion as distinct disorder within the bipolar spectrum in the list of rare disorders is an important recognition for the women affected. If women are given this initial "postpartum diagnosis", they will not be misclassified as "bipolar" too early in their disease course. One of the major challenges in this field is the ability to predict which women will experience multiple episodes (bipolar disorder) and which women have an isolated postpartum episode. In our study we were able to distinguish three phenotypic clusters. At this point, we do not know whether these are predictive to the disease course. Because of the low prevalence of the disorder, an international collaborative effort, including data sharing, is vital for consistent assessment and follow-up of women with first onset PP. Hopefully, this will lead to predictors of the disease course.

We showed that disturbance of consciousness, disorientation, and depersonalization/derealization were less prevalent than previously suggested in the literature. These symptoms remain enigmatic and clearly warrant further neuroscientific research. In first onset PP, euphoric manic symptoms were less prevalent compared to bipolar episodes. Instead, irritability seems to be a hallmark of the disease. Lastly, we showed that depressive symptomatology was at least as prevalent as manic symptomatology. This is an important diagnostic consideration, and clinicians should think of PP when a woman presents with acute severe depression, anxiety or agitation postpartum, even if psychotic symptoms are not present yet. Adequate recognition of these symptoms could lead to shorter disease episodes and prevent tragic outcomes such as suicide or infanticide.

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SUPPLEMENTARY TABLE 1. List of symptoms assessed through questionnaires and diagnostic interview

Symptom	Reference	Description/ criteria for presence
Elevated mood	YMRS	Definite subjective elevation (2) – euphoric (4)
Increased motor activity/energy	YMRS	Animated, gestures increased (2) – motor excitement (4)
Increased sexual interest	YMRS	Definite subjective increase (2) – overt sexual acts (4)
Decreased need for sleep	YMRS	Sleeping less more than 1 hour (2) – denies need for sleep (4)
Irritability	YMRS	Subjectively increased (2) – hostile (8)
Increased rate or amount of speech	YMRS	Feels talkative (2) – uninterruptible, continuous speech (8)
Language/ thought disorder	YMRS	Distractible, racing thoughts (2) – incoherent (4)
Thought content	YMRS	Questionable plans (2) – delusions, hallucinations (8)
Disruptive/aggressive behavior	YMRS	Sarcastic (2) – assaultive, destructive (8)
Appearance	YMRS	Poorly groomed (2) – completely unkempt (4)
Insight	YMRS	Admits behaviour change, denies illness (2) – denies any behaviour change (4)
Depressed mood	EPDS	Felt sad or miserable quite often (2) or most of the time (3)
Anhedonia	EPDS	Looked forward with joy definitely less (2) or hardly at all (3)
Feelings of guilt	EPDS	Blamed herself some of the time (2) or most of the time (3)
Anxiety or worrying	EPDS	Anxious or worried sometimes (2) or very often (3)
Panic or scared	EPDS	Felt scared or panicky sometimes (2) or quite a lot (3)
Insomnia (due to unhappiness)	EPDS	Had difficulty sleeping sometimes (2) or most of the time (3)
Suicide	EPDS	Thought of harming herself sometimes (2) or quite often (3)
Early morning awakening	HAM-D	Early awakening each day or more than 1 hour (2)
Psychomotor retardation	HAM-D	Obvious retardation (2) – complete stupor (4)
Psychomotor agitation	HAM-D	Playing with hands, hair (2) – hand wringing, hair pulling (4)
Loss of appetite	HAM-D	Marked reduction of appetite and food intake (2)
Loss of libido	HAM-D	Severe loss of libido (2)
Diurnal worsening of mood	SCID	Usually worse mood in the morning (3)
Delusion of reference	SCID	Events, objects, or other people in the individual's immediate environment have a particular or unusual significance
Persecutory delusion	SCID	Feeling of being attacked, harassed, cheated, persecuted, or conspired against
Grandiose delusion	SCID	Feeling of exaggerated power, knowledge or importance, or a special relationship to a deity or famous person.
Somatic delusion	SCID	Change or disturbance in body appearance or functioning
Erotomanic delusion	SCID	Convinced having a special, secret relationship with someone famous
Delusion of being controlled	SCID	Feelings, impulses, thoughts or actions are experienced as being under the control of some external force

SUPPLEMENTARY TABLE 1. List of symptoms assessed through questionnaires and diagnostic interview *(Continued)*

Symptom	Reference	Description/ criteria for presence
Thought withdrawal	SCID	Thoughts being taken out of one's mind
Bizarre delusions	SCID	Evidently absurd conviction
Other delusions: Religious delusion	SCID	Unusual religious experiences
Other delusions: Delusion of guilt	SCID	Feeling of having done something terrible for which one should be punished
Other delusions: Jealous delusion	SCID	Convinced that spouse or partner is unfaithful
Other delusions: Thought insertion	SCID	Thoughts inserted in one's head by someone else
Other delusions: Thought broadcasting	SCID	The delusion that one's thoughts are audible to others
Auditory hallucinations	SCID	Auditory hallucinations when fully awake, heard either inside or outside of the head
Auditory hallucinations: Commentary voices	SCID	A voice keeping up a running commentary on the individual's behavior or thoughts
Auditory hallucinations: Two or more voices	SCID	Two or more voices conversing with each other
Visual hallucinations	SCID	Visual hallucinations
Tactile hallucinations	SCID	Tactile hallucinations
Other hallucinations: Gustatory hallucinations	SCID	Gustatory hallucinations
Other hallucinations: Olfactory hallucinations	SCID	Olfactory hallucinations
Disorganized behaviour	SCID	Bizarre behaviour, inappropriate appearance, sexual disinhibition or unpredictable agitation
Inappropriate affect	SCID	Affect that is clearly discordant with the content of speech or ideation
Disorganized speech	SCID	Frequent derailment or incoherence
Catalepsy or stupor	SCID	Passive induction of a posture held against gravity of absence of psychomotor activity
Excessive motor activity	SCID	Purposeless agitation
Extreme negativism or mutism	SCID	Opposition to instructions or external stimuli or absence of speech
Peculiarities of voluntary movement	SCID	Posturing, stereotypy, mannerism or grimacing
Echolalia or echopraxia	SCID	Mimicking another's speech or movements
Disturbance of consciousness	Records	Inability to remain awake during daytime, intermittent or persistent
Disorientation	Records	Being disorientated in time, place or person
Inattention	Records	Reduced ability to focus, sustain or shift attention
Pregnancy and childbirth related delusions	Records	Delusions related to pregnancy (e.g. being still pregnant) or to the child (e.g. child has a special gift or is dead)
Infanticide thoughts	Records	Thoughts or wishes on harming the child
Obsessive thoughts concerning the child	Records	Ego dystonic obsessive thoughts concerning the child
Depersonalization and derealisation	Records	Terms "depersonalization" and/or "derealisation" found in medical records

YMRS: Young Mania Rating Scale (1); EPDS: Edinburgh Postpartum Depression Scale (2); HAM-D: Hamilton Rating Scale for Depression (3); SCID: Structured Interview for DSM-IV Axis I Disorders (4).

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Supplement 2. Confirmatory factor analysis procedure and model fit

All 58 assessed symptoms were re-grouped into a smaller substantive based subsets by a panel of psychiatrists. This was a prerequisite, since the number of unique symptoms outnumbered the number of patients in our sample. Then, a confirmatory factor analysis (CFA) was used to evaluate the factor structure. Symptoms with zero prevalence (i.e. "thought withdrawal", "erotomanic delusion", "stupor", "peculiarities of movement", and "echolalia/echopraxia"), and symptoms that lacked a clear clinical definition (i.e. "language and thought disorder", "abnormal thought content") were excluded from analyses. We started with Model 1, consisting of 10 factors. Next the factor structure (number of factors and content of factors) was optimized in a series of adaptations using modification indices (>10.0), R-squared (<0.10), and (negative) residual variances of the estimated parameters. Modifications were only performed if they were clinically justifiable and did not influence the estimates of other parameters in the model. The fit of the models was evaluated using clinical judgement on the interpretability of the factors, and statistical goodness-of-fit indices, e.g. Comparative Fit Index, Tucker-Lewis Index, Root Mean Square Error of Approximation and Weighted Root Mean Square Residuals. Fit is considered good in case of a Ch2/df ratio < 1.5; RMSEA < 0.06, CFI and TLI > 0.95, and WRMR <1.0 (1-4). The best fitting model based on clinical and statistical criteria, was Model 3, consisting of the following conjunctive symptom factors (n=11): anxiety, depression, melancholia, agitation, mania, atypical, catatonic symptoms, disorganization, delusions, hallucinations and child-related symptoms. Factor structures and model fit indices of the best fitting and alternative models are reported in Supplementary Table 2.

SUPPLEMENTARY TABLE 2. Modelling procedure and resulting model fit

	Model 1	Model 2	Model 3[c]	Model 4	Model 5
Model Description		Model 1 minus 4 symptoms[b]	Model 2 plus additional factor	Model 3 using 5 aggregated symptom clusters[d] and single item factors excluded	Model 4 with inclusion of 3 single item factors
Number of factors	10	10	11	8	11
Factors	Depression Melancholia Agitation Mania Atypical Disorganization Delusions Hallucinations Child-related Catatonia	Identical	Identical + Anxiety	Anxiety Depression Melancholia Agitation Mania Disorganization Delusions Hallucinations	Anxiety Depression Melancholia Agitation Mania Disorganization Delusions Hallucinations *Single symptom factors:* Atypical Child-related Catatonia
Performance estimators[a]					
Chi2	1136	990	970	468	588
df	900	774	764	377	470
Chi2/df	1.26	1.28	1.27	1.24	1.25
p	<0.001	<0.001	<0.001	0.001	0.002
RMSEA (90% CI)	0.045 (0.036-0.053)	0.046 (0.037-0.055)	0.046 (0.036-0.054)	0.043 (0.029-0.055)	0.044 (0.031-0.055)
CFI	0.81	0.83	0.84	0.89	0.85
TFI	0.79	0.81	0.81	0.87	0.84
WRMR	1.24	1.24	1.21	1.04	1.10

[a] Fit is considered good in case of a Ch2/df ratio < 1.5; RMSEA < 0.06, CFI and TLI > 0.95, and WRMR <1.0 (Bentler, 1990; Hu & Bentler 1998; 1999; Tucker & Lewis, 1973).

[b] Excluded symptoms based on statistical and clinical criteria:
- "lack of insight" in factor Mania.
- "inattention" and "depersonalization/derealisation" in factor Atypical.
- "language/thought disorder" in factor Catatonia.

[c] Final model, used in analyses

[d] Symptom aggregation with dichotomous (disjunct) scoring of the resulting symptom clusters (a score of 1 indicates that at least one of listed symptoms was present). Clusters are presented per factor the symptoms originate from:
- Factor Atypical: "disturbances of consciousness", "disorientation".
- Factor Delusions: "delusions of reference", "persecutory delusion", "somatic delusion", "bizarre delusions", "other delusions".
- Factor Hallucinations: "tactile hallucinations", "other hallucinations".
- Factor Child-related: "child-related delusions", "child-related obsessive thoughts", "infanticide thoughts".
- Factor Catatonia: "extreme negativism or mutism", "excessive motor activity".

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Chapter 5

Thyroid peroxidase antibodies during early gestation and the subsequent risk of first-onset postpartum depression: a prospective cohort study

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ABSTRACT

Background: During the postpartum period, women are at risk for the new onset of both auto-immune thyroid disorders and depression. The presence of thyroid peroxidase antibodies (TPO-ab) during early gestation is predictive for postpartum auto-immune thyroid dysfunction. The aim of this study was to investigate the association between TPO-ab status during early gestation and first-onset postpartum depression.

Methods: Prospective cohort study (n=1075) with follow-up during pregnancy up to one year postpartum. Thyroid function and TPO-ab status were measured during early gestation. Depressive symptomatology was assessed during each trimester and at four time points postpartum with the Edinburgh Depression Scale (EDS). Women with antenatal depression were not eligible for inclusion. Self-reported postpartum depression was defined with an EDS cut-off of ≥13.

Results: The cumulative incidence of self-reported first-onset depression in the first postpartum year was 6.3%. A positive TPO-ab status was associated with an increased risk for self-reported first-onset depression at four months postpartum (adjusted OR 3.8; 95% CI 1.3-11.6), but not at other postpartum time points. Prevalence rates of self-reported postpartum depression declined after four months postpartum in the TPO-ab positive group, but remained constant in the TPO-ab negative group.

Limitations: Depression was defined with a self-rating questionnaire (EDS).

Conclusions: Women with an increased TPO-ab titer during early gestation are at increased risk for self-reported first-onset depression. The longitudinal pattern of self-reported postpartum depression in the TPO-ab positive group was similar to the typical course of postpartum TPO-ab titers changes. This suggests overlap in the etiology of first-onset postpartum depression and auto-immune thyroid dysfunction. Thyroid function should be evaluated in women with first-onset postpartum depression.

INTRODUCTION

Postpartum depression is a disabling and heterogeneous disorder with a huge variety in biological, psychological and social risk factors (1). In addition, there is substantial difference in the onset timing, severity and course of postpartum depression (2, 3). The most important risk factor for postpartum depression is a depressive episode earlier in life or during pregnancy. In a large study among women with postpartum depression, approximately 60% of women reported an onset of their episode before pregnancy or during the antenatal period (4).

Antenatal depression occurs during an entirely different immune and endocrine state than postpartum depression and may therefore have a different origin (5). Interestingly, the postpartum period is a high risk period for more severe and first-onset episodes of depression (6). Therefore, it is important to consider onset timing when studying risk factors for postpartum depression (4). The postpartum period is also associated with an increased risk for the new onset of auto-immune thyroid disorders (7). The presence of thyroid peroxidase antibodies (TPO-ab) during early gestation is a clear marker for the occurrence of postpartum auto-immune thyroid dysfunction, induced by the typical postpartum rebound phenomena of TPO-ab titers (8-11). Interestingly, TPO has also been named as a predictor for postpartum depression (12).

Four studies reported an association between an increased TPO-ab titer during early gestation and depression postpartum (13-16). However, none of these studies focused on first-onset depression and three out of four studies did not take into account antenatal depression (13, 15, 16), while one study only briefly mentioned this in a sub analysis (14). Together, as acknowledged by Dama and colleagues in their recent review, in previous studies antenatal depression may have confounded the association between a TPO-ab positive status during pregnancy and postpartum depression (12). Accordingly, the current study was designed to investigate the association between a positive TPO-ab status during early gestation and first-onset postpartum depression. We hypothesized that women are particularly at increased risk for first-onset depression three to four months postpartum, during the typical rebound of TPO-ab titers.

METHOD

Participants

Participants were included in the Holistic Approach to Pregnancy and the first Postpartum year (HAPPY) study, a large prospective cohort that is described in detail elsewhere (17). In sum, the HAPPY-study focuses on maternal wellbeing during pregnancy and the postpartum period. During a recruitment period of 18 months (2013-2014), Dutch-speaking pregnant women were informed about the study during their first trimester appointment at 17 community midwives offices in the South-East of the Netherlands. Women with a non-singleton pregnancy or history

of a severe psychiatric disorder were not eligible for inclusion. We excluded women with a self-reported lifetime history of depression as well as all women with depression during the full course of their pregnancy. In addition, women with a known thyroid disease at baseline as well as other endocrine/auto-immune disorders were not eligible for inclusion. The HAPPY-study was approved by the Medical Ethical Committee of the Maxima Medical Centre Veldhoven and the Psychology Ethics Committee of Tilburg University (protocol number EC-2012.25).

Data collection, procedures and definitions

This study is reported in line with the STROBE guidelines (18). Questionnaires were used to collect baseline demographic information, as well as relevant medical, obstetric, psychological and lifestyle data. If applicable, data were verified with medical records. Standardized blood measurements were performed at 10-12 weeks gestation and included TPO-ab, as well as thyroid releasing hormone (TSH) and free thyroxine (FT4). Measurements were performed in Li-heparin plasma using electrochemiluminescence assays (Cobas® e 601, Roche Diagnostics, Mannheim Germany). We defined a positive TPO-ab status with the commonly used threshold of >20 IU/ml (19). This cut-off is probably not appropriate throughout the full course of pregnancy (12). Therefore, we performed the TPO-ab measurement during early pregnancy, before downsizing of maternal auto-immune processes emerges (8).

Depressive symptomatology was assessed repeatedly every trimester and four times during the postpartum period (6 weeks, and 4, 8, and 12 months) using the Edinburgh Depression Scale (EDS). The EDS is validated to detect women with a high probability of major depression both during pregnancy and postpartum. In this study, self-reported depression was defined with the following validated EDS cut-off scores: trimester 1, ≥11; trimester 2 and 3, ≥10; (20); postpartum period ≥13 (21-23). Women who scored above the trimester cut-offs during the course of their pregnancy were not eligible for inclusion in our study.

