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Bipolar disorder during pregnancy and the postpartum period:

Patients' considerations, course of bipolar disorder and impact of sleep loss

Agnes Wilhelmina Margaretha Maria Stevens

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Patients' considerations, course of bipolar disorder and impact of sleep loss

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Voor Jules (S.G.) Stevens

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Bipolar disorder during pregnancy and the postpartum period:
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Mother and child - Sabine van de Pol

Chapter 1

Introduction

Eva, a woman aged 29 without a prior psychiatric history, gave birth to a healthy son after a pregnancy without any problems. She was breastfeeding. After three days she became confused and developed paranoid ideas, being convinced her son was ill and her husband cheated on her. The house doctor was consulted and advised her to stop breastfeeding so she could sleep undisturbed during the night. He prescribed her haloperidol and lorazepam. On and off she felt better, although her confusion varied over time. At moments she still was convinced that her husband cheated on her. Five days after the start of haloperidol and lorazepam she consulted a senior resident in psychiatry together with her husband. During the interview she was alert and had no psychotic symptoms, She and her husband reported that her symptoms had disappeared since about one day, apart from short moments of confusion. Although the resident advised admission to a mother-baby unit, the couple decided to stay at home. They agreed on a treatment plan for that night (continuing medication, not going out alone, contacting the psychiatric ward in case of worsening of symptoms) and an appointment for the next day with the psychiatrist to monitor her symptoms. Unfortunately, that night Eva committed suicide by jumping from the balcony of her apartment.

The resident was me, and the tragic story of this young mother had a major impact on me and my professional interests, especially since at that time I was mother of a four month old girl.

Eva was suffering from postpartum psychosis, the most severe form of psychiatric illness following childbirth with a high risk of suicide and infanticide. Postpartum psychosis also has a huge negative impact on the family. Instead of having the family together with the joy of a newborn in the house, a woman with postpartum psychosis is often admitted to a psychiatric hospital, preferably with her baby. This introductory chapter will give a brief overview of bipolar disorder, postpartum mood disorders, and the role of sleep in these psychiatric conditions.

Bipolar disorder

Bipolar disorder (BD) is a chronic psychiatric illness characterized by recurrent episodes of mania, hypomania, and depression (Goodwin & Jamison, 2007). A recent epidemiological study in the Netherlands (Nemesis-3) (ten Have et

al, 2022) reported a lifetime prevalence of 2.1% and a 12-months prevalence of 1.2%, with no significant differences between males and females. This is comparable to the results of an earlier study (Nemesis 2) (de Graaf et al., 2012) and the prevalence in other countries (Merikangas et al., 2011). There are two major subtypes: bipolar I disorder (BD-I) and bipolar II disorder (BD-II). Patients with BD-I experience at least one episode of mania, while patients with BD-II experience at least one episode of hypomania also in addition to one or more episodes of major depression. What differentiates episodes of mania from hypomania is the severity, duration of symptoms, and the impact on psychosocial functioning. In contrast to mania, a hypomanic episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic symptoms. The mean age of onset of BD is estimated around age 25, with a majority of the patients reporting an age of onset before the age of 20 years, although late-onset BD does exist (Baldessarini et al., 2010; Benazzi, 2009). This indicates that BD is especially an illness of young adults. Especially for women, it can affect family planning, pregnancy, and parenting in many ways.

A recent review estimated that 54.9% of women with a prior BD diagnosis were found to have at least one bipolar-spectrum mood episode in the perinatal period; 51.4% in pregnant women and 54.8% in postpartum women (Masters et al., 2022).

Long-term medication treatment is recommended in most patients with recurrent BD. Lithium is the most effective prophylactic treatment to prevent or diminish the recurrence of mood episodes (Maj, 2000). In pregnancy, maintenance treatment can be recommended depending on the previous course and severity. It is important to weight potential fetal risks and effects on child neurodevelopment when using medication against the risk of maternal relapse (Belzeaux et al., 2019). Valproate and carbamazepine should be avoided during pregnancy because of the increased risk of neural tube defects and later impairment of cognitive development (Malhi et al., 2015; Yatham et al., 2018). Lithium, among all available mood stabilizers, has long been the safest option despite the association of lithium with a slightly increased risk of congenital heart defects (Malhi et al., 2015; McKnight et al., 2012). However, more recent studies gave a solid base for teratogenity of lithium in the first trimester. In a meta-analysis of six study sites (22.124 eligible pregnancies of which 727 pregnancies in the lithium-exposed

group) the risk of any major malformation (including cardiac malformations) was increased in lithium-exposed pregnancies (OR 1.62, 95% CI 1.12–2.33) compared to non-exposed pregnancies in mothers with a mood disorder (Munk-Olsen et al., 2018). In a large cohort study (1,325,563 pregnancies with 663 lithium-exposed infants) maternal use of lithium during the first trimester was associated with an increased risk of cardiac malformations (Patorno et al., 2017). On the other hand, continuation of prophylactic medication (lithium or lamotrigine) during pregnancy is associated with a relative risk reduction of recurrence of a mood episode of 66% (Stevens et al., 2019).

Postpartum psychosis

Postpartum psychosis is rare in the general population with a prevalence of 1-2 per 1000 deliveries (Brockington, 2004; Kendell et al., 1987). It is the most serious psychiatric disorder following childbirth because of high rates of suicide and infanticide (Appleby et al., 1998).

In most cases the onset is rapid and occurs within two weeks after delivery (Heron et al., 2008). Insomnia, restlessness, and irritability are early symptoms, followed by more severe manifestations such as fluctuating mood with symptoms of mania, depression, mixed states, psychotic features, and cognitive dysfunction (Brockington, 2004; Kendell et al., 1987; Sit et al., 2006). Postpartum psychosis has an amentia-like clinical picture with periods of apparently normal behavior alternating with periods in which affective and/or psychotic symptoms occur more frequently (Brockington et al., 1981). Most profound phenotypical characteristics of postpartum psychosis were irritability, abnormal thought content and anxiety in a prospective study of 130 women with a postpartum psychosis and three symptom profiles were revealed, a manic (34%), a depressive (41%) and an atypical (25%) profile (Kamperman et al., 2017). The nosological status of postpartum psychosis remains controversial. Although not all cases of postpartum psychosis fall into the bipolar spectrum, there is a strong association with BD (Bergink et al., 2016; Chaudron & Pies, 2003).

Women who already suffer from BD have an overall postpartum recurrence rate of 37%; women with BD who continued prophylactic medication during pregnancy had a recurrence rate of 23%, compared to 66% in those who discontinued their prophylactic medication during pregnancy (Wesseloo et al., 2016).

The strongest risk factor for postpartum psychosis is a history of BD or a history of postpartum psychosis (Jones et al., 2014). A family history of postpartum psychosis or BD is also a well-known risk factor (Jones & Craddock, 2001).
Other risk factors for developing postpartum psychosis are primiparity, longer duration of bipolar illness, earlier age of onset of illness, and a shorter period of clinical stability since the last episode preceding conception (Akdeniz et al., 2003; Viguera et al., 2007). No association was found with psychosocial factors (Akdeniz et al., 2003; Jones et al., 2014).
The risk of psychiatric re-admission following childbirth is much higher for women with a history of BD than those with a history of other psychiatric disorders (Munk-Olsen et al., 2009). Inpatient psychiatric treatment for postpartum psychosis is usually required for safety assessment and treatment initiation.
Lithium is the drug of first choice for treating postpartum psychosis, and antipsychotic medication and benzodiazepines are useful adjunctive treatments (Bergink et al., 2016).

Sleep
Sleep is essential for mental and somatic health. During sleep brain and body can recover from all sensory stimuli, experiences, stressors, and activities. Sleep can be divided into four sleep phases, during which brain activity significantly differs:

- wake
- rapid eye movement (REM) sleep (dream sleep)
- light sleep
- deep sleep

These sleep phases alternate in so-called 'sleep cycles'. Deep sleep mainly occurs in the first half of the night, REM sleep and non-REM sleep mainly in the second half of the night. Because deep sleep is essential for healthy functioning, the first four hours of sleep are crucial. Therefore, it is called 'core sleep'. With age, sleep architecture changes with less deep sleep.