Our primary outcome measure was the occurrence of first-onset self-reported depression (i.e. incidence of new cases) at four months postpartum. Women with an increased TPO-ab titer during early gestation show a subsequent decline of their titer throughout pregnancy, with a typically rebound between three to five months postpartum and a gradual decline afterwards (9-11). Therefore, we considered four months postpartum to be the most optimal time point available to assess a possible association between a positive TPO-ab status during early gestation and the occurrence of first-onset self-reported depression postpartum. First-onset self-reported depression at other postpartum time points (6 weeks, 8 and 12 months) were used as secondary outcome measures.

Statistical methods

SPSS (version 24, IBM) was used for the statistical analyses. Binary logistic regression was used to evaluate the association between TPO-ab status during the first trimester (exposure) and the incidence of new cases of self-reported depression at four months postpartum (primary outcome), and at 6 weeks, 8 months and 12 months postpartum (secondary outcomes). To facilitate interpretation of the results, we plotted point prevalence rates of self-reported postpartum depression (EDS ≥13) over time (at 6 weeks, 4, 8 and 12 months postpartum) according to TPO-status. A multiple logistic regression analysis was performed to adjust for potential confounders. Based on previous literature, we included the following confounding variables: anxiety during pregnancy (Generalized Anxiety Disorder (GAD-7) scale sum score at 12 weeks gestation, continuous), age (years, continuous) and preterm delivery (<37 weeks of gestation, dichotomous) (12), primiparity (dichotomous) (1, 24) and recent life-events (self-reported, dichotomous) (14). In addition, we considered the following confounding variables: mode of delivery (vaginal delivery or cesarean section), health problems of the baby (self-reported, dichotomous) and social support during the postpartum period (Tilburg Support Scale sum score, continuous). All potential confounding variables were introduced both separately and simultaneously into the unadjusted model to verify a potential effect on our exposure of interest (TPO-ab status). Logistic regression analyses were evaluated with Wald tests (χ^2, distribution, α=0.05). Results are presented with crude and adjusted odds ratio's (OR's) together with corresponding 95% confidence intervals.

Additionally, we tested whether a positive TPO-ab status during pregnancy was associated with differences in mean TSH and FT4 concentrations by using T-tests. TSH data was log-transformed to meet the assumption of normality, and log transformed mean TSH values are reported. Cohen's d are used to report the size of the effect (25). Finally, we used a sensitivity analysis to assess the robustness of the findings. For this aim, we changed the dichotomous TPO-ab variable into a categorical variable (3 categories: ≤ 20 IU/ml; 21-100 IU/ml; ≥101 IU/ml).

Women were included in the final study sample if 1) at least two out of three pregnancy EDS scores were available and 2) the EDS score at four months postpartum (primary outcome measure) was available.

As a result of our data selection strategy we did not have any missing data on our primary outcome measure (EDS score ≥13 at 4 months postpartum). During pregnancy, the proportion of missing EDS measures varied between 1.7% and 2.5%. Regarding the secondary outcome measures, the proportion of missing data varied between 8.3% and 23.3%. Missing data was handled with the multiple imputation algorithm as implemented in SPSS version 24 (IBM). Ten imputed datasets were created and all predictor and outcome variables were used for imputation modelling. Analyses were run on the imputed data and pooled estimates are reported (26). To explore the impact of the imputation procedure on our results, we repeated all analyses using the original dataset.

RESULTS

Study sample

A detailed overview of the participant selection process is presented in Figure 1. In total, n=3160 Dutch-speaking pregnant women were informed about the HAPPY-study, of which 71.8% (n=2269) provided informed consent. A self-reported lifetime history of depression (n=300) and one or more EDS scores above the trimester specific cut-offs during pregnancy (n=386) were the most important reasons for exclusion. Of the women that were eligible for this study (n=1364), follow-up data at four months postpartum was available for n=1075 (78.8%) women. According to the baseline demographic study characteristics (Table 1), the vast majority of women had the Dutch nationality, a high educational level, a paid job and was married or living together. Most baseline characteristics did not differ substantially between women that were included and excluded because of missing follow-up data during pregnancy or at four months postpartum (n=289, 21.2%). However, excluded women showed a higher prevalence of unplanned pregnancies (7.8% versus 3.7%), preterm delivery (6.6% versus 3.5%), smoking during pregnancy (8.6% versus 2.6%) and a lower prevalence of high education level (50.8% versus 69.3%).

FIGURE 1. Flow chart inclusion

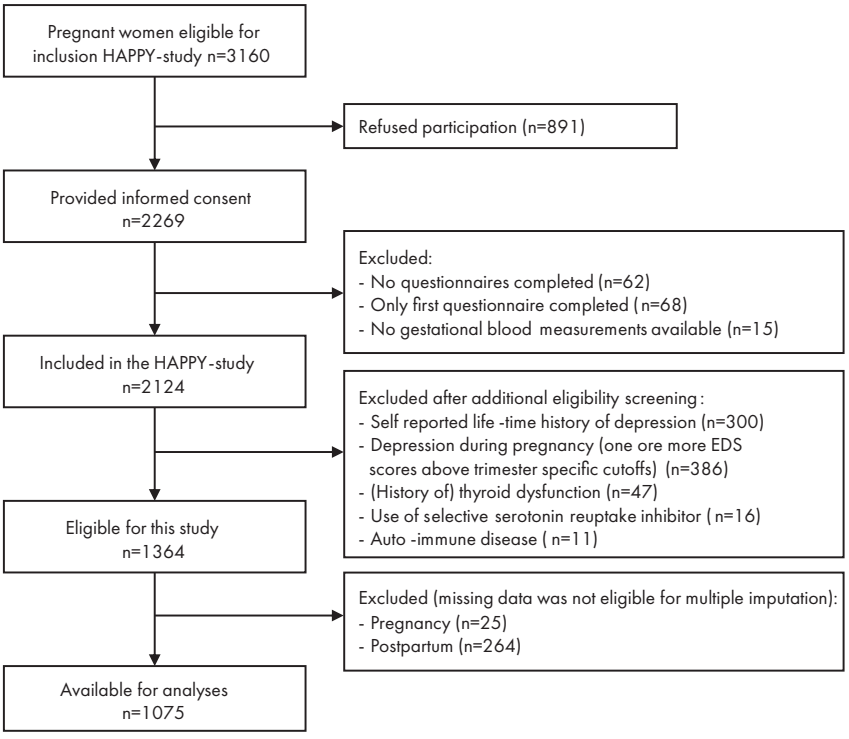


TABLE 1. Baseline characteristics (n=1075)

	Mean (SD)	n (%)[a]
Age (years)	30.4 (3.5)	
Gestational age (days)	278 (10)	
Preterm delivery (<37 weeks)		38 (3.5)
Married or living together		1044 (99.0)
High educational level[b]		764 (69.3)
Dutch nationality		1038 (98.4)
Paid job		1014 (96.2)
Primiparous		525 (49.9)
Unplanned pregnancy		39 (3.7)
Smoking during pregnancy		27 (2.6)
Alcohol consumption during pregnancy		13 (1.2)

[a] In case of missing data (maximum n=22), valid percentages are presented
[b] Bachelor and/or master degree

Thyroid measurements and EDS scores during pregnancy

In total, 121 out of 1075 women (11.3%) had a positive TPO-ab status (>20 IU/ml) at 12 weeks of gestation. The median of the positive TPOA-ab measurements was 74.0 IU/ml, with an inter quartile range (IQR) of 29.0 – 170.0. In the full sample, we observed a median TSH blood level of 1.4 mU/L (IQR 1.0-2.1 mU/l) and median FT4 of 14.4 pmol;/L (IQR 13.4-15.4 pmol;/L).

TSH concentrations were significantly higher in the group with a positive TPO-AB status (log-transformed mean 0.3 mU/L, SD 0.4) compared to the group with a negative TPO-ab status (log-transformed mean 0.1 mU/L, SD 0.3); t(1073) = -4.9, p<0.0001, cohen's d=0.43, medium effect size). FT4 concentrations were significantly lower in the group with a positive TPO-AB status (mean 14.2 pmol/L, SD 1.8) than in de group with a negative TPO-ab status (mean 14.6 pmol/L, SD 1.7; t(1073)=2.2, p=0.028, Cohen's d=0.23, small effect size).

We excluded women with an EDS score above the trimester specific cut-offs, which resulted in the following mean EDS scores of the remaining women: trimester 1, 2.7 (SD 2.5); trimester 2, 3.4 (SD 2.6); trimester 3, 3.3 (SD 2.6). Mean EDS-scores did not significantly differ between women with a positive versus negative TPO-ab status during any of the trimesters.

The association between thyroid peroxidase antibodies status and first-onset postpartum depression

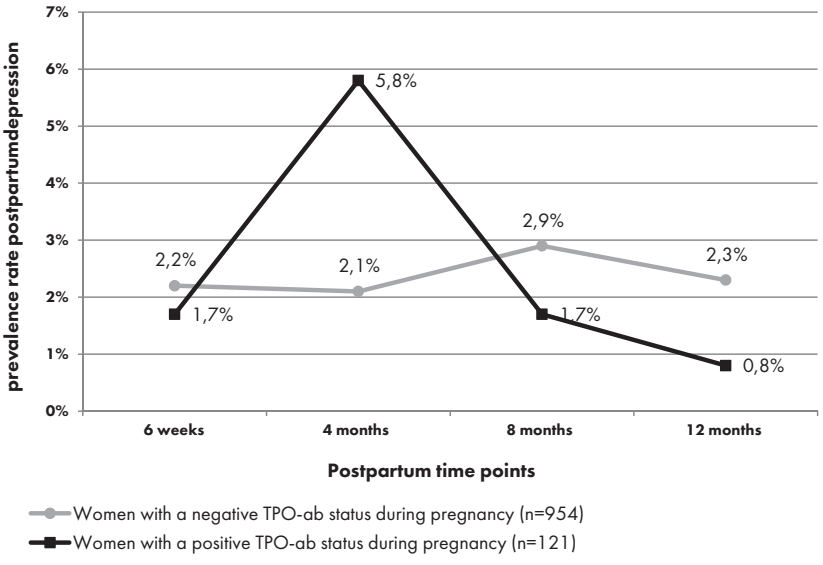
In the total sample, 6.3% (68/1075) of the women fulfilled the definition of self-reported postpartum depression at one or more of the four assessments during the first postpartum year (n=43 once; n=16 twice; n=6 three times; n=3 four times).

At four months postpartum, we observed a risk of self-reported first-onset postpartum depression of 5.0% (6/119) among women with a positive TPO-ab status, compared to 1.5% (14/934) among women with a TPO-ab negative status (crude OR 3.5, 95% CI 1.3–9.4, p=0.016). This effect remained significant after adjustment for potential confounders (see method section) (adjusted OR 3.8, 95% CI 1.3-11.6, p=0.017).

The association between TPO-ab status and self-reported first-onset depression was not significant at 6 weeks, 8 months and 12 months postpartum. The point prevalence rates of self-reported postpartum depression according to TPO-ab status at all postpartum assessments are presented in Figure 2. After a peak of self-reported postpartum depression at four months postpartum among women with a positive TPO-ab status, the point prevalence rates of self-reported postpartum depression linearly declined from 5.8% (7/121) to 0.8% (1/121) at 12 months postpartum. Among women with a negative TPO-ab status, the prevalence rates of self-reported postpartum depression remained relatively constant across all time points in the first postpartum year (2.1%, 20/954 – 3.0%, 29/954).

A sensitivity analysis showed that the direction of the association between TPO-ab and self-reported first-onset depression at four months postpartum remained constant after changing our dichotomous exposure TPO-ab status into a categorical covariate (≤ 20 IU/ml; 21-100 IU/ml; ≥101 IU/ml). Repeating the analyses in the original (non-imputed) dataset supported our findings regarding the direction, size and significance of the reported associations.

FIGURE 2. Point prevalence rates of self-reported postpartum depression (EDS≥13) across the first postpartum year according to TPO-ab status during pregnancy (n=1075)



DISCUSSION

In this large prospective cohort study including n=1075 women, the cumulative incidence of self-reported first-onset postpartum depression during the first postpartum year was 6.3%. A positive TPO-ab status during pregnancy was associated with a threefold increased risk of self-reported first-onset depression at four months postpartum but not at other postpartum time points. Point prevalence rates of self-reported postpartum depression declined after four months postpartum among women with a TPO-ab positive status, but remained constant among women with a TPO-ab negative status throughout the first postpartum year. These findings suggest a link between the typical postpartum rebound phenomena of the maternal immune system and first-onset postpartum depression.

Previous studies reported a substantially higher overall risk for postpartum depression (i.e. regardless of TPO-abs status). For example, in the study of Harris and colleagues (15), 27.3% (66/242) of the women had an EDS score ≥13. In the study of Kuijpens and colleagues (14), an even higher proportion of women (117/291, 40.2%) was classified with a clinical diagnosis of postpartum depression during one or more assessments (according to the RDC-criteria). This is probably due to the high proportion of women with depression in history or depression during pregnancy. In the same study, the association between an increased TPO-ab titer at 12 weeks gestation and postpartum depression remained significant after exclusion of women with an episode of depression earlier in life and/or at 12 weeks gestation (sub-analysis (n=191), OR 2.9, 95% CI 1.8-4.3). This is in in line with the odds ratio that we observed at four months postpartum (OR 3.8, 95% CI 1.3-11.6). However, in contrast to our study, Kuijpens et al. did not focus on first-onset depression since women with depression during the second and/or third trimester were not excluded. In addition, the onset timing of postpartum depression was not reported. Our study was not confounded by antenatal depression and we could therefore show evidence for a causal link between the new occurrence of thyroid autoimmunity and depression postpartum.

There is accumulating evidence that immune system dysregulation is one of the underlying biological mechanisms that play an important role in the etiology of depression (5, 27). A mechanism that may be specifically related to first-onset postpartum depression, is the shift from immune tolerance during pregnancy towards a pro-inflammatory state during the postpartum period (5, 28). Interestingly, self-reported postpartum depression prevalence rates of the women with a positive TPO-ab status showed a pattern that is similar to the typical course of postpartum TPO-ab titers (9-11, 29): particular highly increased levels during the early (four months) postpartum period and a subsequent decrease (but still above the threshold) up to one year postpartum.

There is a well described link between the postpartum rebound of TPO-ab titers and clinical thyroid dysfunction (30). Consequently, among women with a positive TPO-ab status during

pregnancy, first-onset postpartum depression may be related to a transient hypothyroid phase of postpartum thyroid dysfunction (31). Interestingly, the results of a previous study from Harris and colleagues (15) revealed that a positive TPO-ab status postpartum was predictive for an increase in depressive symptomatology postpartum, regardless of the presence of thyroid dysfunction. An explanation for this phenomenon could be that immune activation postpartum leads to increased risk of depression instead of clinical thyroid dysfunction. Interestingly, a disturbance in the suppression and activation of several T-cell subpopulations have been associated with both increased TPO-ab titers and psychiatric disorders (30, 32-34). Therefore, T-cell abnormalities may also play a shared role in the etiology of postpartum depression and postpartum thyroid dysfunction.

Clinical considerations

The postpartum period is known to be a trigger for first-onset psychiatric disorders (6). In this study we were able to identify a new risk factor for the occurrence of self-reported first-onset postpartum depression at four months postpartum. The findings of the current study support the general statement that the etiology of postpartum depression is multifactorial. There seems to be a sub-group of women (especially during the first four months) in whom thyroid auto-immunity plays a role in the development of depressive symptomatology. We follow the view that thyroid function should be evaluated during the postpartum period if women present with first time depressive symptomatology. Measurement of thyroid-stimulating hormone is a first diagnostic step for the detection of thyroid dysfunction.

Another clinical consideration is the increased risk for women with increased TPO-ab titers for both thyroid dysfunction (particularly hypothyroidism) and depression later in life (8, 35, 36) The risk for hypothyroidism is especially high for women with both increased TPO-ab titers and TSH concentrations, even if TSH concentrations are still within the normal range (19, 35).

Strengths, limitations and directions for future research

To our knowledge, this is the first study that evaluated the association between TPO-ab titers during early gestation and (self-reported) first-onset postpartum depressive episodes. We included a large number of women and adjusted for potential confounders. However, our study also has several limitations. First, we did not assess TPO-ab titers, thyroid function and immune system parameters during the postpartum period. Consequently, it is unknown, to what extend thyroid dysfunction and immune system dysregulation was present among women with self-reported first-onset postpartum depression. Second, we used a self-rating questionnaire (EDS) to define depression. Therefore, it is unclear which proportion of the women with an EDS above the cut-off in our sample would fulfill the criteria of a clinically established diagnosis of postpartum depression. Third, we were not able to adjust for the presence of sexual child-abuse,

which is a potential confounder of the studied association (37). Finally, the findings of our study are not generalizable to women with a psychiatric history and/or women with antenatal depression, because we designed our study to investigate first-onset episodes of depression. Future studies on first-onset depression should also include longitudinal assessments of thyroid function (including TPO-ab titers) and immune system parameters (e.g. screening for potential abnormalities in T-cell subpopulations) during the postpartum period. This strategy will be helpful to further understand the role of immune system dysregulation in first-onset postpartum depression.

Conclusions

In this large prospective cohort study, we demonstrated that women with a positive TPO-ab status during early gestation are at increased risk for self-reported first-onset depression at four months postpartum. This period coincides with the typical postpartum rebound phenomena of the maternal immune system, which suggests an overlap in the etiology of first-onset postpartum depression and auto-immune thyroid dysfunction. Evaluation of thyroid function is essential in the clinical assessment of first-onset postpartum depression.

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Chapter 6

Lithium: a general introduction

History

Lithium is listed in the periodic table of elements as an alkali metal and was discovered in 1817 by Johan August Arfwedson, a Swedish chemist who identified lithium-aluminum-silicate in the mineral petalite (1, 2). The word lithium derives from "lithos" (Greek), which means stone. Lithium is an abundant element, mined as a salt at numerous places all over the world and is isolated with electrolysis and solar evaporation. It is used as a flux during processes such as welding and the production of glass but is most commonly known as a component of batteries and medication (lithiumcarbonate) (2).

Lithium salts were first used as medication in 1847 by Alfred Baring Garrod, an internist working in London who discovered that lithium could be used to dissolve uric acid in the blood of patients that suffered of gout and rheumatoid arthritis (3). The first psychiatric report about lithium for the treatment of mania was published in 1871 by William Hammond, a professor in New York. It was about 80 years later when John Cade, a psychiatrist in Melbourne, considered the presence of uric acid as the cause of "psychotic excitement" in patients with mania. He published a trial about the effectiveness of lithium citrate in ten patients. A few years later, Erik Strömgren (psychiatrist) and Mogens Schou (medical doctor and clinical biochemist), both working at the Aarhus University psychiatric clinic in Denmark, conducted one of the first clinical trials in psychiatry (lithium versus placebo) (4, 5). The results of this study were published in 1954 and firmly demonstrated the efficacy of lithium therapy in the treatment of mania (5). After the Coleman flame photometer was introduced in 1958, lithium blood levels could be measured more precisely and lithium was increasingly used in psychiatry (3).

In the subsequent decades, multiple trials and follow-up studies demonstrated that lithium was highly effective for the treatment of mania and (to a lesser extent) depression, but also as maintenance treatment for bipolar disorder. Finally, lithium is the only pharmaceutical that has been associated with a decrease in suicide risk (3, 6).

Current use in psychiatry

Nowadays, lithium has the largest evidence base for both the acute and maintenance treatment of bipolar disorder (6). However, studies from several countries including the United States, United Kingdom, Sweden and Denmark demonstrated that lithium use has declined over the last decades (7-10). During the same period, there has been a huge increase in polypharmacy (e.g. combination with antidepressants) and prescriptions of other mood stabilizing medication such as lamotrigine, olanzapine and quetiapine (introduced in 1991, 1996 and 1997 respectively) (11).

Aggressive marketing of (new) pharmaceuticals that received approval for the treatment of bipolar disorder is probably the most important reason for the shift from lithium towards other moodstabilizing medication (11, 12). Other proposed reasons are concerns regarding potential (severe) side effects, the necessity of blood level monitoring and lack of education about lithium therapy among psychiatry residents (11, 13).

Mechanisms of action

Over the last decades, there has been an exponential increase in publications focusing on the potential mechanisms of action of lithium in bipolar disorder (14).

A consistent finding among longitudinal imaging studies is that lithium use is associated with an increase in grey matter volume in regions that are part of the fronto-limbic network (15, 16). This finding suggests that lithium may have neuroprotective/neuroproliferative effects. Interestingly, this hypothesis is supported by (pre-)clinical studies that indicated that lithium inhibits apoptosis by activating neuroprotective and anti-inflammatory pathways. For example, lithium inhibits glycogen synthase kinase 3β (GSK-3). This enzyme regulates multiple neuroprotective cellular processes and is involved in circadian rhythm gene expression. In addition, inhibition of GSK3 modifies several neuronal systems (14, 16). Furthermore, lithium increases brain-derived neurotrophic factor (BDNF), a neuroprotective protein that can induce modification of neuronal structures (14, 16).

Recent studies indicate that lithium has pre- and post-synaptic effects and modifies both excitatory (dopamine, glutamate) and inhibitory (GABA) neurotransmitter systems (14). However, it is still unknown how these effects result in the clinical effects of lithium among patients with bipolar disorder.

Clinical practice

Lithium is absorbed in the upper gastro-intestinal tract and reaches its maximum blood level concentration 1.5 - 2 hours after administration (4 - 6 hours for sustained-release formulation). Afterwards, lithium slowly crosses the blood-brain barrier and is excreted through the kidneys (17, 18). The elimination half-life time of lithium is one to three days and a steady state is reached after approximately 5 days (19).

Lithium has a small and clearly defined therapeutic window (0.6-1.2 mmol/l). Consequently, blood level monitoring is necessary to avoid both sub-therapeutic and increased/toxic blood levels. When lithium is initiated in the acute phase of a manic or depressive episode, it is necessary to aim at high blood levels (0.8-1.2 mmol/l), while lower blood levels (0.6-0.8 mmol/l) are sufficient when lithium is used as maintenance treatment (19, 20). Lithium blood level monitoring should be performed 3 and 5 days after the initiation of lithium therapy, 5-7

days after each dose adjustment and every 3-6 months in patients with stable lithium blood levels. Obviously, it is important to take into account individual patient characteristics (e.g. age, compliance, potential interactions, proposed target blood level) when deciding on the exact frequency of blood level monitoring (20, 21). Finally, immediate blood level monitoring is required if patients present with severe side-effects or signs of lithium toxicity, which typically include: vomiting, worsening tremor, vertigo, ataxia, dysarthria, somnolence, confusion, fasciculation, nystagmus and ultimately seizures and coma (13, 19).

The most common side effects of lithium (when dosed within the therapeutic range) are: nausea, diarrhea polydipsia, polyuria, fatigue, tremors, sexual dysfunction, cognitive impairment and abdominal pain (13, 19, 22). It is important to realize that some side effects may disappear over time and are often dose related (20, 23). In case of disabling and persisting side-effects that do not diminish after lowering the lithium dose, further strategies to manage side effects include: changing the time of administration, switching to a different formulation, use of antidotes for specific side effects and finally a switch to other moodstabilizing medication (13, 23). The most important potential long term side effects of lithium are a gradual decline in renal function, hypothyroidism and weight gain. Therefore, it is necessary to perform regular monitoring of renal clearance (creatinine, estimated glomerular filtration rate (eGFR)), thyroid function (thyroid stimulation hormone (TSH)) and body weight (13, 20, 22).

Lithium is often prescribed in multiple daily doses (e.g. 2 d.d. 400 mg instead of 1 d.d. 800 mg) to avoid peak blood level related side-effects. However, the evidence for the benefits of multiple daily dosing is not convincing and it may decrease compliance. Therefore, there is growing consensus to prescribe lithium in one daily dosage (17, 20).

It has been proposed that use of sustained-release formulations (Priadel©, camcolit©) results in more stable lithium blood levels than immediate release formulations, thereby decreasing both side effects and the risk of a potential decline in renal function (18). However, clear evidence for this potential advantages is lacking and it has been argued that the term "sustained" (or "prolonged") is actually misleading because peak blood levels are only delayed and not necessarily lower (17, 19). Nevertheless, sustained release formulations can be beneficial because they have a coating which may prevent irritability of the stomach and masks the unpleasant taste of lithium salt. In addition, sustained release formulations are only available in 400 mg capsules (10.8 mmol li+), which may prevent potential dosing mistakes (20).

Finally, it is important to be aware of somatic illness (e.g. dehydration) and potential drug interactions that can induce lithium blood level alterations. For example, diuretics, non-steroidal anti-inflammatory drugs (NSAID's), and angiotensin converting enzyme (ACE) inhibitors will increase lithium blood levels, while lithium can enhance extra-pyramidal effects of antipsychotic co-mediation (19).

Lithium use during pregnancy and the postpartum period

In part II of this thesis we present a study on lithium dosing strategies during pregnancy and the postpartum period (**chapter 7**), followed by a study in which we compared the efficacy lithium and lamotrigine use during pregnancy in the prevention of postpartum episodes (**chapter 8**).

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Chapter 7

Lithium dosing strategies during pregnancy and the postpartum period: a retrospective cohort study

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ABSTRACT

Background: Lithium is challenging to dose during pregnancy.

Aims: To provide guidance for dosing lithium during pregnancy.

Method: Retrospective observational cohort study. Data on lithium blood level measurements (n=1101), the daily lithium dose, dosing alterations/frequency and creatinine blood levels were obtained from 113 pregnancies of women receiving lithium treatment during pregnancy and the postpartum period.

Results: Lithium blood levels decreased in the first trimester (–24%, 95% CI –15 to –35), reached a nadir the second trimester (–36%, 95% CI –27 to –47), increased in the third trimester (–21%, 95% CI –13 to –30) and were still slightly increased postpartum (+9%, 95% CI +2 to +15). Delivery itself was not associated with an acute change in lithium and creatinine blood levels.

Conclusions: We recommend close monitoring of lithium blood levels until 34 weeks of pregnancy, then weekly until delivery and twice weekly for the first 2 weeks postpartum. We suggest creatinine blood levels are measured to monitor renal clearance.

INTRODUCTION

Lithium is currently the most effective mood stabilizer and widely used as a first-line treatment in bipolar spectrum disorder. It has beneficial treatment effects during manic episodes, is associated with a reduction in suicide risk and is highly effective for relapse prevention (1). However, lithium needs to be dosed very carefully because of its narrow therapeutic window. In clinical practice, serum measurements provide crucial guidance to avoid both sub-therapeutic (<0.5 mmol/L) or toxic (>1.2 mmol/L) blood levels (2-5). In addition, it is important to check for renal dysfunction, natrium depletion, dehydration and drug interactions, which can all cause lithium blood level changes (5, 6). Dosing of lithium is particularly challenging during pregnancy as a result of the normal physiological adaptations of renal function. During pregnancy, increased glomerular filtration rate (GFR) leads to substantial reductions in lithium blood levels and an increased risk of relapse (7). Therefore, clinicians are often inclined to increase patients' lithium dose during pregnancy in an effort to maintain adequate prophylactic blood levels. However, later in pregnancy and during the early postpartum period when GFR returns to preconceptional levels, the increased lithium dose can result in toxic lithium blood levels (7, 8). Toxic lithium levels are concerning not only for the mother, but particularly for the infant in whom the adverse neonatal effects of lithium, such as hypoglycaemia, cardiac arrhythmia, thyroid dysfunction and neonatal lithium toxicity are dose-related (9, 10). Moreover, during the early postpartum period, lithium dosing is challenging because of the very high risk for postpartum relapse (37%, 95% CI 29–45%) in women with bipolar disorder (11). Therefore, increased therapeutic lithium blood levels are warranted during this high-risk period. Current clinical guidelines provide limited details regarding the optimal approach for monitoring lithium blood levels during pregnancy and the postpartum period. Therefore, in an effort to define an evidence-based strategy for dosing lithium during pregnancy, we investigated a cohort of women (n=85 representing n=113 pregnancies) for whom lithium blood levels were measured (n=1101) longitudinally during pregnancy and the postpartum period.

METHOD

Participants

All women referred to the psychiatric and obstetric out-patient clinics of Erasmus University Medical Centre and Leiden University Medical Centre between January 2003 and May 2015 were evaluated for eligibility to participate in this retrospective observational cohort study. Women were included if they used lithium during pregnancy and at least one lithium blood level measurement was obtained. This study was approved by the Institutional Review Boards of the Erasmus University Medical Centre (MEC-2013-319 ABR NL.45670.078.130) and Leiden University Medical Centre (P15.182).

Data collection and procedures

This study was conducted and reported in accordance with the STROBE guidelines (12). Data were extracted from medical records and processed with data manager OpenClinica (13). For each woman, we obtained lithium blood level measurements and all prescribed medication during the period from 25 weeks before conception through 25 weeks postpartum, including the daily lithium dose, dosing alterations and the dosing frequency. We extracted creatinine blood levels to evaluate whether alterations in lithium blood levels were consistent with alterations in the GFR. In addition, we obtained relevant demographic, psychiatric and obstetric data for each woman and her corresponding pregnancies included in the study. Each lithium blood level measurement represented one observation. Lithium-citrate (Litarex© 564 mg = 6 mmol lithium) dosages were multiplied by 0.395 in order to obtain lithium-carbonate prescription equivalents (400 mg = 10.8 mmol lithium). The peripartum time course of lithium blood levels were synchronized between women based upon the date of delivery. Perinatal time windows were defined as preconception (25 weeks preceding the estimated date of conception), first trimester (week 0-13), second trimester (week 14-26), third trimester (week 27-40) and postpartum (25 weeks following delivery).

Statistical analysis

Data management and descriptive statistics were performed using SPSS version 21.0. Linear mixed-effect modelling was implemented using the procedure MIXED to account for both the non-independence of repeated lithium blood level measurements within individuals, and differences between women in the observation frequencies and time intervals. Since our primary hypothesis was that pregnancy-induced changes in GFR are responsible for corresponding alterations in lithium blood level, we used lithium blood level as our primary outcome measure, and time (representing gestational age) and lithium dose as our main predictor variables. We also considered the daily frequency of lithium administration, preterm birth (<37 weeks), parity status and number of included pregnancies per woman as candidate predictors. Models with linear, quadratic and cubic effects of time and piecewise models with transition points at conception and delivery were fitted to capture the longitudinal effect of pregnancy-related alterations of GFR on lithium blood levels. We also used a mixed model analysis to study the effect of pregnancy on renal function. Creatinine blood levels were used as the response variable with time as a predictor. Finally, we evaluated the association between renal dysfunction (creatinine >90 µmol/L, dichotomous predictor variable) and lithium blood levels (response variable) among those measurements for which a corresponding creatinine blood level was available within a maximum of two weeks prior to obtaining the lithium blood measurement. Model selection was based on maximum likelihood tests (nested models) and Akaike's iInformation criterion (AIC). Sensitivity analyses were performed to assess if the

modelling of lithium blood levels over time was affected by the manner in which we computed the change in lithium blood levels. The standard approach was compared with time-lag models, autoregressive models, and change or variance-covariance models. Individual effects in the model were examined using Wald's test with $\alpha = 0.05$.

RESULTS

Study characteristics

We identified 89 women that were eligible for study inclusion. Four women were excluded because lithium blood measurements were not available in their medical records as testing was performed at another centre. In total, we included 85 women that were referred to the specialized out-patient university clinics of Rotterdam (n=59) and Leiden (n=26). The most common psychiatric diagnosis was a bipolar spectrum disorder (n=75, 88.2%). The remaining women (n=10) were diagnosed with a schizoaffective disorder, depressive disorder or borderline personality traits. There were 61 women with a single pregnancy, 22 women with two pregnancies, 1 woman with three and 1 woman with five pregnancies. In total, we have evaluated 113 pregnancies and 1,101 lithium blood level measurements. In these 113 cases, lithium was either initiated during pregnancy as treatment for an episode (n=12), or as a change in mood stabilizer to reduce the risk of teratogenicity (n=1) or lithium was initiated prior to conception and maintained during pregnancy and the postpartum period (n=100).

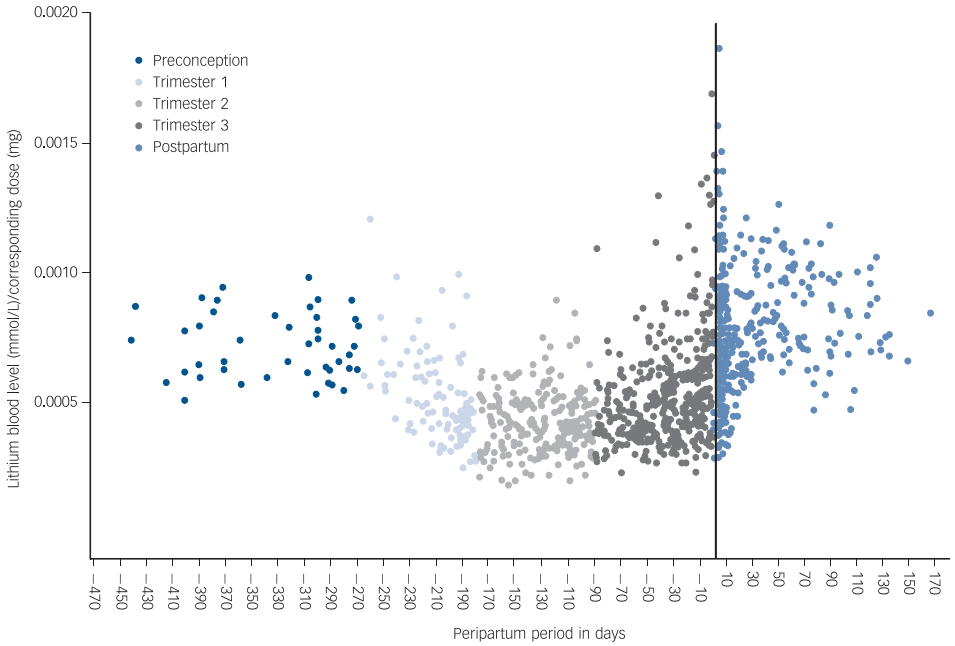
Ten women relapsed despite continuous lithium use during pregnancy and the postpartum period. Of these ten women, five relapsed during pregnancy, of whom three also relapsed postpartum. Five women relapsed exclusively in the postpartum period.