In healthy pregnant women, alterations in sleep patterns and behavior are present from early pregnancy through the postpartum period (Mindell et al., 2015; Santiago et al., 2001; Suzuki et al., 1994). A total of 66% to 94% of all

pregnant women report alterations in sleep. During the first trimester, total sleep time, insomnia, and nocturnal awakenings increase, and overall sleep quality decreases. In the second trimester sleep appears to normalize (Santiago et al., 2001; Suzuki et al., 1994). In the third trimester, women awaken 3-5 times per night and experience more insomnia and, as a consequence, diminished daytime alertness. REM- sleep decreases in the third trimester (Karacan et al., 1969; Lee, 1998; Santiago et al., 2001).
In the early postpartum period, there are significant changes in sleep patterns, including a decrease in sleep efficiency, a decrease in total sleep time, and an increase in waking after sleep onset (Hunter et al., 2009; Lee, 1998). Sleep efficiency decreases especially during the second postpartum week because of frequent awakenings at night (Horiuchi & Nishihara, 1999; Shinkoda et al., 1999). Subjective sleep quality is worse than objective parameters of sleep in pregnant women and a stronger association between subjective report of sleep disturbance and postpartum mood than with objective sleep measurement has been reported in women with a mental disorder (Coo et al., 2014; Van Ravesteyn et al., 2014).

In BD, there is a temporal relationship between sleep disruption and mood change, especially between sleep loss and the occurrence of a hypomanic or manic episode (Bauer et al., 2006). Alterations in sleep often predict a worsening in clinical state, and in turn duration of sleep shortens further during an episode (Jackson et al., 2003). It is hypothesized that sleep reduction, which can be caused by various psychological, interpersonal, environmental, and pharmacological factors, can be the ultimate trigger to mania. (Murray & Harvey, 2010; Wehr et al., 1987).
Insomnia is a prominent early symptom in women with postpartum psychosis (Brockington, 1982; Hunt & Silverstone, 1995). Lack of sleep, being a potential risk factor for a manic or mixed episode, mostly occurs in late pregnancy and the early postpartum period (Lee, 1998; Santiago et al., 2001). Even historical accounts of "puerperal insanity" noted that the almost universal early symptom is loss of sleep (Jones, 1902a, 1902b).
An interesting hypothesis, first stated by Sharma, is that alterations in sleep may represent a final common pathway by which various risk factors produce psychosis in susceptible women (Ross et al., 2005; Sharma, 2003; Sharma &

Mazmanian, 2003). A retrospective study of 21 pregnant women and 21 controls, using chart reviews, found that those who developed postpartum psychosis had a longer duration of labor and more often gave birth at night (Sharma et al., 2004). A case study of three women without a history of postpartum psychosis found that they became (hypo)manic following induced sleep deprivation in the postpartum period (Strouse et al., 1992). However, a prospective study comparing 23 pregnant women with a history of BD postpartum psychosis with 15 pregnant healthy women found no significant differences in sleep/wake patterns (Bilszta et al., 2010).
Furthermore, pregnant women with BD who reported sleep loss triggering episodes of mania were twice as likely to have experienced an episode of postpartum psychosis compared to women who did not report this (Lewis et al., 2018).
All in all, a relationship between sleep disturbance and postpartum psychosis is often assumed although the evidence is still scarce and controversial.

Management of bipolar disorder in pregnancy and the postpartum period in the Netherlands

Preferably, women with BD who want to become pregnant, are referred to a Psychiatric-Obstetric-Pediatric (POP) outpatient clinic, where a multidisciplinary team of a Psychiatrist, Obstetrician, and Pediatrician give the patient and her partner an integral medical advice (Paarlberg et al., 2015). Together with the patient and her partner the pros and cons of stopping medication must be weighed against the pros and cons of continuing medication. This is always personalized depending on the kind of medication used and the course of patient's BD. Shared decision making is important in which the professional gives adequate information and professional and patient together decide the best treatment options during pregnancy and postpartum period. An individualized treatment plan during pregnancy will be made with the healthcare provider. Lithium is still considered the mood stabilizer of first choice in the Netherlands if the patient chooses to continue medication, especially in patients in which it has been effective. Lamotrigine (in bipolar type II) or second-generation antipsychotics may be an alternative. Monitoring medication blood levels is more frequently needed during pregnancy, especially in the first and third trimester. When medication is stopped during pregnancy, it is recommended to restart

immediately after delivery to prevent a postpartum episode. Delivery should take place in hospital where neonatal evaluation and monitoring can take place and psychiatric and obstetrical care for the mother is provided.

Outline and aims of this thesis

The general aim of this thesis is to study the course of BD in pregnant women and the influence of sleep during pregnancy and the peripartum period on postpartum mood symptoms. Another aim is to better understand the opinions about family planning and pregnancy of women with BD.

Chapter 2 presents a qualitative study reporting thoughts and considerations of women with BD about family planning. In chapter 3, a systematic review on the recurrence of mood disorder in pregnant women is presented. Chapter 4 describes the protocol of the Sleepreg-bd study presented in chapter 5, addressing the impact of sleep during pregnancy and the perinatal period on postpartum psychopathology. In chapter 6 the study comparing the course of BD in pregnant women to non-pregnant women is presented. Finally, in addition to all previous chapters addressing pregnant women, chapter 7 presents a case report of a man with BD who developed mania a few weeks after he became father and discusses the role of sleep loss in triggering a mood episode postpartum in men.

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2

Mother and child - Peter van de Pol

Chapter 2

Thoughts and considerations of women with bipolar disorder about family planning and pregnancy: a qualitative study

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ABSTRACT

Background
Women with bipolar disorder have an increased risk of relapse during pregnancy and the postpartum period, and often express broad concerns about family planning.

Objective
To explore the thoughts and considerations of women of childbearing age with bipolar disorder, about family planning and pregnancy.

Design
A qualitative study was conducted: 15 women with bipolar I disorder were individually interviewed. Content analysis was applied.

Results
Women worried about heritability of bipolar disorder, medication issues and risk of relapse during pregnancy. They mentioned their fear to be incompetent as a mother during future mood episodes. Support of partner, family/friends, and professionals was mentioned as essential.

Conclusions
Family planning is an essential topic in the treatment of every woman with bipolar disorder of childbearing age. These women expect early consultation with professionals for support, and specific information about heritability of the illness and use of medication during and after pregnancy.

Keywords
bipolar disorder, desire to have children, family planning, pregnancy

INTRODUCTION

Bipolar disorder is a severe mental illness with an estimated lifetime prevalence ranging from 1.3% to 2.4% (de Graaf, ten Have, van Gool, & van Dorsselaer, 2012; Merikangas et al., 2011; Pini et al., 2005). It is a chronic disorder characterized by recurrent episodes of mania, hypomania, depression, and mixed episodes (Goodwin and Jamison, 2007). Patients with bipolar disorder show considerable illness-related morbidity (Post et al., 2003) and the disorder significantly influences their wellbeing and social, occupational, and general functioning (Altshuler et al., 2006; Bonnin et al., 2012).

Pregnancy is associated with a wide range of potential problems in women with bipolar disorder. They have an increased risk of relapse during pregnancy (up to 25%) and especially in the postpartum period (52%; Viguera et al., 2011). However, in a systematic review Sharma concluded that there may be a positive effect of pregnancy on the course of bipolar disorder (Sharma et al, 2012). Women with bipolar disorder who discontinue medication during pregnancy even have a 71% risk of relapse (Viguera et al., 2007). In the first month after delivery the risk of psychiatric admission increases strongly (RR 37.2) in women with affective and especially bipolar disorder (Munk-Olsen et al., 2009). A recent meta-analysis showed that the relapse rate in the postpartum period is more than 30% (Wesseloo et al, 2016). Psychotropic medication can have pharmacological and teratogenic effects on the fetus. However, psychiatric symptoms in the woman also can present risks to the developing fetus (Boden et al., 2012). Several studies showed that psychological problems of the pregnant woman can affect the cognitive and emotional development of the child (Mennes, Van den Bergh, Lagae, & Stiers, 2009; Raikkonen et al., 2011).

In clinical practice we often hear women express their concerns about the heritability of bipolar disorder to offspring, and about the impact of the illness and the medication on pregnancy and the unborn child. First-degree relatives' risk of getting bipolar disorder is estimated at 5-10% (e.g. 8 times higher than in the general population) and of unipolar depressive disorder at 8-20% (Craddock and Jones, 2001).

Women with bipolar disorder who sought consultation about treatment options and risks regarding pregnancy have been followed up regarding reproductive decisions (Viguera, Cohen, Bouffard, Whitfield, & Baldessarini, 2002). Of these women, 45% previously had been advised by a health care professional to avoid

pregnancy. After consultation, 63% of this group attempted to conceive and 37% chose to refrain from pregnancy. The most commonly reported reasons to refrain from pregnancy were: fear of adverse effects of medication on the development of the fetus (56%), fear for illness recurrence (50%), concerns of genetic transmission of bipolar disorder to offspring (22%), reluctance to repeat previous pregnancy associated illnesses (17%), and fear that recurring mania or depression would affect the fetus (17%). Another study reported maternal outcome after preconception consultation in women with bipolar disorder. The main object of that study was pharmacological management during pregnancy (Wieck, Kopparthi, Sundaresh, & Wittkowski, 2010). Of the 32 women with bipolar disorder, 9 (28%) were being advised to continue their medication, 4 (12.5%) to stop their medication, and 19 (60%) to switch to other medication. During one year follow-up 20% of these women developed a mood episode. In all women pharmacologic recommendations had been followed, but in only one the medication had been stopped.