The parity of the women during each of the included pregnancies was: parity 0 (n=54), parity 1 (n=35), parity 2 (n=12), parity ≥3 (n=12). The mean age at the time of delivery was 34.5 (s.d. 4.21) years. In 22 pregnancies (19.5%), the delivery was classified as preterm birth (<37 weeks' gestation). Overall, the deliveries occurred at a median –7 days (IQR –18 to +1) prior to the estimated term date.

Course of lithium blood levels in the peripartum period

The distribution of lithium blood level measurements (n=1101) were as follows: preconception (n=46), first trimester (n=93), second trimester (n=232), third trimester (n=374) and postpartum (n=356). Preconception lithium blood level measurements were unavailable for most pregnancies (n=89, 78.8%) since the majority of women were referred during the first or second trimester.

FIGURE 1. Course of lithium blood level/dose ratio during the peripartum period



Delivery is represented by the vertical line (i.e. day zero).

During pregnancy, lithium citrate (Litarex©, slow release) was used during n=40 pregnancies and lithium carbonate (Camcolit©, Priadel© or generic lithium) was used during n=73 pregnancies. As shown in Table 1, dosing strategies varied over time. Both the mean and variance of lithium dose was increased relative to preconception levels during the second and third trimester and postpartum period. Multiple (≥2) daily dosing of lithium was used in nearly all pregnancies (n=111, 98.2%), of which most transitioned to single daily dosing immediately after delivery (n=79) while the remainder continued using multiple daily dosing in the postpartum period (n=32). Two women (n=2, 1.8%) used single daily dosing throughout pregnancy and the postpartum period.

The longitudinal pattern of observed lithium blood levels is presented in Figure 1. In order to reliably compare lithium blood levels, we normalized lithium blood levels to the total daily dose. The lowest normalized lithium levels occurred during the second trimester, in gestational week 17. Notably, women were prescribed the highest total mean daily dose during the second trimester (Table 1). A substantial proportion of lithium blood levels were definitely below the therapeutic threshold for effective mood stabilization (<0.5 mmol/L): preconception (7/46, 15.2%), first trimester (58/93, 62.4%), second trimester (144/232, 62.1%), third trimester (144/374, 38.5%) and postpartum (35/356, 9.8%).Mixed effect models with response variable lithium blood levels were fitted, leading to a final model with time (categorical) and the

corresponding prescribed lithium dose as predictor covariates (fixed effects). Other candidate predictors, including the frequency of daily lithium administration, preterm birth, parity and the number of included pregnancies per woman, did not significantly improve the performance of the model. The results of the final model are presented in Table 2. At a standardized daily dose of 1000 mg, mean lithium blood levels were lower in all trimesters compared with the preconception period. The second trimester was associated with the largest decrease in lithium blood levels (–36%, 95% CI –27 to –47).

TABLE 1. Lithium dosing strategies in the peripartum period

	Lithium blood measurements, n	Lithium dose (mg), mean (s.d.)		Dosing scheme, n(%)			
				1 daily dose		≥ 2 daily doses	
Preconception	46	925	242	14	30.4	32	69.6
Trimester 1	93	922	252	11	11.8	82	88.2
Trimester 2	232	1100	357	15	6.5	217	93.5
Trimester 3	374	1090	323	10	2.7	364	97.3
Postpartum	356	1034	270	291	81.7	65	18.3

TABLE 2. Mean lithium blood levels at a given dose of 1000 mg[a]

	Lithium blood level (mmol/L), mean (95% CI)	Change (%), mean (95% CI)[b]
Preconception	0.66 (0.61 to 0.71)	Reference
Trimester 1	0.50 (0.40 to 0.60)	–24 (–15 to –35)
Trimester 2	0.42 (0.32 to 0.52)	–36 (–27 to –47)
Trimester 3	0.52 (0.43 to 0.62)	–21 (–13 to –30)
Postpartum	0.72 (0.62 to 0.81)	+9 (+2 to +15)

[a] Linear mixed model analysis. Preconception is reference category.
Naïve model: lithium blood level = intercept + dose.
Final model: lithium blood level = intercept + dose + time (categorical).
Restricted log likelihood ratio test: χ^2 = 439.5, df=4, p<0.00001.
[b] Intervals for the % change are ranges based on the 95% confidence interval of the lithium blood level.

To quantify the influence of delivery on lithium blood levels, we restricted our analysis by comparing lithium blood level measurements during the final week of pregnancy (n=47) and the first postpartum week (n=186). However, including this categorical time covariate within the naïve model containing dose as the only predictor covariate did not significantly improve the performance of the model (restricted log likelihood ratio test: χ^2=3.5, df=1, p=0.174). A graph of the observed data is presented in Figure 1 of the data supplement. Sensitivity analyses were performed to evaluate the robustness of the final model. There were no significant differences in the beta estimates between the various models tested. Moreover, model performance did not improve by including centre (Erasmus Medical Centre or Leiden University Medical Centre),

number of days between conception and the first lithium blood measurement, or time between the estimated and actual dates of delivery as covariates.

Renal function

In total, 620 creatinine blood levels were included. In 84% of all pregnancies (n=95), at least one creatinine measurement was available. A graph of the observed data is presented in Figure 2 of the data supplement. We obtained the following mean creatinine blood levels using a mixed model analysis (response variable, creatinine blood levels; predictor covariate, time): preconception (70 µmol/L, 95% CI 66–74), first trimester (58 µmol/L, 95% CI 50-66), second trimester (56 µmol/L, 95% CI 48-63), third trimester (60 µmol/L, 95% CI 52–67), postpartum (75 µmol/L, 95% CI 67–82) (restricted log likelihood ratio test: χ^2=293.6, df=4, p<1x10^{-5}). Creatinine blood levels exhibited a similar longitudinal pattern as observed for lithium blood levels (reference period–preconception): first trimester (–17%, 95% CI –11 to –24), second trimester (–20%, 95% CI –14 to –27), third trimester (–14%, 95% CI –9 to –21), postpartum (+7%, 95% CI +2 to +12). We did not observe a significant difference in creatinine blood levels when comparing the first postpartum week with the final week of pregnancy (restricted log likelihood ratio test: χ^2=3.6, df=2, p=0.165). In total, 6.5% (n=40/620) of all creatinine blood levels were beyond the upper threshold of 90 µmol/L, suggestive of renal dysfunction. The median of these 40 suprathreshold measurements was 98 µmol/L (IQR 93–109), of which the highest observed value was 130 µmol/L.

The association of renal dysfunction and lithium blood level was evaluated among the subsample of lithium blood levels for which corresponding creatinine measurements were available (n=558/1101). The correlation between these measurements is shown graphically in Figure 3 of the data supplement. In this subsample, we observed creatinine blood levels beyond the clinical threshold for renal dysfunction (>90 µmol/L) in 3.8% of measurements (n=21/558) (median 98 µmol/L, IQR 92–108). Mixed model analysis revealed that renal dysfunction was significantly associated with elevated lithium blood levels (restricted log likelihood ratio test: χ^2=21.2, df=1, p=0.00001).

Lithium blood levels and relapse

Five women relapsed during pregnancy despite continuous use of lithium. Three women had sub-therapeutic lithium blood levels (0.41, 0.36 and 0.31 mmol/L, respectively), one woman discontinued lithium against medical advice and one woman relapsed without a recent lithium blood level. Further, of these five women with relapse during pregnancy, three women also relapsed postpartum (their postpartum blood levels were 0.64, 0.58 and 0.57 mmol/L, respectively).

Five women had a relapse exclusively in the postpartum period – one woman had a sub-therapeutic lithium blood level (0.55 mmol/L), while the remaining four women had lithium blood levels of 0.88, 0.82, 0.76 and 0.74 mmol/L.

Lithium blood levels above the therapeutic window

Eight women (n=8/85, 9.4%) had lithium blood level measurements above the therapeutic window (>1.2 mmol/L) (Table 3). A thorough review of their medical records yielded no evidence to suggest that these measurements were erroneous (for example shortened time interval between administration and blood sampling). Patients 1, 5 and 6 used substantially higher lithium doses than the mean prescribed dose in the overall cohort (Table 1).

TABLE 3. Characteristics of patients (n=8) with lithium blood level measurements beyond the therapeutic threshold (1.2 mmol/L)

Patient	Day of blood level measurement (delivery is day 0)	Total pregnancy duration, weeks	Lithium blood level, mmol/L	Corresponding lithium dose, mg	Creatinine blood level, µmol/L[a]	Plausible cause
1	- 6	36	1.21	1600	68	Pre-eclampsia
2[b]	- 4	26[c]	1.90	889[d]	107 (↑)	Decreased renal function (pre-eclampsia)
3	+ 1	39	1.33	1000	92 (↑)	Decreased renal function (pre-eclampsia)
4	+ 1	30[c]	1.26	800	61	Non-steroidal anti-inflammatory drug prescription[e]
5[f,g]	+ 2	41	1.38	1600	56	Aimed at high target level[h]
6[f]	+ 2	40	1.24	2000	66	Insufficiently anticipated on shift in renal function
7	+ 2	34[c]	1.21	1100	119 (↑)	Decreased renal function
8	+ 48	40	1.27	1000	53	Aimed at high target level[h]

[a] Creatinine levels were obtained within a maximum of 2 weeks prior to obtaining the lithium blood measurement except for patient 5 (+1 day) and patient 6 (–16 days).
[b] Twin pregnancy. This patient had a lithium blood level of 1.51 mmol/L on the subsequent day.
[c] Preterm birth.
[d] Lithium carbonate equivalent of 2256 mg lithium citrate (Litarex©).
[e] Non-steroidal anti-inflammatory drug use can decrease renal function (indication was pain relief after caesarean section).
[f] Lithium treatment initiated during pregnancy.
[g] This patient also had an elevated lithium blood level (1.24 mmol/L) 35 days postpartum while treated for the same relapse episode.
[h] Higher target blood level because of hospital admission for severe relapse episode.

In the majority of women (n=7/8), the supratherapeutic lithium blood levels occurred during the week preceding (n=2) or following (n=5) delivery. Notably, four of these seven women had pre-eclampsia and decreased renal function (patient 1, 2, 3 and 7), one was using non-steroidal anti-inflammatory medication (patient 4), another was prescribed a dose with the documented intention to achieve a therapeutic blood level for acute treatment (patient 5)

and another had evidence of insufficient anticipation of pregnancy-induced changes in GFR (patient 6). With regard to partient 6, the difficulty in interpreting blood level fluctuations might have been further exacerbated by the de novo initiation of lithium treatment during pregnancy. Two women (patient 5 and 8) were found to have supratherapeutic blood measurements outside the peripartum period. In both cases these women were being treated for acute relapse. Therefore, the physician prescribed a lithium dose with the documented intention of achieving a higher therapeutic blood level.

DISCUSSION

Main findings

In this study, we have quantified for the first time the longitudinal pattern of lithium blood levels during the peripartum period using 1101 lithium blood level measurements in 113 pregnancies of 85 women. Lithium blood levels decreased an average of 24% and 36% during the first and second trimesters, respectively. In the third trimester and postpartum period, lithium blood levels gradually returned to the preconception level. Interestingly, we did not observe a shift towards higher lithium and creatinine blood levels immediately following delivery.

Comparison of our findings with existing guidelines

During pregnancy, dynamic changes in GFR necessitate careful monitoring of lithium blood levels, as highlighted in several prominent international guidelines (including ones from the British Association for Psychopharmacology (BAP) (14), American Psychiatric Association (APA) (5), Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders (CANMAT/ISBD) (15) and Royal Australian and New Zealand College of Psychiatrists (RANCP) (4)). Although these guidelines emphasize the importance of close monitoring, they lack specific recommendations regarding the frequency of monitoring and the methodology by which dosing should be adjusted, because of the previously limited available data. The UK National Institute for Health and Care Excellence (NICE) (16) and the Netherlands Association for Psychiatry (NVVP) (17) guidelines currently recommend monthly monitoring during the initial 7-8 months of pregnancy. Notably however, our results suggest that more frequent monitoring could be considered because of declining blood levels. We found that most women used multiple daily dosing in pregnancy; the rationale for this strategy is to minimize peak lithium levels (10). Given the increased risk of non-adherence with multiple daily dosing, we recommend twice-daily dosing rather than more frequent administration (18). As expected, lithium and creatinine blood levels showed a highly similar longitudinal pattern throughout the study period. Therefore, the simultaneous evaluation of lithium and creatinine blood levels during pregnancy can be helpful to distinguish between lithium blood level

alterations because of fluctuations in renal function versus other factors such as non-adherence.

In line with the current NICE (16) and NVVP (17) guidelines, we recommend weekly monitoring beginning in the thirty-fourth week of pregnancy until delivery. For the majority of women in our study, it was necessary to decrease the prescribed lithium dose in the final months preceding delivery. Especially in those patients with a relatively large decrease in lithium blood levels during the first half of pregnancy, a strong rebound effect in the third trimester should be expected. In these cases, in particular, close monitoring of lithium blood levels during the final phase of the third trimester is clearly warranted. Preconception blood levels and corresponding preconception doses can be used as personalized reference values. Particular attention is required for women presenting with symptoms of preterm birth, pre-eclampsia or other illnesses that can affect renal function (7, 9, 19).

Several guidelines suggest to decreasing (4, 5, 14) or even discontinuing (16, 17) lithium prophylaxis when a woman exhibits the first signs of labor, because of the association between elevated maternal lithium blood levels and neonatal complications (9). This strategy will indeed minimize lithium levels in the newborn, but should also be weighed against the risk of maternal relapse during a period of exceptionally high risk (11). Accordingly, we share the opinion of Deligiannidis and colleagues in recommending careful lithium blood level monitoring instead of discontinuation in all cases (7). Finally, medications (such as non-steroidal anti-inflammatory drugs) that are known to increase lithium blood levels should be avoided (7).

We recommend relapse prevention prophylaxis in women with bipolar disorder with a higher lithium target level (for example ≥0.8 mmol/L) during the first month postpartum. In our recent meta-analysis (n=5105 pregnancies), 37% (95% CI 29-45%) of women with a history of bipolar disorder experienced a postpartum relapse (11). Given this very high risk of relapse, we hold the view that the benefits of higher lithium target blood levels during the 1-month period following delivery outweighs the potential risks. In our study we observed that normalization of renal function can take up to a few weeks after delivery as both mean lithium and creatinine blood levels were higher in the postpartum period than in the preconception period (+9% and +7% respectively). Therefore, we recommend frequent monitoring (twice weekly) of lithium blood levels for the first 2 weeks postpartum.

Limitations and directions for future research

Our study has a number of limitations. The observational study design might have introduced information bias. Most women were treated in an out-patient setting. As a result, it is uncertain that a 12-hour interval between dose intake and blood level measurement was always strictly maintained. This effect might have caused higher variability of measured blood levels. Furthermore, some degree of non-adherence might have occurred without our knowledge, particularly during delivery and among women using multiple daily dosing. Finally, preconception blood level measurements were unavailable for most women. Besides

the potential risk of neonatal complications, an important concern among clinicians is the potential for lithium-induced teratogenicity. Several older studies have reported that lithium exposure during the first trimester increased the risk of Ebstein's anomaly (20, 21). In contrast, a recent meta-analysis found no increase in the odds of any congenital malformations, including Ebstein's anomaly (22). However, the authors of the meta-analysis also concluded that an accurate estimate of the risk of teratogenicity because of lithium exposure still remains uncertain because of the potential that many of the included studies were inadequately powered to detect such rare events (22). Clearly, there is an urgent need for larger studies regarding the potential adverse effects of lithium during pregnancy as well as acute and long-term outcomes for children with in utero lithium exposure. These studies should include women with untreated bipolar disorder as a control group, because bipolar disorder itself seems to be associated with adverse pregnancy outcomes (23).

Recommendations

Women of childbearing age requiring mood stabilization should be given the opportunity to weigh the risks and benefits of lithium treatment during pregnancy and the postpartum period and to develop an individualized treatment plan together with their healthcare providers in a specialized centre (24-27). Women with bipolar disorder are at very high risk for postpartum relapse without medication during pregnancy (66%, 95% CI 57–75), and for some women the benefits of lithium therapy may outweigh the potential risks (11, 28). However, for those women that are clinically stable without mood stabilization for an extended period prior to pregnancy, initiation of lithium prophylaxis immediately postpartum is probably sufficient (11, 29). In this study, we evaluated the pharmacokinetics of lithium during pregnancy and in the period closely surrounding delivery. We confirmed that lithium dosing is challenging in this period and we have therefore summarized suggestions for dosing strategies:

Pregnancy

1) Monitor lithium blood levels frequently (for example once every 3 weeks) until 34 weeks of pregnancy, and then at least once weekly until delivery.
2) Before 17 weeks of pregnancy, anticipate progressively decreasing lithium levels. Afterwards, expect lithium levels to begin increasing.
3) Lithium blood levels should be maintained using a therapeutic blood level as low as possible and based on the personal history of the patient. It is therefore important to obtain preconception (reference) lithium and creatinine blood levels, and the corresponding lithium doses.
4) Consider twice-daily lithium dosing to minimize peak lithium blood levels.
5) Consider regular creatinine blood level monitoring. A significant decrease in creatinine

levels during the first or second trimester suggests a clinically-meaningful pregnancy-related increase in renal function.

6) Increase the frequency of lithium and creatinine blood level monitoring for women exhibiting signs of preterm birth, pre-eclampsia, dehydration or other illnesses that can affect renal function.

Delivery/postpartum

1) Obtain lithium blood levels after delivery and twice weekly during the first 2 postpartum weeks.
2) Consider increasing the target therapeutic lithium blood level immediately after delivery and during the first month postpartum to optimize relapse prevention (for example ≥0.8 mmol/L).
3) Be aware of pharmacokinetic interactions with other medications such as non-steroidal anti-inflammatories.

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DATA SUPPLEMENT

FIGURE 1. Observed lithium blood levels in the perinatal period

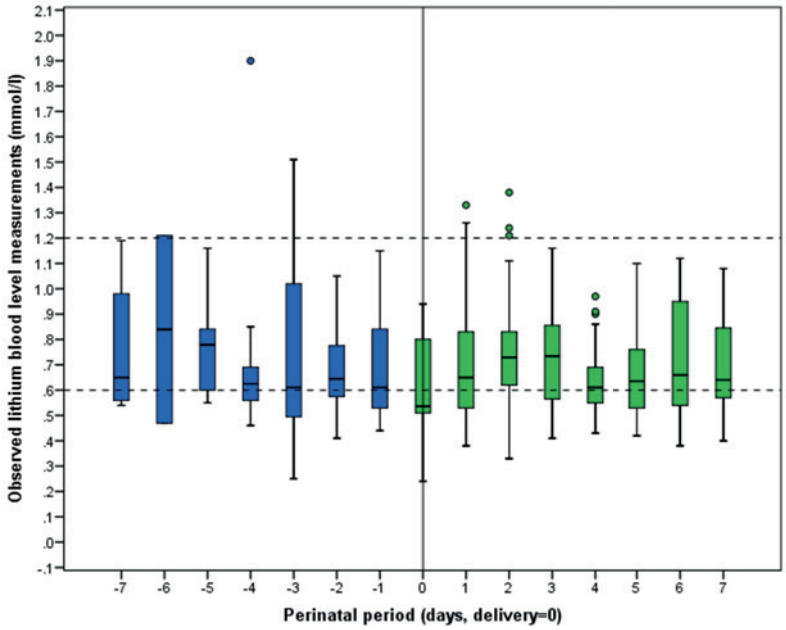


FIGURE 2. Creatinine blood levels during the peripartum period

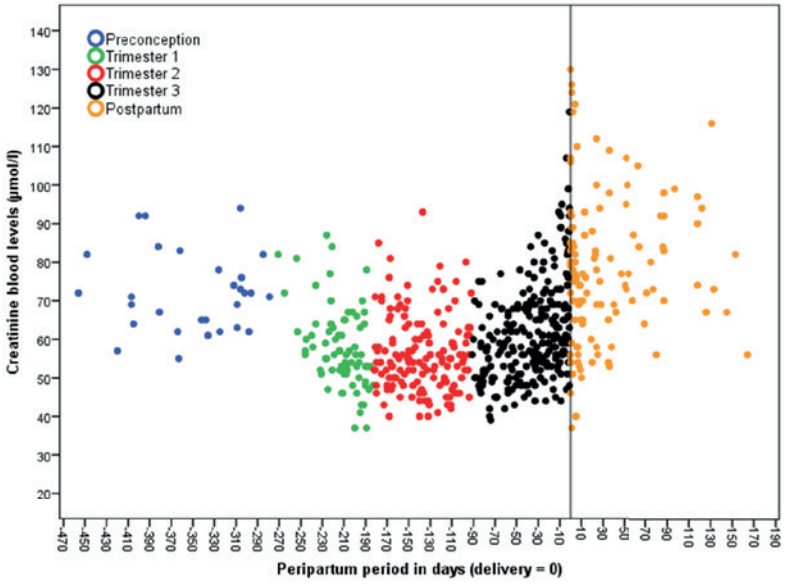
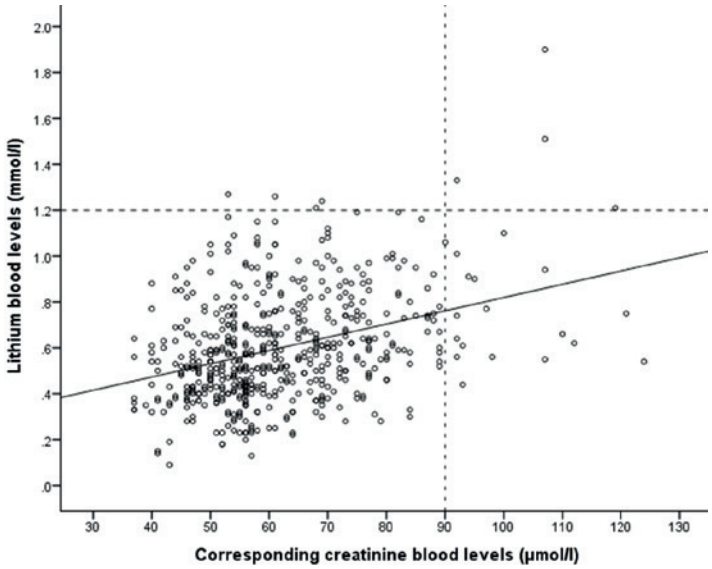


FIGURE 3. Correlation between lithium and corresponding creatinine blood levels[a]



[a]Dotted lines indicate upper thresholds for lithium and creatinine blood levels

Chapter 8

Risk of postpartum episodes in women with bipolar disorder after lamotrigine or lithium use during pregnancy: a population-based cohort study

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ABSTRACT

Background: Women with bipolar disorder are at high risk for relapse/recurrence postpartum. Among all mood stabilizers, lithium has the largest evidence base for efficacy in the peripartum period, but lamotrigine is increasingly prescribed for bipolar spectrum disorders during pregnancy. The aim of this study was to investigate whether lamotrigine use during pregnancy is as effective as lithium in the prevention of severe episodes postpartum.

Methods: Danish National registries were used to identify pregnancies of women with a diagnosis of bipolar spectrum disorders at the time of conception who used lamotrigine or lithium during pregnancy. We compared the risk of inpatient psychiatric admission within three months postpartum between women who used lamotrigine (N=55) versus lithium (N=59) during pregnancy. A logistic regression model was used to calculate crude and adjusted odds ratios.

Results: We did not find a significant difference in the risk of postpartum psychiatric admission between women who used lamotrigine versus lithium during pregnancy (7.3% versus 15.3% respectively, adjusted OR 0.83; 95% CI 0.22–3.14). We adjusted for year of delivery, parity, previous admissions and antidepressant/benzodiazepine use during pregnancy. Other variables did not differ substantially between groups.

Limitations: We used an observational design and therefore patients were not randomized to lamotrigine or lithium. The study has a small sample size.

Conclusions: Lamotrigine was not inferior to lithium in the prevention of severe postpartum episodes. Our findings suggest lamotrigine could be a reasonable alternative treatment option for bipolar disorder during pregnancy in patients with vulnerability for depression and may prevent severe episodes postpartum.

INTRODUCTION

Guiding women with bipolar disorder through pregnancy and the postpartum period is a challenge for psychiatrists and obstetricians, especially because these women are at very high risk for relapse and recurrence postpartum (37%, 95% confidence interval 29% - 45%) (1). Treatment with a mood stabilizer increases the likelihood of maintaining mood stability during pregnancy and preventing postpartum episodes (2, 3). However, the benefits of medication use during pregnancy need to be carefully weighed against the risks to the fetus. Lithium is the most effective known mood stabilizer and therefore remains the gold standard for the treatment of bipolar disorder (4). However, data on lithium teratogenicity have been inconclusive, thereby complicating decision-making for women with bipolar disorder during pregnancy. In a recent meta-analysis, the association between lithium use during pregnancy and fetal malformations was non-significant, but the results were mainly based on small case-control studies (total n=264, range n=13-89 cases) (5). Over the past couple of decades, lamotrigine has increasingly been used during pregnancy as an alternative treatment option to lithium, due to its more favorable reproductive profile (6, 7). Large register-based studies including women with epilepsy (n=1019 and n=1280) reported finding no evidence for an increased risk of fetal malformations associated with in utero lamotrigine exposure (8, 9). However, the efficacy of lamotrigine during the peripartum period is largely unknown (3). Therefore, the aim of this study was to compare mood stabilization during pregnancy with lamotrigine versus lithium in the prevention of severe postpartum episodes.

METHODS

We conducted a population-based cohort study using Danish National registers. This was possible as all live births and residents in Demark are assigned an unique personal identification number and registered in the Danish Civil Registration System, which allows linkage of data at the individual level within and between registers (10). Women with a history of bipolar spectrum disorder (including bipolar disorder I, II and not otherwise specified classifications) were identified in the Danish Psychiatric Central Research Register (DPCRR) (11) with International Classification of Diseases (ICD) codes 296.xx, 298.19 (ICD-8, 1969 - 1993) and F30-F31 (ICD-10, 1994 – present). Afterwards, pregnancies of women with at least one live born child in the period of 1996–2012, occurring after the diagnosis of bipolar disorder, were identified by linking the DPCRR to the Danish Medical Birth Registry (12) Our exposure of interest was lamotrigine or lithium use during pregnancy. The information on the dispensation of prescriptions was extracted from the Danish National Prescription Registry (13). We defined medication use during pregnancy as at least two prescriptions dispended between conception and delivery, with at least one prescription after the first trimester. Pregnancies in which women were prescribed more than one of the following mood stabilizers were not eligible for inclusion: lithium, lamotrigine, carbamazepine, oxcarbazepine, valproic acid, topiramate, or gabapentin.

The primary outcome of the study was severe psychiatric relapse or recurrence, defined as any psychiatric admission for mental disorders (ICD-10 codes F00–F99) within three months postpartum. Unfortunately, we were not able to examine less severe psychiatric relapse/recurrence (operationally defined as episodes not resulting in an inpatient psychiatric admission). The Danish Registers do not allow for access to individual patient records, and therefore symptom-based information at outpatient visits during pregnancy and in the postpartum period was not available. We analyzed the data using Stata 13.1 (StataCorp, College Station, TX, USA). To compare the postpartum relapse/recurrence risk between women with lamotrigine or lithium use during pregnancy, a logistic regression model was used to calculate crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Robust standard errors were used to account for multiple pregnancies in the same woman during the study period. We divided the total dose of all prescriptions during pregnancy by gestational age (in days), in order to calculate the average prescribed dose of lamotrigine and lithium during pregnancy.

Antipsychotic co-medication during pregnancy may prevent relapse/recurrence. Therefore, we performed a sensitivity analysis by repeating the analyses after exclusion of women with prescriptions of concurrent antipsychotic medication during pregnancy. The study was approved by the Danish Data Protection Agency. No informed consent is required for a register-based study with public health interest based on encrypted data in Denmark.

RESULTS

We identified N=891 women with bipolar spectrum disorders and N=1201 corresponding pregnancies. In the majority of pregnancies (N=1066) women received prescriptions of antidepressants, antipsychotics, other mood stabilizers, a combination of these prescriptions or no medication. In N=135 pregnancies, women received lamotrigine or lithium prescriptions. We excluded N=21 pregnancies because prescriptions were restricted to the first trimester (lamotrigine N=10, lithium N=0) or because women were prescribed more than one mood stabilizer (N=11). In total we included N=114 pregnancies with either lamotrigine (N=55) or lithium (N=59) use in our study. During pregnancy, the estimated average daily lamotrigine dose was 206 mg (SD 145); the average daily lithium dose was 721 mg (SD 330).

A detailed overview of relevant patient characteristics of both groups is presented in Table 1. We found a sharp increase of lamotrigine use during pregnancy across our study period (1996-2007 N=11 pregnancies; 2008-2012 N=44 pregnancies).

Within the two-year period before conception, the proportion of outpatient visits was higher in the lamotrigine group compared to the lithium group (81.8% versus 49.2%); similarly the proportion of psychiatric admissions was higher in the lamotrigine group (43.6% versus 28.8%). Finally, in the lamotrigine group, women more frequently had depressive episodes (30.9% versus 8.5%).

TABLE 1. Characteristics of women with either lamotrigine or lithium use during pregnancy[a,b]

	Lamotrigine (N=55)	Lithium (N=59)
Postpartum psychiatric admission (<3 months)	4 (7.3)	9 (15.3)
Demographics		
Age at delivery (years), mean ± SD	31.8 ± 4.7	34.1 ± 4.5
Year of delivery[c]		
1996 – 2007	11 (20.0)	34 (57.6)
2008 – 2012	44 (80.0)	25 (42.4)
Married or cohabiting	39 (70.9)	46 (78.0)
Income above the lowest quartile	38 (69.1)	33 (55.9)
Preconception		
Age at bipolar disorder diagnosis (years), mean ± SD	26.8 ± 4.1	25.2 ± 4.6
First lithium/lamotrigine prescription <1 year before conception	8 (14.5)	7 (11.9)
Other mood stabilizer prescriptions <1 year before conception	<4 (<7.3)	0
Psychiatric admissions < 2 years before conception[c]	24 (43.6)	17 (28.8)
Psychiatric outpatient visit(s) < 2 years before conception	45 (81.8)	29 (49.2)
Depressive episodes < 2 years before conception	17 (30.9)	5 (8.5)
(Hypo)manic episodes < 2 years before conception	8 (14.5)	12 (20.3)
Pregnancy		
Antipsychotic co-medication	18 (32.7)	19 (32.2)
Antidepressant co-medication[c]	34 (61.8)	20 (33.9)
Benzodiazepine co-medication[c]	8 (14.5)	17 (28.8)
Psychiatric admissions(s)	<4 (<7.3)	4 (6.8)
Outpatient visit(s)	23 (41.8)	23 (39.0)
Primiparity[c]	30 (54.5)	27 (45.8)
Caesarean section	12 (21.8)	14 (23.7)
Preterm birth	8 (14.5)	10 (16.9)
Obstetric complications[d]	17 (30.9)	14 (23.7)
Postpartum[e]		
Continuation lamotrigine / lithium postpartum	45 (81.8)	53 (89.8)
Antipsychotic co-medication	19 (34.5)	35 (59.3)
Antidepressant co-medication	40 (72.7)	30 (50.8)
Benzodiazepine co-medication	17 (30.9)	32 (54.2)

[a] Medication use during pregnancy was defined as the dispensation of two prescriptions between conception and delivery, with at least one prescription after the first trimester.
[b] Figures are numbers (%) unless stated otherwise.
[c] Variables included in a multivariate logistic regression model: year of delivery, psychiatric admission <2 years prior to conception, antidepressant and benzodiazepine co-medication during pregnancy and primiparity.
[d] Pre-eclampsia, fetal stress, gestational diabetes, gestational hypertension, nausea/vomiting or postpartum hemorrhage.
[e] These proportions are likely to be an underestimation, because we could not include prescriptions written during inpatient hospitalization.

During pregnancy, combination therapy with antidepressants was used more often in the lamotrigine group (61.8% versus 33.9%); whereas benzodiazepines were prescribed more often in the lithium group (28.8% versus 14.5%). Other variables relevant to our analyses included age, marital status, income, parity, obstetric complications, age of disease onset, use of antipsychotic co-medication, and admissions/outpatient visits during pregnancy, but none of these differed substantially between the two groups.

We found an overall risk for postpartum psychiatric admission of 11.4% (N=13/114). There was no significant difference in risk of postpartum psychiatric admission between women with lamotrigine use during pregnancy (N=4, 7.3%) compared to those with lithium use (N=9, 15.3%). We further adjusted for variables that were unequally distributed between groups (year of delivery, psychiatric admission <2 years prior to conception, antidepressant and benzodiazepine co-medication use during pregnancy) and for primiparity because this variable is strongly related to relapse/recurrence risk. After these adjustments, lamotrigine use during pregnancy was not associated with an increased risk of postpartum psychiatric admission compared to lithium use (adjusted OR 0.83; 95% CI 0.22 – 3.14). The polarity of the N=13 postpartum episodes was as follows: mania or psychosis (N=7, 53.8%), depression or other diagnosis (N=6, 46.2%). We observed no significant difference in the polarity of postpartum episodes between the lamotrigine and lithium group (Fisher exact test, p=0.20).