Many women with bipolar disorder, regardless of educational and socioeconomic background, as well as many providers who treat them, are ill-informed about the relative risks of perinatal exposure to psychotropics and the high rates of relapse especially in the postpartum period without treatment (Cantilino et al. 2014, Ververs et al. 2009, Walton et al, 2014). In an editorial Freeman (2007) describes that routine treatment planning for female patients should systematically include a discussion about (un)planned pregnancy because often both health care providers and patients are uncertain what to do when a pregnancy is revealed. Concerns about medication exposure of the fetus may lead to abrupt discontinuation of mood stabilizers (Freeman, 2007).

Evidence from a large study suggests that use of antipsychotics early in pregnancy generally does not increase the risk for congenital malformations overall or cardiac malformations in particular (Huybrechts et al, 2016). With the exception of valproate and carbamazepine, the majority of mood stabilizers can be thoughtfully utilized throughout pregnancy. With close monitoring, lithium can be safely utilized in pregnancy (Wichman, 2016).

A collaborative care approach is recommended with close liaison between obstetric, mental health services and the general practitioner for women suffering from a severe mental illness who are pregnant or intent to become pregnant (Howard et al, 2014; Kupka et al, 2015; SIGN 2012; (Meltzer-Brody & Jones, 2015).

The aim of preconception counseling is to present all information available to support informed decisions (Frayne, Nguyen, Allen, & Rampono, 2009).
Various guidelines give recommendations how to respond to an expressed desire to have children concerning the heritability of bipolar disorder, the choice whether or not to continue medication, and how to decrease the risk of recurrence during pregnancy and postpartum (Howard et al, 2014; Kupka et al, 2015; SIGN, 2012). These recommendations stem from a professionals' point of view. To our knowledge, no study has been conducted addressing the questions and needs with respect to a desire to have children, family planning, and pregnancy from the perspective of women with bipolar disorder. An extensive search in Medline, Embase, PsycINFO, CINAHL, and the Cochrane Database of systematic reviews did not reveal any scientific literature addressing these topics.
The aims of this study are:
1. to explore the considerations of women with bipolar disorder when making decisions about family planning and pregnancy, and
2. to ascertain which information and/or support these women expect from their treatment team. This information may serve to inform health care professionals treating women with bipolar disorder.

METHODS

Study design

A qualitative research methodology was chosen to explore the considerations, thoughts, and support needs of women about pregnancy and motherhood. The essence of their experiences was explored, in order to get a complex, detailed understanding about these issues (Creswell, 2012).

Recruitment of participants

We used purposive sampling: professionals of two mental health centers for bipolar disorder in the Netherlands asked childless bipolar women whether they wanted to participate. The choice to include only childless women was made to exclude the possible influence of already being a mother on thoughts and support needs. Participants were also recruited via the Dutch patient association for bipolar disorder (VMDB, Dutch Association for Manic Depressives and their Relatives, nowadays called Plusminus). Participants were included regardless of illness duration, marital status, and residency. At the time of participation in the

study women had to be euthymic. Participants were asked to score their mood on a Visual Analoge Scale (VAS) (Denicoff et al., 2000). This scale varies from 0 to 100, score 0 represents severely depressed, score 100 means extremely manic. To be eligible for the study participants needed to score between 40 and 60. A total of fifteen women were included in this study. Coincidentally, all eligible and consented patients had bipolar I disorder.

Data – collection

Prior to the start of each interview anonymity of personal data was discussed, the procedure of the interview was explained, and demographic and illness-related information was collected. An open interview was started, and the initial question was: "For you, as a woman with bipolar disorder, in childbearing age, what are your considerations and thoughts about family planning and pregnancy?" All interviews were performed by the same researcher (MK) in August and September 2012. A topic list was used by the interviewer as a helping tool to guide the participant back to the starting question if necessary and to keep exploring specific statements in depth. During the data-collection and analysis a few items were added to the topic list (Table 1). The interviews were recorded with an audio recorder and transcribed verbatim afterwards. The interviewer wrote field notes after each interview, for example about the non-verbal communication. After a week a telephone call was made with each participant to ask if there were any additional thoughts or considerations that the participant would like to make after an overview of the interview was given. The transcript of the interview was not sent to the participants.

Table 1. Topic list

First interview	- family planning
	- role as a mother
	- considerations about medication
	- hereditary
	- role of professionals
	- influence of partner, family members, friends
After two interviews	- fear for relapses
	- experiences of other people/examples
	- behavior of children, depending on age
After five interviews	- possible help from others
	- identity of a mother
	- information

Data analysis

A qualitative content analysis was conducted (Hsieh and Shannon, 2005; Boeije et al, 2009). Through open coding the text of the interviews was examined, i.e., the transcripts were read and reread, and relevant text fragments, related to the research questions were coded. The first three interviews were coded independently by two researchers, and discussed, until consensus was reached about the given codes. After the phase of axial coding an evaluation of the fragments under a specific code was done, and the codes were put in a certain order. Discussion within the research team about the granted codes and their connection followed. After the analyses of the twelfth interview, no new codes came up, so data saturation was assumed. Three more interviews were held to confirm data saturation. The final step in the data analysis was selective coding: a category system was made, relations between categories were discussed in the study team, and so the final category system was established. The MAXQDA 2007 software (VERBI GmbH, Berlin, Germany) was used to support this data analysis process.

Ethical considerations

The study was approved by the Institutional Review Board (METC) of the University Medical Center Utrecht, The Netherlands, as well as by the Board of the two mental health institutions where participants were recruited. All participants gave informed consent prior to the interview.

RESULTS

Of the 20 women who showed interest to participate in this study, fifteen gave informed consent and were interviewed. The reasons for not participating were: two women explained that their therapist advised them not to participate; one woman did not consent that the information would be stored for 15 years; one woman withdrew without mentioning a reason and with one woman an appointment could not be made. All fifteen participants had bipolar I disorder, they were living in different parts of The Netherlands, and their age varied between 28 and 45 years. Ten of these women desired children, five of them mentioned that they had already decided to become a mother, one had decided not to choose for pregnancy and four of them were still in doubt. (see Table 2)

Table 2. Information on participants

Participant	Age	VAS score[1]	Married*/ In a relation[2] Y/N	Desire to have children Y/N	Choice for pregnancy[3] Y/N/Doubt
P1	28	45	Yes	Yes	Yes
P2	31	50	Yes	Yes	Doubtful
P3	35	45	No	Yes	Doubtful
P4	41	55	Yes*	Yes	No
P5	28	50	Yes	Yes	Yes
P6	45	50	No	Yes	Yes
P7	32	50	Yes*	Yes	Yes
P8	41	45	Yes	No	No
P9	30	50	Yes	Yes	Doubtful
P10	40	45	Yes	No	No
P11	39	50	No	Yes	Doubtful
P12	37	50	Yes	Yes	Yes
P13	40	45	Yes*	No	No
P14	31	50	Yes	No	No

[1] VAS score at the start of the interview

[2] Having a partner relation

[3] Reporting she made the decision for future pregnancy

Analysis of the interviews resulted in five themes referring to the research questions: (1) considerations and thoughts related to having bipolar disorder; (2) the support of partner, family and friends; (3) the support and care of their regular treatment team; (4) the information needed, and (5) when and how support was expected.

Considerations and thoughts in making decisions about family planning

Participants thought much about family planning and pregnancy: they felt themselves, together with their partner, responsible for their choices and they realized that the choice for motherhood is an important one. For most of them, having a mental health problem was seen as a risk factor in family planning and pregnancy. Some participants looked for specific information about bipolar disorder and pregnancy. Others reported practicing motherhood-skills through babysitting: as an opportunity to experience being active as a mother. These actions helped participants to become more aware of their own considerations and decisions about family planning.

Considerations related to bipolar disorder:

Most participants worried about the heritability of their illness. They did not want their children to be at risk for developing bipolar disorder and wanted information about that risk.

> *"Maybe you do not pass the disease, but there is a chance of course. I do not know how fair it is to take that risk. It is sort of selfish." (P2)*

Another very important issue was concern whether pregnancy could be combined with the current medication. Participants were very aware of an increased risk of relapse if they would change their medication. Their expectation was that the period of pregnancy would be a difficult one, a period of great, unpredictable changes with potentially great consequences for their baby and themselves.

> *"For me pregnancy is also a bit scary, because of all the changing hormones: which effect will that have? And I have heard several stories of women who became psychotic again.*
> *It scares me, if that's the beginning of the birth of your child. (P7)*

Motherhood was not only seen as a major task in life but also as something that could be disrupting. Participants experienced their life with bipolar disorder as an ongoing struggle, and some of them doubted whether that could be combined with being successful as a mother.

> *"I am not so good in coping with stress. Stress is a trigger for me to get an acute episode again. And with children . . . . . (participant is thinking) that will be hard years." (P3)*

Women were anxious that one day their child would say that they had suffered from the bipolar disorder of their mother. An often-mentioned item was the fear that they would be unable to take care of their child during a future manic or depressive episode and worried who then should take care for their child.

> *"So when I get hospitalized again, who will take care of the child then? I cannot do it then, that's clear. And even if I have an adequate partner: it will be hard for him too." (P15)*

Considerations related to the support of partner, family and friends:
Most of the participants mentioned that a good, stable relationship with their partner was essential for them in deciding whether or not to choose for children. The possibility of becoming a mother without a partner was not an option for most of them. The support of a partner, their families, and friends in caring for the child was seen as an essential condition.

> *"It depends on the relationships you have. If I can trust that my partner will take care of everything when I become ill again, together with family or friends, then I probably decide for pregnancy. But it will be difficult anyhow." (P3)*

Another participant mentioned:

> *"Being a mother... I think I cannot handle this alone: being a mother as a woman with a bipolar disorder. With a stable partner I will manage....." (P6)*

Participants feel the responsibility to make arrangements with family and friends who can support in case they will have an episode.

> *"I have responsibilities, for myself, for my child, but also for my family and friends. They should know what should be done when I am in a depressive or manic mood again... Then one person can do this and another can take care of that...(P11)*

Considerations related to the support and care of their regular treatment team:
A stable and trustful relationship with professionals of their regular treatment team and continuity of care were mentioned as very important. To know that ongoing support is available at any moment during pregnancy and motherhood is important.
"I think professional care is important, as prevention, for people like me with so

many years of treatment. I still need professional help in some way, also for the benefit of the child." (P1)

A place where information and support could be shared about all problems and concerns associated with pregnancy and motherhood when having bipolar disorder was seen as useful by most of the participants.

Expectations about information and support by their treatment team

Items of needed information

Themes about which the participants wanted to be informed were the heritability of the disorder and the risk of passing bipolar disorder to their offspring, risks of their current medication during pregnancy, and possible solutions when problems would occur in the future. They knew that bipolar disorder has a high heritability and would like to know facts about the risk to pass the illness on, translated to their personal situation.

> *"I thought about that and looked for information. I was interested: if I would become a mother, what's the chance the baby has bipolar too? About 10%? Or was this the percentage when my partner also had the disease? Yes, I did check it!" (P14)*

Most of the participants knew something about the risks of using medication during pregnancy, but still had many questions: about risks of specific medications, about the dosage of medications, and about the frequency of monitoring medication during pregnancy and after childbirth.

> *"I read something about it: that indeed you should visit the psychiatrist more often. You need to be monitored better, and the medication should be lowered." (P12)*

They were worried about the possible effect of medication on the development of the fetus and about a possible relapse if the advice would be to lower or stop certain medications during pregnancy. Many would like to discuss at an early stage all possible scenarios in order to make a concrete plan in case things went wrong during pregnancy or after childbirth. Having this opportunity would facilitate to make decisions about pregnancy and motherhood.

> *"I did talk to her [i.e., the professional] about it, and she said that during the process of pregnancy, that I should tell her when I would think about becoming pregnant. And she would guide me." (P5)*

Support: how and when

Most participants wanted an open discussion with the professionals of their treatment team about family planning, at a relevant moment in the childbearing age.

> *"I am curious about what she [i.e., the professional] thinks about this theme. She knows me for a long time now. She often helps me to get my own thoughts more clear. So how will it be to discuss this?" (P1)*

Regardless of whether or not there was an actual desire to have children, such a conversation was considered necessary and useful, although some women mentioned their reluctance to discuss such highly personal issues. This conversation should preferably take place during a euthymic period, and initiating it was seen as a shared responsibility of themselves and the treatment team.

> *"According to me, we both have a responsibility: we have been working together for a long time now, and my psychiatrist is a kind of certainty for me.... He should not only think about the illnesses I have, but also about the phase of life I am in. If there is no attention for this, then there is no treatment." (P10)*

Several participants had experienced that the professional took the initiative to discuss this theme, which was often felt as an invitation. It gave them hope and a feeling of collaboration to have the possibility to talk about their considerations, questions and concerns. Apart from facts, participants wanted personal opinions. Some were expecting an independent professional opinion. Still, it was clear to them that it would be their own decision to choose or not choose for pregnancy.

> *"I do want to know what my treatment team thinks about it, because we know each other for so long. But finally their opinion is not that important: it is not because of the opinion of someone else, even if it is your therapist, that you decide to become pregnant or not." (P1)*

Information about bipolar disorder and family planning in a leaflet was highly appreciated; some found or received such information, others missed written information.

The desired attitude of the professional was described as asking, being informative, supportive, understanding, and not judgmental.

> *"For me it is very important that the professional asks questions, gives information and is not being suppressive." (P11)*

DISCUSSION

We studied the considerations and expectations of women with bipolar disorder in childbearing age about family planning and pregnancy. With regard to bipolar disorder there were concerns about the heritability of the illness, questions about current medication during pregnancy, and fear of relapse if that medication would have to be changed. Pregnancy was seen as a time of increased risk, both for the unborn child and themselves. Living with bipolar disorder was an ongoing struggle for several patients, and they worried about how this would be when being a mother. A frequently mentioned concern was being unable to care for a child during a future depressive or manic episode. Support from their partner, family, and friends in caring for a child was considered of vital importance. This was also true for a stable and trustful relationship with professionals of the treatment team. Participants expressed their expectations about what kind of information they needed: about the heritability of the illness medication, and possible extra support during future episodes. An open and thorough discussion with professionals of their treatment team about family planning, even before there are actual plans for pregnancy, was desired, and it was perceived as a shared responsibility to initiate this. The required and most helpful attitude of the professional was described as: asking, being informative, supportive, understanding, and not judgmental.

The results of our study show that family planning and pregnancy are important issues for women with bipolar disorder which raise a broad spectrum of thoughts and considerations. Some of these are recognizable as common considerations for women in the childbearing age, but these are easily overshadowed by considerations and concerns which are associated with having bipolar disorder. Our study reveals how important the initiative and the attitude of the treating professional is, to discuss these issues with the patient and her partner. Such a conversation should refer to all aspects of family planning and pregnancy, and not be restricted to issues about having bipolar disorder. Although this was not part of our study, from our clinical experience we consider it important to involve the partner in these consultations.

A review by Seeman (2004) addresses ethical issues in the treatment of mothers with schizophrenia, related to maternal psychosis. It is recommended that a professional should explore the implications of the illness and all questions about family planning and of motherhood both with each woman individually, and

with her partner and family, since the patient's decisions are influenced by the important people in her life. The independent opinions of women should be a starting point. In caring for mentally ill mothers one should meet patients, family, and other involved professionals in order to ensure fully informed decisions about family planning, pregnancy, prevention and treatment of postpartum psychosis, and parenting skills.

Griffiths et al. (2008) and Lavender et al. (2010) studied the experiences of women with diabetes mellitus who became pregnant. Women spoke about the pregnancy with professionals of their regular multidisciplinary treatment team. Some received preconception counseling and felt anxious afterwards. Lavender et al. (2010) described how women reported that their pregnancy at moments was overshadowed by having diabetes. For the involved professionals it was a challenge to find a balance in discussing the usual aspects of pregnancy versus specific issues of being pregnant while having a chronic disease. These women reported that it was very important to be primarily seen as a normal pregnant woman. In both studies some women had received preconception care in hospital-based clinics, which was, for most of them, no guarantee for finding the support they had wished. These experiences are consistent with the results of our study. Despite receiving guidance, some women did not feel appropriately supported.

The attitude of the professional is perceived as very important. Our study shows that being informative, supporting, and not judgmental, is highly appreciated. In various guidelines for the treatment of bipolar disorder (Howard et al, 2014; Kupka et al, 2015; SIGN 2012) recommendations are given to professionals about topics that should be discussed with women who express a desire to have children. The participants in our study agreed with these topics, but also made clear that the conversation itself was important, regardless of whether they would become a mother in the near future.