A sensitivity analysis among women without concurrent antipsychotic medication during pregnancy showed no significant difference between the lamotrigine and lithium group in the risk of a subsequent postpartum psychiatric admission (adjusted OR 0.55; 95% CI 0.12–2.51).

DISCUSSION

In this population-based study, we found similar postpartum inpatient admission risks after lamotrigine and lithium use during pregnancy. If replicated, this finding is of clinical importance, since lamotrigine is considered to be a more favorable option than lithium with regard to the risk of adverse neonatal outcomes (14). In line with a previous study from the United Kingdom (7), we found an increase in lamotrigine use over the last decades in Denmark. Previous studies demonstrated that lamotrigine is particularly effective in bipolar disorder for the prevention of depressive episodes (15). Indeed, in our study women using lamotrigine were more likely to have a history of depressive episodes. Accordingly, two-thirds of the women in the lamotrigine group used antidepressant co-medication. Therefore, in an effort to reliably compare outcomes of women using lamotrigine or lithium, we adjusted for several clinical variables, including the use of antidepressant medication.

Overall, our study sample is likely to reflect women with a more severe disease course, as exemplified by the high proportion with psychiatric admissions in the two years prior to

conception and the high rate of antipsychotic and antidepressant co-medication. Moreover, the vast majority of women received their initial lamotrigine or lithium prescription more than one year before conception, indicating long-term use of maintenance treatment.

Our study has several limitations. First, our study has a small sample size. Consequently, we may have insufficient statistical power to detect significant difference between the two groups. Second, our study could suffer from confounding by indication because lithium was predominantly prescribed in patients with a history of manic episodes, while lamotrigine was primarily prescribed to women with a particular vulnerability for depressive episodes. Notably, this is consistent with the current bipolar disorder treatment guidelines. Third, we had an insufficient number of cases to conduct any stratified analyses for postpartum medication use. Fourth, our study was not designed to detect less severe postpartum episodes, and therefore our results cannot be generalized to such episodes. Lastly, the perinatal effectiveness of lamotrigine is largely unknown for patients with predominantly manic episodes in history.

Clinical considerations

In women with bipolar disorder, discontinuation of mood stabilizing medication has been associated with an increased risk of relapse/recurrence during pregnancy (2, 3). Accordingly, the benefits of continuing medication during pregnancy appear to outweigh the potential risks, especially in patients with a recent history of severe mood episodes. If patients and clinicians decide to continue medication, dosing can be challenging because pregnancy-related physiological changes induce substantial blood level fluctuations (16, 17). Both lithium and lamotrigine blood levels decrease across pregnancy, with a resultant increased risk of symptom worsening. To maintain mood stability, the doses of both lithium and lamotrigine often need to be increased to adjust for declining blood concentrations. Accordingly, frequent blood level monitoring is recommended during pregnancy for both lithium and lamotrigine (e.g., once every three to four weeks) (16, 17).

For lithium, blood levels usually start to increase during the third trimester and therefore monitoring should be performed once a week beginning in week 34 (16). Postpartum, clinicians could aim at higher lithium blood levels (e.g. 0.8 mmol/L) because of the high relapse/recurrence risk during this period, and monitoring twice a week is advised (16). Lamotrigine blood levels rapidly normalize to pre-pregnancy concentrations during the early postpartum period. If the dose is titrated during pregnancy, it must be tapered immediately postpartum to the therapeutic preconception dose to prevent toxicity. During the postpartum period, lamotrigine plasma concentrations should be monitored weekly for patients with dose increases during pregnancy (17).

With regard to breastfeeding, lamotrigine may be a more favorable option than other mood stabilizers according to a recent review (18). However, close monitoring of infants exposed to lamotrigine via breastmilk for signs of toxicity (e.g. apnea and rash) is recommended. With the

exception of one case of apnea, no adverse reactions have been reported in infants exposed to lamotrigine through breastmilk (18).

Although the literature is inconsistent regarding whether lithium is contraindicated during breastfeeding, case series from breastfeeding mothers with lithium do not report toxicity or developmental delays. Although no serious adverse effects have been observed, close observation and monitoring of thyroid and renal function is recommended (18).

Conclusions

Management of bipolar disorder during and after pregnancy is challenging, especially because the postpartum period is associated with the highest lifetime risk of hospitalization for women with bipolar disorder (19). In this study, lamotrigine was not inferior to lithium in the prevention of severe postpartum episodes. Lamotrigine could be a reasonable alternative treatment option for bipolar disorder during pregnancy in patients with vulnerability for depression and may prevent severe episodes postpartum. Notably, our results will require replication before reaching definitive conclusions.

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Chapter 9

General discussion

MAIN CONCLUSIONS OF THIS THESIS

Bipolar disorder during pregnancy and the postpartum period

- Women with a history of bipolar disorder are at very high risk of recurrence during the postpartum period (chapter 2).
- Lithium use during pregnancy and the postpartum period is associated with a low recurrence risk (chapter 7 and 8).
- Lamotrigine use during pregnancy and the postpartum period may be a reasonable alternative to lithium for women with vulnerability for depressive episodes (chapter 8).
- There is substantial fluctuation in lithium blood levels during the peripartum period because of physiological adaptions of renal function. Sub-therapeutic lithium blood levels may increase the risk of recurrence, while toxic lithium blood levels increase the risk of (neonatal) adverse effects. Accordingly, it is important to perform regular monitoring of lithium blood levels and renal function (chapter 7).
- The benefits of continuing moodstabilizing medication both during pregnancy and the postpartum period may outweigh the potential risks in women with bipolar disorder that suffered of recent and severe mood episodes (chapter 2, 3 and 8).

Postpartum psychosis: prevention, course and phenomenology

- Women with a history of postpartum psychosis are at higher risk of severe postpartum episodes than women with bipolar disorder (chapter 2)
- In case of a subsequent pregnancy, the initiation of lithium prophylaxis immediately postpartum is sufficient to prevent postpartum recurrence. Consequently, in utero medication exposure to the fetus can be avoided (chapter 2 and 3).
- Postpartum psychosis is an affective disorder. Besides psychotic symptomatology, its phenomenology is characterized by the presence of depressive and/or manic symptomatology. In some cases, women also present with atypical symptoms such as disturbance of consciousness, disorientation and depersonalization (chapter 4).
- Even though there is a close link between postpartum psychosis and bipolar disorder, it is of clinical importance to maintain the diagnostic concept of postpartum psychosis (chapter 1, 2 and 3).

First-onset postpartum depression and auto-immune dysfunction

- A positive TPO-ab status during early pregnancy is associated with an increased risk of self-reported first-onset postpartum depression. This finding suggests that auto-immune dysregulation may be an underlying biological mechanism that is related to the etiology of first-onset postpartum depression (chapter 5).
- Evaluation of thyroid function is essential in women with first-onset postpartum depression (chapter 5).

EFFICACY OF MAINTENANCE TREATMENT DURING THE PERIPARTUM PERIOD IN WOMEN WITH BIPOLAR DISORDER

Previous literature

In this thesis we demonstrated that the postpartum period is a major trigger of recurrence among women with bipolar disorder. The efficacy of moodstabilizing medication during this vulnerable period is poorly studied. In our systematic review and meta-analysis, we could not identify any randomized controlled trials. This is probably a result of concerns among researchers regarding ethical aspects and feasibility. Regarding observational research, two studies (n=28; n=89) (1, 2) specifically assessed the efficacy of lithium during pregnancy. One additional study compared the risk of recurrence between n=10 patients that continued lamotrigine versus n=5 patients that discontinued (n=5) lamotrigine during pregnancy (3). The results showed that discontinuation of both lithium and lamotrigine during pregnancy was associated with an increased risk of recurrence. Six small studies (4-10) (range n=11-41) assessed the efficacy of maintenance treatment during the postpartum period (lithium n=4, olanzapine n=1, valproate n=1). Women that used lithium and olanzapine during the postpartum had a lower risk for recurrence than medication-free women. Immediate initiation of valproate during the postpartum period was not effective in the prevention of postpartum episodes (control group medication-free women).

Previous studies regarding the efficacy of maintenance treatment during the peripartum period have several important limitations. First, all studies have a (very) small sample size. Second, in none of the studies estimates were adjusted for potential confounders (this is particularly concerning because of the high risk of confounding by indication). Third, none of the studies compared the efficacy of different moodstabilizers. Notably, no studies focused on the antenatal efficacy of second generation antipsychotics, while this group of medication is increasingly used during pregnancy (11).

This thesis

The results of this thesis increase the knowledge about the efficacy of mood-stabilizing medication during the peripartum period in women with bipolar disorder. First, the results of our meta-analysis showed that women who used maintenance treatment during pregnancy and the postpartum period were at much lower risk for recurrence than medication-free women. Notably, this pooled analysis included only n=66 women that used maintenance treatment postpartum (mostly lithium). Second, we demonstrated that maintenance treatment with lithium during pregnancy and the postpartum period was associated with a low recurrence risk in both a Dutch clinical cohort (n=89 women) and a Danish population based cohort (n=59 women). Third, we performed the first study comparing the efficacy of two different moodstabilizers (lithium versus lamotrigine) and adjusted our analyses for several potential confounders. We

observed low and similar postpartum inpatient admission risks after lamotrigine and lithium use during pregnancy. This is of clinical importance, because lamotrigine might be a safer option than lithium with regard to the risk of adverse neonatal outcomes.

The studies in this thesis have several limitations. In our Danish population based cohort study, we compared the risk of recurrence postpartum between women that used lithium and lamotrigine during pregnancy. Although we adjusted for several potential confounders, our study may still be at risk of confounding by indication because detailed clinical information (e.g. disease severity) is not available in the Danish registers. Second, because of the limited sample size and small number of events (postpartum episodes) our study may have been underpowered for appropriate adjustment for confounders and to detect a potential difference between the two groups. Finally, we were not able to perform stratified analyses for postpartum medication use. Accordingly, it is unclear to what extend potential changes in postpartum medication regimes (e.g. sub-therapeutic blood levels, dose adjustments, initiation of co-medication) have influenced the observed recurrence rates.

In our meta-analysis, we observed substantial heterogeneity across studies regarding the risk of recurrence. Methodological differences in study design (e.g. clinical cohort versus population based studies) and the severity of recurrence were important sources of heterogeneity. However, data from included studies was insufficient to take into account clinical predictors of recurrence that have been previously described in the literature, such as psychiatric history (e.g. number of previous (peripartum) mood episodes, recent admissions), psychosocial factors, parity, recurrence during pregnancy, family history, obstetric complications and co-medication (6, 12-19). Accordingly, the recurrence risk estimates of our meta-analysis are probably not accurate for individual patients.

RISKS OF MAINTENANCE TREATMENT DURING PREGNANCY IN WOMEN WITH BIPOLAR DISORDER

In utero exposure to (psychiatric) medication can potentially result in an increased risk of neonatal complications (20). Examples include spontaneous abortion, congenital malformations, preterm birth, low birth weight, persistent pulmonary hypertension of the newborn (PPHN) syndrome, poor neonatal adaptation syndrome (PNAS), and an increased risk of autism or other negative long-term effects on neuro-cognitive development (20). Accordingly, cautiousness is required when prescribing medication to women during their childbearing ages/pregnancy (20).

A careful evaluation of potential teratogenic effects of medication is particularly relevant for women with bipolar disorder because the onset of the illness is typically during the childbearing ages, maintenance treatment is often prescribed for a long period and there is an increased risk of unplanned pregnancies (21, 22). In the next paragraphs, we will briefly summarize the current evidence regarding potential risks of in utero exposure to medication that is commonly used as maintenance treatment for women with bipolar disorder.

Lithium

The evidence regarding the potential risks of lithium use are already subject of debate for several decades. The first study about the association between lithium use during pregnancy and neonatal malformations in humans was published in 1973 (23). In this retrospective study, data from "the register of lithium babies" (n=118) showed a high prevalence of congenital malformations (7.6%). In a subsequent study (published in 1975), including data from the same register (n=212), the authors observed an even higher risk of malformations (10.4%) and a specifically increased risk of cardiac malformations (24). Notably, the authors emphasized in the abstract of their publication that the data probably overestimates the risk of teratogenicity (high risk of selection bias) (23). Several subsequent cohort- and case control studies showed conflicting results. In a recent meta-analysis of case-control studies (2012), the association between lithium exposure during pregnancy and both the risk of overall malformations and Ebstein's anomaly was not significant (25). However, the authors stated that the risk the risk of teratogenicity is still uncertain because only a small number of events were included in the analyses (25). Recently, Patorno and colleagues (26) published the largest study to date about the association between lithium use during the first trimester of pregnancy and (cardiac) malformations. The study was conducted with non-private US health care insurance data (Medicaid) and included lithium exposed pregnancies (n=663), lamotrigine exposed pregnancies (n=1945; control group 1) and non-exposed pregnancies (n=1,322,955; control group 2). Lithium use was associated with an increased risk of both overall malformations (OR 1.85, 95% CI 1.23-2.78) and cardiac malformations (OR 2.25 95% CI 1.17-4.34) (reference=lamotrigine exposed pregnancies). The authors also observed a dose-response effect regarding the risk of cardiac malformations. Taken together, lithium is probably associated with an increased risk of (cardiac) malformations, but the magnitude is much lower than initially was reported (26).

Because of its small therapeutic window, lithium use during pregnancy can also potentially result in other neonatal complications. However, data about this topic is scarce. The results of a small cohort study (n=32) suggested that high lithium blood levels may increase the risk of several neonatal adverse events (lower APGAR-scores, longer hospital stays, low muscle tone) (27). In this thesis, we performed the first pharmacokinetic study that focused on the longitudinal course of lithium blood levels during the peripartum period. We found that pregnancy induces substantial fluctuation in lithium blood levels and that there is a particularly increased risk of high lithium blood levels during the last phase of the third trimester. Accordingly, the risk of neonatal adverse effects can be reduced with regular blood monitoring.

Anticonvulsants and second generation antipsychotics

The results of studies on teratogenic effects of in utero exposure to valproate are consistent: there is a ~10% risk of malformations (including neural tube defects, cranio-facial anomalies, cardiac defects) (20, 28, 29). In addition, studies reported an increased risk of PPHN

syndrome, delayed neuro-cognitive development and autism (20, 29-31). Therefore, use of valproate should be avoided during the childbearing ages. Use of carbamazepine is also associated with an increased risk of malformations (neural tube defects, cranio-facial anomalies and several other malformations) (20, 29, 32), but the risks are smaller than for valproate. According to a systematic review, the prevalence of major congenital malformations after use of carbamazepine (monotherapy) during the first trimester is 3.3% (95% CI 2.7-4.2) (32). In an additional case control-study regarding the risk for specific malformations, the authors only found a significantly increased risk for spina bifida (OR 2.6, 95% CI 1.2-5.3). Studies on potential negative neuro-cognitive development reported conflicting results (29).

Lamotrigine has a more favorable risk profile than other anticonvulsants (valproate and carbamazepine) (33). Several large register studies showed no increased risk of malformations after lamotrigine during pregnancy (34, 35). However, potential risks of neonatal and long-term developmental adverse effects are poorly studied (36, 37).

A recent very large study that included n=9,237 women that used atypical antipsychotics during the first trimester of pregnancy found no increased risk of congenital malformations after adjustment for a wide range of potential confounders. The analyses for individual agents showed that risperidone was associated with a slightly increased risk of overall malformations (OR 1.26, 95% CI 1.02-1.56) (38). The risk for other adverse effects need further investigation because some studies indicated that use of second generation antipsychotics may be associated with an increased risk of obstetric or neonatal complications such as prematurity, both low and high birth weight, gestational diabetes and PNAS (39, 40). Potential negative long term effects of in utero exposure to second generation antipsychotics are poorly studied (40).

CLINICAL RECOMMENDATIONS

Clinicians encounter a lot of uncertainty with regard to the treatment of women with bipolar disorder during the peripartum period. The efficacy of maintenance treatment during this vulnerable period is poorly studied. Data on the risks of in utero exposure to medication are often inconclusive or lacking, especially with regard to potential long-term adverse effects. Decision making is highly complex because the potential risks of maintenance treatment should be carefully weighed against a higher vulnerability for the onset of mood-episodes in medication-free women, with resultant illness-related risks for both the mother and her (unborn) child (39). In Table 1 we provide general clinical recommendations that may be helpful to guide women with bipolar spectrum disorder throughout the peripartum period (20, 41-43).

TABLE 1. General clinical recommendations

- Encourage shared-decision making.
- Use clinical information (e.g. current use of maintenance treatment, recent mood episodes) to estimate a patients' individual risk of (postpartum) recurrence.
- Carefully weigh both medication and illness related risks of maintenance treatment during pregnancy.
- In case women are not using maintenance treatment during pregnancy and there are no signs of recurrence, we recommend to initiate prophylaxis with moodstabilizing medication immediately after childbirth (e.g. lithium, ≥0.8 mmol/l).
- Be aware of pharmacokinetic alterations that occur because of pregnancy related physiological adaptations in renal and hepatic function.
- Do not prescribe valproate during pregnancy because of a highly increased risk of teratogenicity.
- Prescribe the lowest effective dose.
- Avoid polypharmacy.
- Draft an individualized peripartum plan, if possible before the onset of pregnancy.
- Work in a multidisciplinary setting, together with gynecologists and pediatricians.
- Ensure close monitoring during the first weeks postpartum period, be aware of potential signs of recurrence.