Some participants had contacted a POP team (Dutch model for collaboration between Pediatric, Obstetrical and Psychiatric care), and were positive about the expertise and information they received. Such a team offers preconception counseling for women with psychiatric problems. They and their partners are informed and supported about various issues related to family planning and pregnancy, after which a pregnancy plan is made. This facilitates early recognition of women at increased risk for (multiple) psychiatric problems during

or after pregnancy. The effects of this collaborative care model deserves future study (De Waal et al. 2010).
Participants in our study reported their concerns about relapse during pregnancy, but relapse after delivery were less mentioned. It is important to inform patients about risks of relapse both during pregnancy and in the postpartum period, as recommended in the already mentioned guidelines. Ongoing alertness about adequate information, repeatedly given at the right moment is important. The participants in our study were not yet pregnant. It is known that pregnant women are primarily focused on their pregnancy and delivery. Thoughts, expectations, and concerns about the postpartum period often only become to awareness after the child has been born (De Boer and Zeeman, 2008). This implies that information about possible postpartum problems should be given already before and during pregnancy, and again early in the postpartum period. Still, in all of these discussions, there should be enough room for the usual, non-psychiatric, aspects of pregnancy, delivery, motherhood, and the first months post-partum.

Strengths and limitations of the study
The study sample was diverse since participants were living in urban and rural parts of The Netherlands, and the participant's ages ranged from 28 to 41 years. Five of the 15 participants did not have a desire to have children at the time of the interview. Data saturation was achieved: after the 12th interview no more new information emerged. The participants were asked after the interview whether they had additions to their text: no additions were made.
Since coincidentally only women with bipolar I disorder were included, our findings may only refer to women who have the past experience of severe mania. Therefore, a limitation of our study is that no experiences of patients with bipolar II disorder or bipolar disorder NOS were obtained. In addition, in general, results in qualitative research, with a relative small sample, cannot be generalized to the entire population, in this case to all women with bipolar disorder. Another limitation is that all women were interviewed by one interviewer, which entails a risk for bias. Therefore, our research team had repeated discussions about the process of data collection and the data analysis to improve the confirmability of the study. Peer debriefing was done to prevent researcher bias.

Practice implications:
In addition to what is recommended in guidelines, family planning and pregnancy should be explicitly discussed with every woman with bipolar disorder in childbearing age, together with her partner. An open invitation by the professional to talk about these highly personal issues, including heredity, and the use of medication, is helpful for patients. Women with bipolar disorder in childbearing age should be encouraged to express their thoughts and considerations about family planning. This is an important role for nurses. Mental health professionals should be alert to provide education to other involved professionals (for example obstetricians, gynecologists) when necessary. The attitude of professionals should be supportive, informative, and not judgmental.

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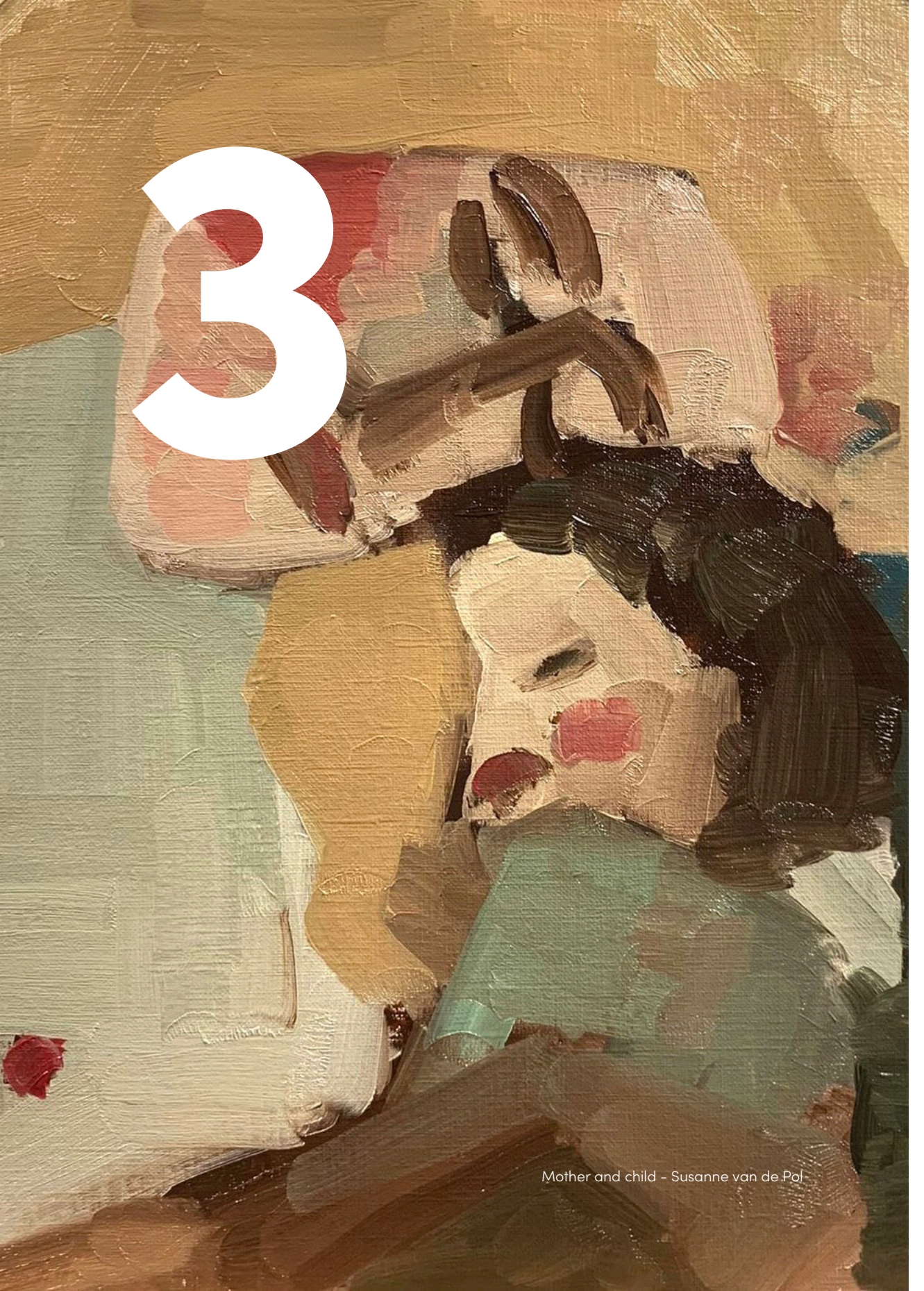

Mother and child - Susanne van de Pol

Chapter 3

Risk of recurrence of mood disorders during pregnancy and the impact of medication: A systematic review

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ABSTRACT

Background
Mood disorders may be difficult to treat during pregnancy. There is still lack of proof whether pregnancy influences the natural course and whether continuation of pharmacotherapy, despite potential risks for the unborn child, is beneficial in preventing recurrence of mood episodes during pregnancy.

Methods
Pubmed, PsycINFO, Embase and Cochrane databases were searched up till January 9th, 2018. This review has been conducted according to the PRISMA guidelines. Recurrence rates and different measures of risk were calculated. Results: Out of 1387 articles from an initial search 22 studies met the inclusion criteria. Included studies reported a wide variation in the recurrence rate of bipolar disorder and major depressive during pregnancy (BD: mean = 24%, range = 4-73%; MDD: mean = 8,3%, range = 1-75%). Observational data showed a relative risk reduction of maintenance therapy during pregnancy of 66% in women with BD and 54% for women with MDD, a significant difference (95% CI 9.4-14.6; $p<0.001$).

Limitations
Heterogeneous samples, study designs, and reported outcomes in included studies.

Conclusions
Despite the importance of the topic there is a paucity of evidence on recurrence of mood episodes during pregnancy among women with MDD or BD. Unlike the impact of the postpartum period, it is still uncertain whether the course of mood disorders is influenced by pregnancy.
Non-randomized studies show that maintenance pharmacotherapy during pregnancy in women with mood disorders significantly ($p<0.01$) reduces the risk of recurrence.

INTRODUCTION

Women with bipolar disorder (BD) or major depressive disorder (MDD) who want to become pregnant often have pressing questions about the prognosis and treatment during pregnancy. First: what is the risk for recurrence of mood episodes? Second: should medication be continued or discontinued?
Although some studies suggest that pregnancy may protect against symptoms of BD (Kendell et al ,1987; Kendell, Rennie et al., 1981) or MDD (Vesga-Lopez et al., 2008), other studies suggest that pregnancy is a risk factor for recurrence of an episode of BD (Freeman et al., 2002) and for recurrence of MDD in women with a history of MDD (Stewart, 2011). However, there is a paucity of evidence on the rate of recurrence of BD during pregnancy (Salim et al., 2018) and to the best of our knowledge there are no published data on the recurrence of MDD during pregnancy were not published. It is therefore still uncertain whether the course of mood disorders is influenced by pregnancy.
Evidence on the course of mood disorders in the postpartum period is more robust. In a recent meta-analysis 5105 deliveries in 3495 patients with BD were examined resulting in a recurrence rate in the postpartum period of 37% (Wesseloo et al., 2016). The prevalence of postpartum depression differs across countries from 8% in Europe to 26% in the Middle East (Shorey et al., 2018). Gavin et al. (2005) differentiated between minor and major depression and found prevalence rates of 19% for minor and 7% for major depression. Although the prevalence rate for postpartum depression is roughly the same in women with or without a history of MDD (Shorey et al., 2018), women with a previous postpartum depression have an increased risk for developing another postpartum depression. Indeed, a Danish nationwide, population-based cohort study reported that women who had been treated with antidepressants after their first childbirth had a 27 and 46 times higher recurrence rate of postpartum depressive episodes following a second child birth, in comparison to women who had never been treated with antidepressants after their first childbirth (Rasmussen et al., 2017). Also, having a previous mood episode during pregnancy is one of the known risk factors for development of postpartum mood disorders in established BD and in MDD (Howard et al., 2014; Jones et al., 2014; Norhayati et al., 2015).

BD and MDD, both untreated and (medication) treated, have been associated with negative pregnancy outcomes. In a population-based study (Boden et al.,

2012), BD in pregnant women was associated with increased risks of adverse pregnancy outcomes. Untreated (n=554) and (medication) treated (n=320) women with BD were compared with all other women giving birth (n=332137). The risk of preterm birth in both treated and untreated bipolar women was increased by 50%. Also, induced deliveries or planned caesarian sections occurred more often among women with BD. A recent systematic review (Gentile, 2017) revealed that untreated MDD and even symptoms of depression (without fulfilling the criteria of MDD according to DSM IV) may have harmful effects on the developing fetus (hyperactivity; irregular fetal heart rate), newborn (increased cortisol and norepinephrine levels; increased rates of premature deaths), and child (increased salivary cortisol levels; internalizing and externalizing problems). Mitchell and Goodman (2018) systematically reviewed the literature on comparative effects of women with MDD who were treated with antidepressants during their pregnancy and women with MDD who did not receive any antidepressants. They found no difference in negative birth outcomes.

Clinicians should be well informed about the course of mood disorders during pregnancy and the consequences of continuation versus discontinuation of pharmacotherapy. Only then it will be possible to share this information with the pregnant woman and her partner and to weigh the risks and benefits of either decision (Scrandis, 2017).
However, evidence on the course of mood disorders in women with BD or MDD during pregnancy is sparse, and even recent treatment guidelines (National Institute for Health and Care Excellence, 2014; Scottish Intercollegiate Guidelines Network, 2012; Dutch Multidisciplinary Guideline for Bipolar Disorders, 2015) give little information on the course of mood disorders during pregnancy. Moreover, the influence of medication during pregnancy is still unclear.

Hence, the aims of the present study are to systematically review the literature to determine the proportion of pregnant women with BD or MDD who experience a recurrence of any mood episode (including all depressive, hypomanic, manic or mixed episodes) according to Salim et al. (2018), and to assess the risk of such recurrence due to discontinuing medication immediately prior to or during pregnancy (within 6 months before pregnancy to 16 weeks gestation).

METHODS

Literature search

The initial systematic literature search was performed on Jan 09, 2018, in Pubmed, Embase, PsychInfo, and Cochrane, using the search terms "bipolar", "major depressive disorder", "pregnant", "course". The reference lists of the found articles were also carefully examined.

Selection of studies

The selection procedure was conducted according to the PRISMA guidelines (Liberati et al., 2009). Studies were eligible for inclusion if they were written in English, published in a peer-reviewed journal, if patients were diagnosed with BD or MDD prior to pregnancy according to DSM criteria, ICD criteria or the Research Diagnostic Criteria (RDC), and if information about the course of mood disorder was given. All longitudinal study designs (cohort studies, randomized controlled trials and birth register studies) were suitable for inclusion. No limits were set on date of publication.

Two reviewers (AS, PG) independently screened all articles on title and abstract. The resulting full text articles were then independently reviewed by the two reviewers and any discrepancies where resolved by consensus.

Data extraction and analysis

Data were extracted independently by two reviewers (AS and PG), using a data collection worksheet developed for this review. Study design, study population, sample size, medication (dis)continuation, diagnostic and assessing course instruments, recurrence rates and timing of medication discontinuation were extracted. Reviewers were not blind to authors, institutions, or journals. In case of difference in assessment a decision was made by consensus. If no consensus could be reached, a third reviewer (EK) was asked to help making a decision. Polarity of the mood episodes has been reviewed elsewhere (Salim et al., 2018). Recurrence rates were calculated for the BD and MDD studies. Relative risks and relative risk reductions were calculated for the different medications that were described in the included studies. Given the nominal measure of recurrence of an episode, chi-square tests were used to determine the relationship between maintenance therapy and recurrence. All calculations were done with a statistical calculator for Windows (MedCalc).

Assessment of quality

Two authors (AS, PG) independently assessed the methodological quality of the included studies using a predefined checklist based on the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies (EPHPP). The EPHPP quality assessment tool has been identified as one of the most appropriate for assessing non-RCTs as well as RCTs (Deeks et al., 2003; Thomas et al., 2004). The Cochrane Public Health Review Group recommended its use in public health and health promotion studies.

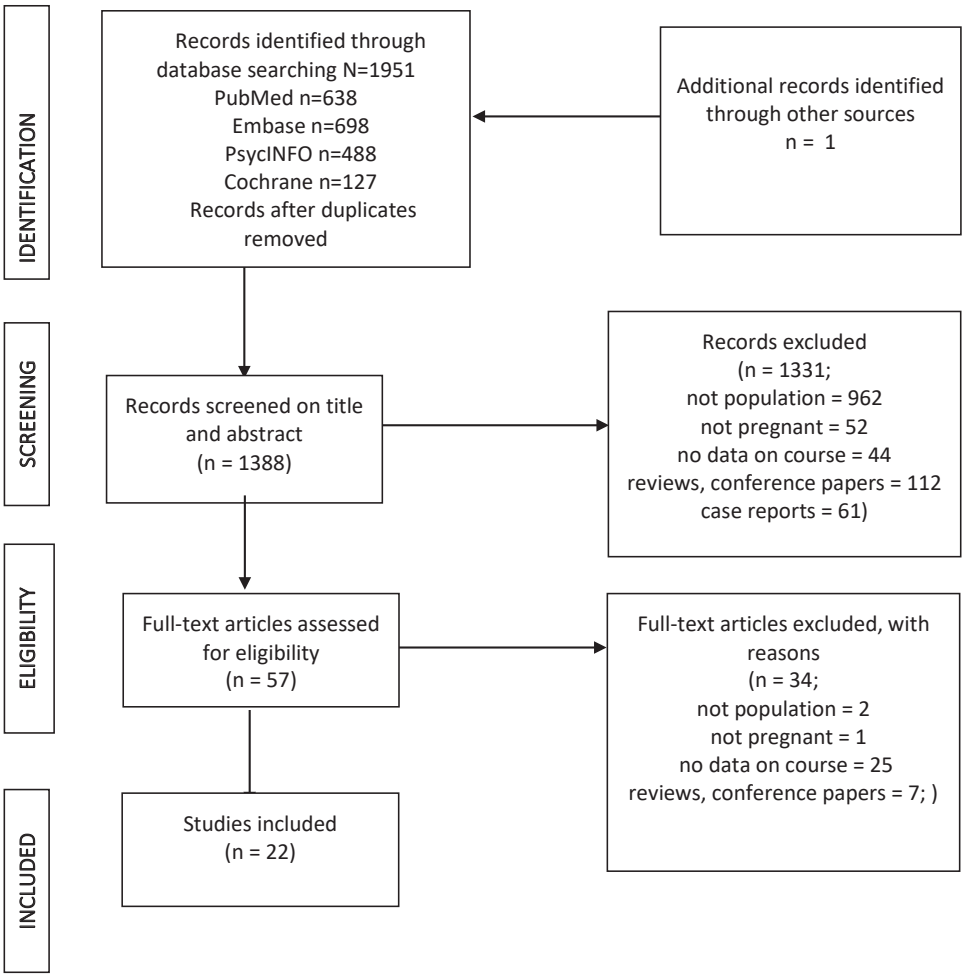
Each paper was scored on a three-point scale (weak, moderate, strong) on seven components of the study: study design, selection bias, confounders, blinding, data collection methods, analysis, and withdrawals and drop-outs. According to the number of 'weak' subscores an overall score of weak, moderate, or strong was given.