DIRECTIONS FOR FUTURE RESEARCH

The National Postpartum Psychosis Prevention study (NP3-study)

The NP3-study is part of the OPPER-study (Onderzoeksprogramma Postpartum Psychose, Erasmus MC Rotterdam) and was designed to further investigate the efficacy and potential (long term) neonatal/child adverse effects of maintenance treatment during the peripartum period in women with a history of bipolar disorder and/or postpartum psychosis. In this study, we prospectively assess the outcome of pregnancies of women at high risk of recurrence. The primary outcome of the NP3-study is recurrence during the postpartum period. We ask participants to complete digital questionnaires at 32 weeks gestation and at 1 week, 6 weeks and one year postpartum. We collect demographic information and use validated questionnaires to assess symptoms of anxiety, depression and/or (hypo)mania, social support and potential symptoms of physical distress (repeated measurements). 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). If necessary, information is verified during a telephone interview. If patients are included in Erasmus MC, we also collect blood cells and serum biomarkers during the third trimester. Finally, we will soon start with follow-up measures at 2 and 3.5 year postpartum. With face-to-face interviews

and questionnaires we will assess the development of the child and the disease course of the mother.

The design of the NP3-study was adapted to match with the design of the Holistic approach to Pregnancy and first Postpartum Year (HAPPY(-Follow)) study. The HAPPY-study is a population based prospective cohort study (n=2269 pregnant women) that was conducted by Prof. dr. V.J.M. Pop (Tilburg University) and will be used as a control group for several NP3-study objectives.

The prospective recruitment of patients for the NP3-study started in 2013 in Erasmus MC and at fifteen hospitals throughout the Netherlands, in collaboration with investigators of the SLEEPREGBD-study (A. Stevens, Prof. dr. R.W. Kupka and Prof. dr. A. Honig). The main aim of the SLEEPREGBD-study is to investigate whether sleep disturbance is a predictor of recurrence during the postpartum period in women with a history of bipolar disorder and/or postpartum psychosis.

To date, we were able to include approximately n=100 patients in the NP3-study, which is convincing giving the low prevalence of pregnant women with a history of bipolar disorder/ postpartum psychosis. Moreover, the NP3-study includes retrospective data of n=150 pregnancies (referrals to Erasmus MC and LUMC between 2003-2013). In the coming years, we will enlarge the NP3-study cohort. The data of the NP3-study will be used for the following topics/objectives:

Individualized postpartum recurrence risk prediction

An individual accurate postpartum recurrence risk estimate is essential to properly weigh the risk and benefits of maintenance treatment during the peripartum period. In our meta-analysis, we observed an one out of three recurrence risk during the postpartum period for women with a history of bipolar disorder or postpartum psychosis. However, as mentioned earlier, this estimate may not be accurate because clinical determinants will influence the risk of recurrence across patients. Accordingly, the data of the NP3-study will be used to identify potential determinants of recurrence (e.g. psychiatric family history, number of previous mood episodes), that can be used to determine the risk of recurrence for individual patients.

Efficacy of maintenance treatment during the peripartum period

Enlargement of the NP3-study cohort and international collaboration will enable us to (further) investigate the efficacy of maintenance treatment during pregnancy and the postpartum period. Specifically, it will be interesting to replicate the findings of our population based study on the efficacy of lamotrigine. In addition, we will compare the efficacy of lithium, lamotrigine and second-generation antipsychotics (quetiapine, olanzapine, risperidone). Detailed clinical data will be used to adjust for potential confounders such as disease severity and the occurrence of

previous mood-episodes during the postpartum period. In addition, it is important to differentiate between women with bipolar I and II disorder and to take into account co-medication. 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.

Risks of maintenance treatment during pregnancy

We will mainly focus on the potential risks of in utero exposure to lithium, because this is the most commonly used moodstabilizer among women that are included in the NP3-study. We are currently investigating whether lithium use during pregnancy is associated with a broad range of adverse effects including pregnancy complications, delivery outcomes, malformations, and neonatal admissions. For this project, we included n=115 children born to mothers with lithium use during pregnancy and a control group of n=88 children born to mothers with a bipolar spectrum disorder. Because of the low prevalence of several outcome measures, we are collaborating with other investigators in an international consortium: the data of the NP3-study will be analysed together with data from five other international study sites in a meta-analysis (aggregate level).

Child development after in utero exposure to maintenance treatment

The follow-up measurements at 2 and 3.5 year postpartum will be used to investigate potential negative long-term effects of in utero-exposure to maintenance treatment on child development. We will focus on language, cognitive and social-emotional development and 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 will be used as control groups.

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Summary

PART I. MOOD DISORDERS DURING THE POSTPARTUM PERIOD

Bipolar disorder and postpartum psychosis

Women with a history of bipolar disorder or postpartum psychosis are at high risk for postpartum recurrence. However, there is high variability in reported recurrence rates across studies. A weighted recurrence risk estimation is essential in order to carefully weigh the risks and benefits of medication use during pregnancy and the postpartum period. Therefore, the aim of the systematic review and meta-analysis that is described in **chapter 2** was to estimate the risk of postpartum recurrence in women with a history of bipolar disorder or postpartum psychosis. We conducted a systematic literature search in all public medical electronic databases and included 37 articles describing the outcome of 5,700 deliveries in the quantitative analyses. We observed an one out of three overall recurrence risk in the combined analysis. The distinction between women with bipolar disorder and those with a history of postpartum psychosis is of substantial clinical relevance because patients with a history of postpartum psychosis were at higher risk for severe episodes postpartum than patients with bipolar disorder.

Studies that assessed the efficacy of moodstabilizing medication during the peripartum period were scarce. Even though we were able to conduct a small sub-analysis that indicated that prophylactic medication (mostly lithium) use during pregnancy was highly effective in the prevention of postpartum recurrence. However, as mentioned earlier, the benefits of prophylactic pharmacotherapy during pregnancy should be weighed against the potential adverse effects of in utero medication exposure. In general, the benefits of continuing moodstabilizing medication during pregnancy appear to outweigh the potential risks, especially in patients with a recent history of severe mood episodes. Polypharmacy should always be avoided, and clinicians should aim at the lowest effective dose.

The aim of **chapter 3** was to discuss diagnostic considerations, treatment and the prevention of postpartum psychosis, and to give clinical recommendations. Postpartum psychosis is a severe psychiatric disease which occurs in the early postpartum period after approximately 1 per 1000 deliveries. Postpartum psychosis is in general considered as a mood disorder, because affective symptoms are a hallmark of the disorder, but is not classified as a separate disorder in the *Diagnostic and Statistical Manual of Mental Disorders (DSM–5)*. The main reason for the absence of a separate disease status is the close link between postpartum psychosis and bipolar disorder. In a substantial proportion of women, first-onset postpartum psychosis is the incipient episode of a bipolar disorder disease course. However, it is of major clinical importance to maintain the diagnostic concept of postpartum psychosis because a substantial group of women with a history of postpartum psychosis is only vulnerable for illness episodes during the postpartum period. Those women have a favorable prognosis and therefore there is no indication for long-term maintenance treatment.

If the diagnosis postpartum psychosis is suspected, an inpatient psychiatric admission (preferably at a mother-baby unit) is necessary to ensure the safety of mother and baby and to exclude known organic causes (e.g. thyroid disorders, encephalitis) of postpartum psychosis. A combined treatment with an antipsychotic and lithium is highly effective. With adequate treatment, almost all patients achieve complete remission. After a subsequent pregnancy, Initiation of prophylaxis immediately postpartum is highly effective for the prevention of postpartum recurrence.

In **chapter 4**, we describe the outcome of a study on the phenotypical characteristics of postpartum psychosis. Besides the presence of psychotic symptomatology, most women also suffer of a broad spectrum of other symptoms. The aim of this study was to describe postpartum psychosis symptomatology, and to identify subgroups of patients based on symptom profiles. Participants in this study were obtained from the OPPER-cohort. We included n=130 women with postpartum psychosis that were admitted to the psychiatric mother-baby inpatient unit of Erasmus MC (2005-2015). We prospectively assessed a wide range of symptoms with several repeated (self-rating) questionnaire assessments and by using information from medical records and a diagnostic interview. The most prevalent symptoms were irritability (73%), abnormal thought content (72%), and anxiety (71%). Using a person-centered analytic approach (latent class analysis), we identified three symptom profiles, a depressive (41%), manic (34%), or atypical (25%) profile, respectively. The depressive profile was characterized by depressive and anxiety symptoms, the manic profile by manic symptoms and agitation and the atypical profile by disturbance of consciousness, disorientation, depersonalization and derealisation. Based on or findings, we concluded that atypical symptoms were less prevalent than previously suggested in the literature. Instead, the depressive profile was the most prevalent, but the depressive profile can easily remain undetected, which could lead to treatment delay and risk of suicide/infanticide.

Thyroid auto-immunity and postpartum depression

During the postpartum period, women are at risk for new onset of both auto-immune thyroid disorders and depression. The presence of thyroid peroxidase antibodies (TPO-ab) during early gestation is predictive for postpartum auto-immune thyroid dysfunction. Interestingly, TPO has also been named as a predictor for postpartum depression. However, previous studies that investigated the association between a positive TPO-ab status during early gestation and postpartum depression are likely to be confounded by the presence of antenatal depression. Therefore, the aim of the study that is described in **chapter 5** was to investigate the association between TPO-ab status during early gestation and first-onset postpartum depression. The study population was recruited from a large prospective cohort (HAPPY-study). We included n=1075 women without a history of psychiatric illness that were followed throughout pregnancy and

the first postpartum year. Women with a self-reported lifetime history of depression were excluded. Since our outcome variable was first-onset depression, we excluded women with a self-reported lifetime history of depression as well as women with depression during the course of their pregnancy. Postpartum depression was defined with a commonly used and validated cut-off score of ≥13 on the *Edinburg Depression scale* (EDS). The cumulative incidence of first-onset postpartum depression within one year after delivery was 6.3%. A positive TPO-ab status was associated with an increased risk for first-onset depression at four months postpartum, but not at other postpartum time points. Interestingly, the longitudinal pattern of postpartum depression in the TPO-ab positive group was similar to the typical course of postpartum TPO-ab titers changes. This suggests overlap in the etiology of first-onset postpartum depression and auto-immune thyroid dysfunction. Based on the findings of our study we advise to evaluate thyroid function in women with first-onset postpartum depression.

PART II. LITHIUM USE DURING PREGNANCY AND THE POSTPARTUM PERIOD IN BIPOLAR DISORDER

Lithium is the most effective moodstabilizer for the treatment of bipolar disorder but its use has declined over the last decades. In **chapter 6**, we provide a general introduction on the history, potential mechanisms of action and clinical aspects of lithium therapy.

In **chapter 7**, we describe a retrospective cohort study that focuses on lithium dosing strategies during pregnancy and the postpartum period. Lithium has a narrow therapeutic window and careful monitoring is specifically warranted during the peripartum period because of physiological changes in renal function. Current clinical guidelines provide limited details regarding the optimal approach for monitoring lithium blood levels during pregnancy and the postpartum period. Therefore, in an effort to define an evidence-based strategy for dosing lithium during pregnancy, we quantified the longitudinal pattern of lithium blood levels during the peripartum period.

All pregnant women that were referred to the psychiatric and obstetric out-patient clinics of Erasmus MC and LUMC between 2003 and 2015 were screened for inclusion. We included n=113 pregnancies for which lithium blood levels were measured during pregnancy and the postpartum (n=1,101). On average, lithium blood levels decreased up to -36% in the second trimester. During this period, it is often necessary to increase a patients' lithium dose to maintain adequate prophylactic blood levels. In the third trimester and postpartum period, lithium blood levels gradually returned to the preconception level. During this period, there is an increased risk for toxic lithium blood levels. Delivery itself was not associated with an acute change in lithium and creatinine blood levels. Based on the findings of our study, we summarized recommendations regarding peripartum lithum dosing that are useful to minimize the risk for both sub-therapeutic and toxic blood levels.

As mentioned earlier, lithium has the largest evidence base for efficacy in the peripartum period among all mood stabilizers. However, data on lithium teratogenicity have been inconclusive, thereby complicating decision-making for women with bipolar disorder during pregnancy. Over the past couple of decades, lamotrigine has increasingly been used during pregnancy as an alternative treatment option to lithium, due to its more favorable reproductive profile. However, the efficacy of lamotrigine during the peripartum period is largely unknown. Therefore, the aim of the study that is presented in **chapter 8** was to compare mood stabilization during pregnancy with lamotrigine versus lithium in the prevention of severe postpartum episodes. Danish National registries were used to identify pregnancies of women with a diagnosis of bipolar spectrum disorders at the time of conception who used lamotrigine or lithium during pregnancy (1996-2012). Afterwards, we compared the risk of inpatient psychiatric admission within three months postpartum between women who used lamotrigine versus lithium during pregnancy. The overall risk for postpartum psychiatric admission was 11.4%. We did not find a significant difference in the risk of postpartum psychiatric admission between women who used lamotrigine versus lithium during pregnancy, even after adjustment for potential confounders. This finding is of clinical importance, since lamotrigine is considered to be a more favorable option than lithium with regard to the risk of adverse neonatal outcomes. However, the findings of our study should be interpreted with caution, because of the small study sample and the risk of confounding by indication. Therefore, our results will require replication before reaching definitive conclusions. We concluded that lamotrigine could be a reasonable alternative treatment option for bipolar disorder during pregnancy in patients with vulnerability for depression and may prevent severe episodes postpartum.

In **chapter 9**, we present the main conclusions of this thesis. Afterwards, we discuss the current evidence regarding the risks and benefits of maintenance treatment during the peripartum period in women with bipolar disorder, followed by general clinical recommendations. Finally, we provide an overview of the design and aims of the National Postpartum Psychosis Prevention study (NP3-study). The NP3-study was designed to further investigate the efficacy and potential risks of maintenance treatment during the peripartum period in women with a history of bipolar disorder and/or postpartum psychosis.

Nederlandse samenvatting

DEEL I. STEMMINGSSTOORNISSEN TIJDENS DE POSTPARTUM PERIODE

Bipolaire stoornis en postpartumpsychose

Vrouwen met een bipolaire stoornis en/of postpartumpsychose in de voorgeschiedenis hebben een sterk verhoogd risico op psychiatrische ziekte-episoden in de postpartum periode. Echter, in de literatuur worden grote verschillen in het risico op een recidief beschreven. Het doel van **hoofdstuk 2** was om met behulp van een meta-analyse een meer precieze benadering te geven van dit risico zodat patiënten samen met hun psychiater een betere afweging kunnen maken tussen de voor- en nadelen van medicatiegebruik tijdens de zwangerschap en postpartum periode. Een systematische zoekopdracht in de meest gebruikte medische databanken resulteerde uiteindelijk in de inclusie van 37 studies, waarin de uitkomst van 5.700 bevallingen werd beschreven. In de gecombineerde analyse werd een postpartum recidiefkans van 1 op 3 gevonden. Vrouwen met alleen een postpartumpsychose in de voorgeschiedenis hadden een hoger risico op een ernstige ziekte-episode dan vrouwen met een bipolaire stoornis. Het is daarom van klinisch belang om onderscheid te maken tussen deze twee groepen.

Buiten de peripartum periode is lithium het best onderzochte en meest effectieve middel ter preventie van stemmingsepisoden bij de bipolaire stoornis. Andere (in meerdere of mindere mate) effectief gebleken psychofarmaca zijn valproïnezuur, carbamazepine, lamotrigine en tweede generatie antipsychotica (olanzapine, quetiapine, risperidon). De effectiviteit van onderhoudsbehandeling tijdens de peripartum periode is echter zeer beperkt onderzocht. Desondanks konden we een meta-analyse uitvoeren met de uitkomsten van een klein aantal studies. De resultaten lieten zien dat vrouwen die tijdens de zwangerschap medicatie (veelal met lithium) gebruikten een lager risico hadden op een recidief dan vrouwen die geen medicatie gebruikten. Echter, medicatiegebruik tijdens de zwangerschap brengt ook potentiële risico's met zich mee. Deze risico's moeten zorgvuldig worden afgewogen tegen de voordelen van medicatiegebruik. Lithiumgebruik tijdens de zwangerschap is mogelijk geassocieerd met een licht verhoogd risico op aangeboren hartafwijkingen. Valproïnezuur en carbamazepine dienen niet te worden gebruikt tijdens de zwangerschap in verband met een verhoogd risico op onder andere neuralebuisdefecten. Tweede generatie antipsychotica en lamotrigine lijken vooralsnog de meest veilige opties, maar zijn minder effectief gebleken dan lithium. Tot slot geldt dat voor al deze middelen de eventuele schadelijke effecten op de lange termijn beperkt of nauwelijks zijn onderzocht.