RESULTS

Selection of studies

The literature search resulted in 1951 papers. After de-duplication, this set was narrowed to 1387 articles. Based on title and abstract, further selection resulted in an initial set of 57 articles. After full-text assessment of these 57 articles, 22 studies met the inclusion criteria and were included in this systematic review (Fig 1).

Figure 1. Flowchart of article selection process



A total of 14 studies examined the course of BD during pregnancy (Akdeniz et al., 2003; Bergink et al., 2012; Blehar et al., 1998; Deiana et al., 2014; Freeman et al., 2002; Grof et al., 2000; Newport et al., 2008; Rosso et al., 2016; Sharma et al., 2013; Uguz, 2017; van Gent and Verhoeven, 1992; Viguera et al., 2000; Viguera et al., 2007). Six studies examined the course of MDD during pregnancy (Cohen et al., 2006; Cohen et al., 2004; Goodman, Tully, 2009; Le, Perry, Stuart, 2011; Psaros et al., 2014; Yonkers et al., 2011), and 2 studies examined the course of both BD and MDD during pregnancy (Di Florio et al., 2013; Viguera et al., 2011).

Table 1. Study characterics

author	study design and description	study population	sample size	control group
Abdel Hay 2011	prospective observational	BD	n=83	no
Akdeniz 2002	retrospective	BD	n=72 women n=252 pregnancies	no
Bergink 2012	prospective open-label	BD I: 27; BD II: 14	n=41	31 cont/10 disc
Blehar 1998	retrospective cohort	BD I	n=51	no
Deiana 2014	retrospective caseseries	BD	n=12 BDI=11 BDII=1	7 cont/5 disc
Freeman 2002	survey retrospective	BD	n=50 BD I: 36; BD II: 13 BD NOS: 1	no
Gent van 1992	prospective cohort	BD	n=11	8 cont/8 disc
Grof 2000	retrospective	IGSLI database	n=28	n=33
Newport 2008	prospective observational study	Women with BD	n=26	10 cont/16 disc
Rosso 2016	prospective observational	BD I	n=18	no
Sharma 2013	prospective	BD II	n=37	
Uguz 2017	case serie	BD	n=8	no
Viguera 2000	retrospective cohort	BD I and II	n=42	n=59
viguera 2007	prospective observational cohort	BD I and II	BD I n=61; BD II n=28	27cont/62 disc
Cohen 2004	prospective cohort study	MDD in history	n=32	no
Cohen 2006	propsective naturalistic	MDD in history	n=201	136 cont/65 disc
Goodman 2009	prospective cohort	MDD	n=41	N=38
Le 2011	RCT	high risk for depression	n=112	CAU; n=105
Psaros 2014	open preliminary intervention study	MDD in history	n=12	no
Yonkers 2011	prospective cohort	MDD current or in history	n=778	no
Di Florio 2013	retrospective cohort	BD I, BD II, MDD	BD I n=980; BD II n=232; MDD n=573	no
Viguera 2011	retrospective cohorten, pooled data	BD I, BD II, MDD	BD I n=283; BD II n=338; MDD n=541	

Notes:
BD = bipolar disorder; MDD = major depressive disorder; DSM III = Diagnostic en Statistical Manual of Mental Disorders, third edition; DSM-IV = Diagnostic en Statistical Manual of Mental Disorders, fourth edition; CAU = care as usual; cont/disc = continuation/discontinuation of pharmacotherapy; NA = not available; ITT = intention to treat; AD = antidepressant; AP = antipsychotic

	diagnostic instrument	course instrument	RR study group	RR control	medication	quality EPHPP
	MINI	recurrence	34%		NA	weak
	NA	recurrence	4,40%		NA	weak
	NA	recurrence	24,40%		lithium +-	weak
	NA	DIGS	37,00%		NA	weak
	NA	recurrence	0%	20%	NA	weak
	SCID	struct clinical interview	50%		NA	weak
	DSM III	NA	25%			weak
	RDC	records and interviews		14%		weak
	SCID	recurrence	30%	100%	AD/ AP/ sedatives	weak
		recurrence	11%		lithium	weak
	SCID-I	recurrence	51%		54% no; 46% mono or combination	moderate
	SCID	recurrence	0%		AP	weak
	DSM-IV	recurrence	52%	58%		weak
	SCID	recurrence	37%	85%		moderate
	SCID-P	SCID-P, HDRS, CGI, BDI	75%		NA	weak
	SCID-P	SCID-P, HDRS, CGI	26%	68%	AD	moderate
	DIS	SCID/BDI	29,50%			weak
	CES-D	BDI	7,8% ITT	9,6% ITT		moderate
	MINI	recurrence	25%			weak
	CIDI	recurrence			AD	weak
	SCID	recurrence	BDI 8,6%; BDII 18,4%; MDD 11%		NA	weak
	DSM IV	recurrence	BDI and II: 22,7%; MDD: 4,62%			weak

Scales used: MINI = Mini International Neuropsychiatric Interview; SCID = Structured Clinical Interview for Axis ! Disorders; RDC = Research Diagnostic Criteria; CES-D = Centre for Epidemiological Studies Depression Scale; CIDI = Composite International Diagnostic Interview; DIGS = Diagnostic Interview for Genetic Studies; HDRS = Hamilton Rating Scale for Depression; CGI = Clinical Global Impressions Scale; BDI = Beck Depression Inventory;

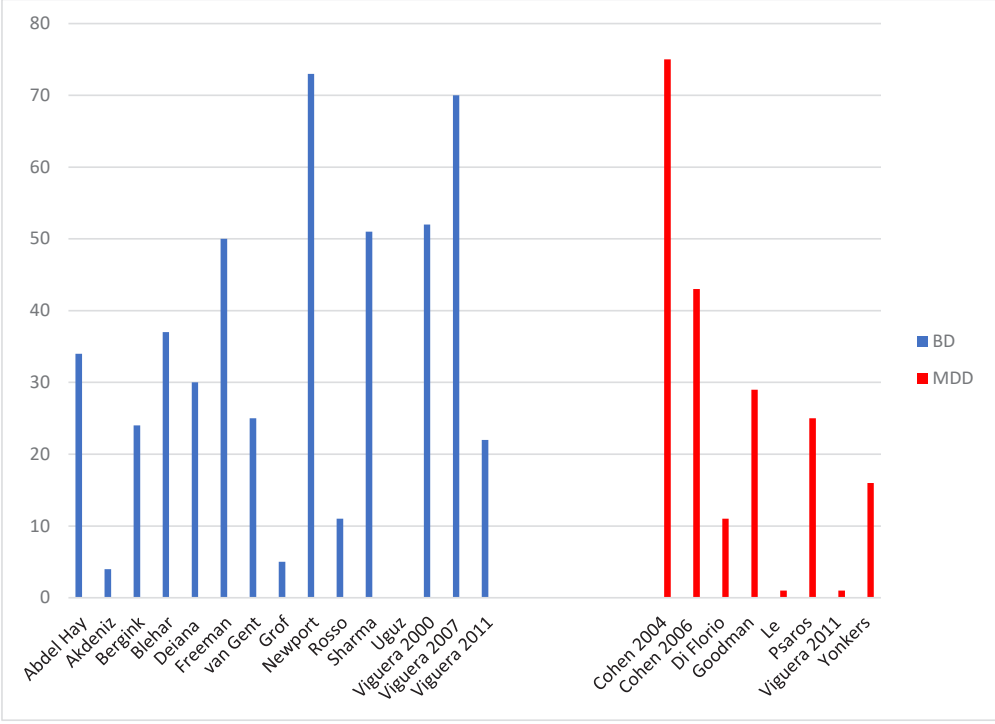
Quality assessment

None of the included studies met all quality assessment criteria. Five of the MDD studies had a prospective observational design (Cohen et al., 2006; Cohen et al., 2004; Goodman, Tully, 2009; Psaros et al., 2014; Yonkers et al., 2011) and one was a RCT (Le et al., 2011). Six of the BD studies had a retrospective design (Akdeniz et al., 2003; Blehar et al., 1998; Deiana et al., 2014; Freeman et al., 2002; Grof et al., 2000; Viguera et al., 2000; Viguera et al., 2011) and eight had a prospective design (Bergink et al., 2012; Newport et al., 2008; Rosso et al., 2016; Sharma et al., 2013; Uguz, 2017; van Gent and Verhoeven, 1992; Viguera et al., 2007). Both studies addressing MDD and BD together had a retrospective design (Di Florio et al., 2013; Viguera et al., 2011). Most commonly missed items were description of withdrawals and drop-outs (n = 16), adjustment for important confounding factors (n = 17), and information on blinding (n = 18).