In algemene zin kan worden gesteld dat indien er sprake is van recente/ernstige stemmingsepisoden, de voordelen van onderhoudsbehandeling tijdens de zwangerschap meestal opwegen tegen de potentiële risico's voor moeder en (het ongeboren) kind. Hierbij dient polyfarmacie echter altijd te worden vermeden. Daarnaast moet worden gezocht naar de laagst effectieve dosering.

Het doel van **hoofdstuk 3** was om een overzicht te geven van de beschikbare literatuur op het gebied van de diagnostiek, behandeling en preventie van postpartumpsychose, gevolgd door klinische aanbevelingen voor de dagelijkse praktijk. Postpartumpsychose is een zeldzaam maar ernstig ziektebeeld dat snel na de bevalling ontstaat en potentieel gevaarlijk is voor moeder en kind. Het ziektebeeld wordt beschouwd als een stemmingsstoornis omdat het naast psychotische symptomen wordt gekenmerkt door de aanwezigheid van depressieve en/of manische symptomen. Bovendien is een postpartumpsychose in een deel van de gevallen een eerste uiting van een bipolaire stoornis (manische depressiviteit). Postpartumpsychose wordt dan ook niet als aparte diagnose vermeld in het handboek voor de classificatie van psychische stoornissen (DSM-5). Het is echter van groot belang om het diagnostische concept postpartumpsychose te handhaven omdat een substantieel deel van de vrouwen met een postpartumpsychose niet gevoelig is voor stemmingsepisoden buiten het kraambed. Bij deze vrouwen is de prognose gunstig en om deze reden geen onderhoudsbehandeling nodig.

Bij het vermoeden van een postpartumpsychose is er sprake van een indicatie voor een psychiatrische (moeder-kind)opname en is het van belang om tijdens de diagnostische fase eventuele bekende lichamelijke oorzaken zoals schildklierziekte of een hersenontsteking (encefalitis) uit te sluiten. Een gecombineerde behandeling met lithium en antipsychotica is zeer effectief en leidt binnen korte tijd tot volledig herstel. Kortdurende profylaxe met lithium na een volgende zwangerschap is effectief ter preventie van een postpartumpsychose.

In **hoofdstuk 4**, beschrijven we de uitkomsten van een studie naar de fenotypische karakteristieken van postpartumpsychose. Zoals eerder gezegd is er naast psychotische symptomen namelijk meestal ook sprake van een breed scala aan andere symptomen die tegelijk of afwisselend kunnen optreden. Het doel van de studie was om op basis van deze symptomen meer homogene patiëntengroepen te onderscheiden. De studiepopulatie bestond uit patiënten met een postpartumpsychose die tussen 2005 en 2015 werden opgenomen op de moeder-kindafdeling van het Erasmus MC en werden geïncludeerd in de OPPER-studie. Deze studie vormt het grootste cohort ter wereld van vrouwen met een postpartumpsychose. Met behulp van vragenlijsten, een gestructureerd interview en dossier-onderzoek werd herhaaldelijk en nauwkeurig navraag gedaan naar een groot aantal symptomen. Er werden 130 patiënten geïncludeerd en de meest voorkomende symptomen waren prikkelbaarheid (73%), abnormale gedachte inhoud (72%) en angst (71%). Met behulp van statistische technieken konden drie profielen worden onderscheiden: in het eerste profiel stonden depressieve symptomen op de voorgrond (41%), in het tweede profiel manische symptomen (34%) en in het derde profiel atypische symptomen (25%) (stoornis in het bewustzijn, desoriëntatie, depersonalisatie en derealisatie). Op basis van deze bevindingen concluderen we dat atypische kenmerken minder vaak voorkomen dan eerder werd verondersteld. Het depressieve profiel komt vaak voor maar kan gemakkelijker onontdekt blijven doordat het onderscheid met een postpartum depressie

minder duidelijk is dan bij het manische of atypische profiel. Dit kan leiden tot vertraging in behandeling en een hoger risico op suïcide en infanticide.

Schildklier auto-immuniteit en postpartum depressie

De postpartum periode is geassocieerd met een verhoogd risico op het ontstaan van auto-immuun schildklierziekten. Gedurende de zwangerschap is het immuunsysteem minder actief om te voorkomen dat het ongeboren kind (dat voor de helft uit lichaamsvreemd materiaal bestaat) wordt afgestoten. Na de bevalling kan er echter sprake zijn van een te sterke activatie van het immuunsysteem. Dit is waarschijnlijk de reden dat auto-immuunziekten vaak optreden of verergeren gedurende de postpartum periode. Bij een auto-immuunziekte treedt er een afweerreactie op tegen lichaamseigen cellen. De aanwezigheid van auto-antistoffen tegen de schildklier (TPO-ab) in de vroege zwangerschap is een belangrijke voorspeller voor het ontstaan van postpartum auto-immuunschildklierziekten, waarbij ook vaak stemmingsklachten optreden. Daarnaast speelt een verstoring van het immuunsysteem waarschijnlijk ook een rol bij het ontstaan van psychiatrische ziekten, zeker wanneer die vaker of specifiek in de postpartum periode optreden, zoals bij postpartumpsychose en postpartum depressie het geval is.

Eerdere studies vonden een verband tussen een verhoogde TPO-ab titer en postpartum depressie. Echter, het gevonden verband in deze studies is mogelijk niet oorzakelijk omdat niet of onvoldoende werd gecorrigeerd voor de aanwezigheid van depressie eerder in het leven en/of de zwangerschap en andere mogelijk verstorende factoren. Dit is problematisch omdat een over-activatie van het immuunsysteem waarschijnlijk vooral betrokken is bij het ontstaan van depressie gedurende de postpartum periode.

Het doel van de studie die we beschrijven in **hoofdstuk 5** was daarom om te onderzoeken of er een relatie bestaat tussen een verhoogde TPO-ab titer in het eerste trimester van de zwangerschap en het ontstaan van een eerste depressie in de postpartum periode. De studiepopulatie was onderdeel van de HAPPY-studie en bestond uit een groot cohort van 1.075 zwangere vrouwen zonder een psychiatrische voorgeschiedenis die intensief werden gevolgd tot een jaar na de bevalling. Vrouwen die reeds bekend waren met schildklierziekte en/of depressieve klachten tijdens de zwangerschap kwamen niet in aanmerking voor deelname aan deze studie. Postpartum depressie werd gedefinieerd met een gevalideerde afkapwaarde (≥13) op een veelgebruikte zelfinvulvragenlijst voor depressieve klachten (*Edinburgh Postnatal Depression Scale*), die herhaaldelijk werd ingevuld tot een jaar na de bevalling. In de hele groep werd een risico gevonden van 6,3% op het ontstaan van een eerste postpartum depressie. De aanwezigheid van een verhoogde TPO-ab titer was gerelateerd aan een hoger risico op het ontstaan van postpartum depressie vier maanden postpartum. Uit eerder onderzoek is gebleken dat bij vrouwen met een verhoogde TPO-ab titer tijdens de zwangerschap vaak in diezelfde periode (3-4 maanden postpartum) een ontregeling optreedt van het immuunsysteem. De bevindingen uit deze studie suggereren dat er mogelijk overlap

bestaat tussen de ontstaanswijze van een eerste postpartum depressie en auto-immuun schildklierziekten. Wij adviseren om bij iedere vrouw waarbij depressieve klachten ontstaan in de postpartum periode de schildklierfunctie te controleren.

DEEL II: LITHIUMGEBRUIK TIJDENS DE ZWANGERSCHAP EN POSTPARTUM PERIODE BIJ DE BIPOLAIRE STOORNIS

In **hoofdstuk 6** beschrijven we kort de geschiedenis en potentiële werkingsmechanismen van lithium. Daarna bespreken we een aantal klinische aspecten die in het algemeen van belang zijn bij lithiumgebruik.

In **hoofdstuk 7** beschrijven we een studie die zich specifiek richt op het monitoren van lithiumgebruik tijdens de zwangerschap en postpartum periode. Tijdens de zwangerschap is er sprake van een natuurlijke aanpassing van de nierfunctie, waardoor veranderingen in de lithiumbloedspiegel optreden. Aangezien lithium een smal therapeutisch venster heeft, brengt dit risico's met zich mee voor zowel moeder als het ongeboren kind. Tot op heden is er echter nooit gedegen onderzoek gedaan naar dit klinisch relevante onderwerp.

Het doel van deze studie was daarom om te kwantificeren hoe groot deze veranderingen zijn en te onderzoeken op welk moment ze optreden. Voor deze studie verzamelden we data middels statusonderzoek in het Erasmus MC en het LUMC (NP3-studie). We gebruikten 1.101 lithiumbloedspiegels die afkomstig waren van 113 zwangerschappen. De resultaten laten zien dat lithiumbloedspiegels geleidelijk tot gemiddeld 36% dalen in het tweede trimester, in deze fase moet de lithiumdosis meestal worden verhoogd. In het derde trimester begint de lithiumbloedspiegel zich te normaliseren en moet de lithiumdosis vaak weer worden verlaagd. De bevalling was niet geassocieerd met een acute verandering in de lithiumbloedspiegel. In het hoofdstuk worden een aantal praktische klinische aanbevelingen gedaan waarmee het risico op te lage en te hoge lithiumbloedspiegels tijdens de peripartum periode kan worden verkleind.

Zoals eerder gezegd bestaat er bij vrouwen met een bipolaire stoornis gedurende de peripartum periode de meeste evidentie voor de effectiviteit van een onderhoudsbehandeling met lithium. Lamotrigine wordt toenemend als alternatief gebruikt tijdens de zwangerschap omdat het een veiligere optie is wat betreft het risico op neonatale complicaties. De effectiviteit van lamotrigine tijdens de peripartum periode is echter nauwelijks onderzocht. Het doel van de studie die wordt gepresenteerd in **hoofdstuk 8** was daarom het vergelijken van de effectiviteit van lithium- en lamotriginegebruik tijdens de zwangerschap bij vrouwen met een bipolaire stoornis. De uitkomstmaat van de studie was het risico op een ernstige stemmingsepisode postpartum die resulteerde in een ziekenhuisopname. De data voor dit cohortonderzoek (periode 1996-2012), werd verkregen uit verschillende Deense registers waarin (medische) informatie van de gehele Deense bevolking wordt vastgelegd. Uiteindelijk werd de uitkomst van 114 zwangerschappen

geanalyseerd. Het risico op een ernstige recidief ziekte-episode postpartum was 11,4%. Een vergelijking tussen patiënten die lithium of lamotrigine gebruikten tijdens de zwangerschap liet geen significant verschil zien op een ernstige recidief episode postpartum, ook niet na correctie voor verschillen in klinische karakteristieken tussen de twee patiëntengroepen. De uitkomsten van dit onderzoek zijn van klinisch belang omdat lamotrigine veiliger kan worden gebruikt dan lithium gedurende de zwangerschap. Echter, de resultaten moeten voorzichtig worden geïnterpreteerd gezien de kleine studiepopulatie en andere methodologische tekortkomingen van het onderzoek. We concluderen dat een onderhoudsbehandeling met lamotrigine tijdens de zwangerschap kan worden overwogen, in het bijzonder bij patiënten die kwetsbaar zijn voor depressieve episodes.

In **hoofdstuk 9** vermelden we de belangrijkste conclusies van de studies uit dit proefschrift. Daarna bespreken we de beschikbare evidentie wat betreft de effectiviteit en risico's van medicatiegebruik tijdens de zwangerschap bij vrouwen met een bipolaire stoornis. Tenslotte bespreken we de onderzoeksopzet en doelen van de Nationale Postpartum Psychose Preventie studie (NP3-studie). De NP3-studie is opgezet om de effectiviteit en risico's te onderzoeken van medicamenteuze onderhoudsbehandeling tijdens de peripartum periode bij vrouwen met in de voorgeschiedenis een bipolaire stoornis en/of postpartum psychose.

PhD Portfolio

PHD PORTFOLIO

Name PhD student:	Richard Wesseloo
Erasmus MC Department:	Psychiatry
Research School:	NIHES
PhD period:	July 2013 – July 2017
Promotoren:	S.A. Kushner, V. Bergink
Supervisor:	A.M. Kamperman

PhD training and activities	**Year**	**ECTS**
Master of science in clinical epidemiology:	2014-2016	70

Core:
- Biostatistics I: basic principles
- Biostatistics II: classical regression models
- Study design
- Clinical epidemiology
- Methodologic topics in epidemiologic research

Erasmus Summer Programme:
- Fundamentals of medical decision making
- The practice of epidemiologic analysis
- Principles of research in medicine
- Methods of public health research
- Clinical trials
- Health economics
- Cohort studies
- Case-control studies
- Causal mediation analysis
- Markers and prediction research
- Logistic regression

Electives
- Repeated measurements in clinical studies
- Psychiatric epidemiology
- Advanced analysis of prognosis studies
- Principles of epidemiologic data-analysis
- Women's health

PhD training and activities (Continued)	Year	ECTS
Other courses		
- Teach the teacher I	2017	
- Biomedical English writing and communication	2016	4.0
- Research integrity	2016	0.3
- Corsendonk cursus, Belgium (one week)	2014	
- Good clinical practice (BROK)	2013	4.0
- Systematic literature retrieval in PubMed	2013	0.3
- Workshop Endnote	2013	0.3
Conference presentations		
- NVVP Voorjaarscongres, Maastricht (oral)	2017	
- MARCE Conference, Melbourne, Australia (oral)	2016	
- NVVP Voorjaarscongres, Maastricht (oral)	2016	
- ISBD Conference, Amsterdam (oral)	2016	
- NVVP Voorjaarscongres, Maastricht (oral)	2015	
- SAP Najaarsdag, Utrecht (oral)	2015	
- ECNP Conference, Amsterdam (poster)	2014	
- MARCE Conference, Swansea, UK (oral)	2014	
Supervision and teaching		
- Master thesis Laurine Alderlieste (MSc)	2014	
- Master thesis Fatima El Morabit (MSc)	2014	
- Minor in psychiatry (BSc)	2015	
Nominations and prizes		
- The publication *"Wesseloo et al. Risk of postpartum relapse in bipolar disorder and postpartum psychosis: a systematic review and meta-analysis"* was selected by the *New England Journal of Medicine* as one of the 10 most important clinical studies in the entire field of psychiatry in 2015.	2015	
- Winner of the *Tijdschrift voor Psychiatrie* resident publication price (€ 1000)	2015	

List of publications

PEER REVIEWED PUBLICATIONS

Wesseloo R, Kamperman AM, Bergink V, Pop VJM
The association between thyroid peroxidase antibodies and first-onset depressive symptomatology postpartum: a prospective cohort study
Journal of Affective Disorders 2018; 225:399-403

Wesseloo R, Wierdsma AI, Van Kamp IL, Munk-Olsen T, Hoogendijk WJG, Kushner SA, Bergink V
Lithium dosing strategies during pregnancy and the postpartum period
The British Journal of Psychiatry 2017; 211(1):31-36

Wesseloo R, Liu X, Clark CT, Kushner SA, Munk-Olsen T, Bergink V
Risk of postpartum episodes in women with bipolar disorder after lamotrigine or lithium use during pregnancy: a population-based cohort study
Journal of Affective Disorders 2017; 218:394-397

Wesseloo R, Kamperman AM, Munk-Olsen T, Pop VJM, Kushner SA, Bergink V
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The American Journal of Psychiatry 2016; 173(2):117-22

Wesseloo R, Burgerhout KM, Koorengevel KM, Bergink V
Postpartumpsychose in de klinische praktijk: diagnostiek, behandeling en preventie
Tijdschrift voor Psychiatrie 2015; *57*(1):25-33

Kamperman AM, Veldman-Hoek MJ, **Wesseloo R**, Robertson Blackmore E, Bergink, V
Phenotypical characteristics of postpartum psychosis: a clinical cohort study
Bipolar Disorders 2017; 19(6):450-457

OTHER PUBLICATIONS

Wesseloo, R *Nederlands-Vlaams toponderzoek:*
Lithium gebruik tijdens de zwangerschap en postpartum periode
Tijdschrift voor Psychiatrie 2017; 59(11):727-728

Wesseloo, R *Nederlands-Vlaams toponderzoek: Terugvalrisico postpartum bij bipolaire stoornis of postpartumpsychose: een systematische review en meta-analyse*
Tijdschrift voor Psychiatrie 2016; 58(2):160-161

Knijff EM, **Wesseloo R**, Bergink V
Hoofdstuk 25: Postpartum psychose
Handboek spoedeisende psychiatrie, de Tijdstroom 2017

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Hoofdstuk 2: De postpartum psychose
Handboek zwangerschapspsychiatrie, de Tijdstroom 2015

Alderlieste L, **Wesseloo R**, Koorengevel KM, Bergink V
Handreiking voor verloskundigen: postpartum psychose in de praktijk
Tijdschrift voor Verloskundigen 2015 (4):16-21