First, the overall recurrence rates for BD and MDD during pregnancy are shown and thereafter we present the recurrence rates, relative risk and relative risk reduction comparing continuing and discontinuing medication in pregnancy among women with a mood disorder.

The outcomes of 3093 pregnancies in 2380 women with BD and of 2919 pregnancies in 2433 women with MDD were provided. In 587 (19%) of the 3093 pregnancies of women with BD a recurrence occurred, ranging from 0%-73% among studies. In women with MDD an episode occurred in 201 (8%) of 2433 pregnancies, with a range of 1%-75%. In the prospective BD studies the recurrence rate (17%) differed significantly from the recurrence rate in the retrospective BD studies (21%; 95%CI 1.4 to 7.0; p<0,003). In the MDD studies the recurrence rate in the prospective studies (17%) also differs significantly from the recurrence rate in the retrospective MDD study (5%; 95%CI 10.3 to 14.5; p<0.0001). (Fig.2).

Figure 2. Recurrence rate (%) in bipolar disorder (BD) and major depressive disorder (MDD) studies.



Bipolar Disorder

Six studies considered the role of medication use on the risk of recurrence of mood episodes during pregnancy in BD (Bergink et al., 2012; Deiana et al., 2014; Newport et al., 2008; van Gent and Verhoeven, 1992; Viguera et al., 2000; Viguera et al., 2007), and three in MDD (Cohen et al., 2006; Cohen et al., 2004; Psaros et al., 2014).

Lithium

In the studies investigating continuation or discontinuation of lithium (Bergink et al., 2012; Deiana et al., 2014; van Gent and Verhoeven, 1992; Viguera et al., 2000; Viguera et al., 2007), lithium was continued as maintenance therapy in 73 pregnancies and discontinued in 127 pregnancies. The recurrence rate in the maintenance group was 23% and in the discontinuation group 68%, with a relative risk of 0.34 and a relative risk reduction of 66%. Hence, by continuation of lithium during pregnancy in women with BD the risk of recurrence decreases with 66%.

When a chi-square test was performed to examine the relation of continuation or discontinuation of lithium and the recurrence rate of BD in pregnant women, a significant relation was found ($X2(1) = 35.89$, $p<0.005$).

Lamotrigine

The recurrence rate of maintaining lamotrigine during pregnancy in 10 women with BD was 30%, whereas the recurrence rate in 16 women who stopped mood stabilizers was 100%, with a relative risk of 0.30 and a relative risk reduction of 70% (Newport et al., 2008). When a chi-square test was performed to examine the relation of continuation or discontinuation of lamotrigine and the recurrence rate of BD in pregnant women, a significant relation was found ($X2(1) = 15.33$, $p<0.01$). Looking at all medication studies in BD, the recurrence rate was 24% with maintenance therapy and 71% without. The relative risk was 0.34 and the relative risk reduction 66%. When a chi-square test of independence was calculated comparing the recurrence rate of BD in pregnant women who continued or discontinued their medication, a significant interaction was found ($X2(1) = 47.16$, $p<0.01$).

Table 2. Recurrence rate medication studies in bipolar disorder

	Medication continuation (n)	recurrence (n)	Medication discontinuation (n)	recurrence (n)
Bergink et al. (2012)	31	6	10	4
Deiana et al. (2014)	7	0	5	4
van Gent et al. (1992)	8	1	8	3
Newport et al. (2008)	10	3	16	16
Viguera et al. (2000)			42	22
Viguera et al. (2007)	27	10	62	53
total	83	20	143	102
Recurrence rate		24%		71%
Relative risk	0.34 (95% CI 0.23-0.50)			
Relative risk reduction	66% (X2(1)=47.16, p<0.1)			

Major Depressive Disorder

In the MDD group only one study with a prospective observational design was suitable (Cohen et al., 2006) for calculating risk measures. Based on this study, the recurrence rate was 31% with maintenance therapy and 68% without, the relative risk was 0.46 and the relative risk reduction when medication was continued 54%. A chi-square test was performed and a significant relation was found ($X2(1) = 24.34$, $p<0.01$). Unfortunately, no information was given about the various

antidepressants used.
The relative risk reduction of 66% in BD is significantly higher compared to the relative risk reduction of 54% in MDD (95%CI 9.4 to 14.6; p<0.0001).

DISCUSSION

To the best of our knowledge this is the first systematic review calculating recurrence rates of mood disorders, relative risk and relative risk reduction of mood disorders with use of medication during pregnancy in women with bipolar and depressive disorders. Our study complements two recent reviews addressing the course of mood disorders during pregnancy (Larsen,and Saric, 2017; Salim et al., 2018).

Our findings suggest that recurrence rates of mood disorders are substantial in pregnancy, especially when women diagnosed with a mood disorder discontinue their maintenance medication (lithium or lamotrigine) in BD or antidepressants in MDD during pregnancy.
Newport et al. (2008) reported the only study that explicitly involved lamotrigine. Of 26 pregnant women, 10 women continued taking lamotrigine and 16 women discontinued taking mood stabilizers (lithium, valproate, lamotrigine). Relative risk of recurrence in the discontinuation group was much larger than in the lamotrigine group.
Studies considering continuation versus discontinuation of antipsychotics in BD are lacking.
We scored the quality of the included studies as weak to moderate according to the EPHPP, due to the observational designs in most studies and the lack of robust RCT's. Still, the recurrence rates of mood disorders in all medication studies that compared continuation of medication with discontinuation of medication during pregnancy point in the same direction: the recurrence rate of a mood episode is considerably higher when medication during pregnancy is discontinued. These findings suggest that pregnant women with BD or MDD who continue their maintenance medication have a significant lower risk of recurrence of the illness. However, these studies also have important limitations, which we will address later.
In the included studies, the range or recurrence rates of mood symptoms during pregnancy was broad, in women with BD 0-73%, and in women with MDD 1-75%. This could be due to the different study designs, the small sample sizes for most

studies, and the sampling method used. The difference in the recurrence rates between retrospective and prospective studies in BD and MDD was significant. In MDD prospective studies reported a significantly higher recurrence rate, whereas in BD the retrospective studies reported a significantly higher recurrence rate. Hence, given these limitations, it is not possible to draw firm conclusions with regard to the effect of pregnancy on the course of mood disorders during pregnancy other than that the risk of recurrence appears to be higher in pregnant women with BD (mean 19%) than in women with MDD (mean 8%).
There are numerous factors that could influence the recurrence of a mood disorder during pregnancy. Among those risk factors are a longer duration of illness and earlier age of onset, complications of pregnancy, unplanned pregnancies, prior hospitalization, shorter clinical recovery since last episode, and a prior history of MDD (Abdel-Hay et al., 2011; Raisanen et al., 2014; Viguera et al., 2007). In pregnant women with BD recurrence of depressive episodes is more prominent than recurrence of hypomania or mania (Salim et al., 2018).

Our study showed that discontinuation of prophylactic medication may be a risk factor for recurrence of mood disorder in pregnancy. An additional consideration is that recurrence risk is higher, and relapse occurs earlier, after rapid discontinuation of medication, e.g. within 14 days, whereas the risk of recurrence is lower after gradual discontinuation of medication (Viguera et al., 2007). This implies that such treatment decisions should ideally already be made before pregnancy.
Although our findings are based on the results of a limited number of mostly observational studies, the results of these studies all suggest that maintenance pharmacotherapy with a mood stabilizer (lithium or lamotrigine) during pregnancy reduces the risk of recurrence of a mood episode in women with BD significantly. Likewise, the study among women with MDD showed lower recurrence rates among pregnant women continuing their antidepressants. However, these findings should be weighted against possible teratogenicity of medication and the risk of obstetrical and perinatal complications due to medication. Patorno et al. (2017) recently showed in a large prospective cohort study that maternal use of lithium during the first trimester was associated with an increased risk of cardiac malformations (2.42% versus 1.15% in non-exposed infants and 1.39% in infants exposed to lamotrigine). Lamotrigine was chosen

for comparison because it is an effective treatment for bipolar disorder and has not been associated with an increased risk of congenital malformations. The magnitude of this effect was smaller than previously mentioned and dose-dependent (Andrade, 2018; Patorno et al., 2017). However, importantly, in a comment to Patorno et al. it is stated that these findings do not imply that lithium treatment should always be discontinued in women who are pregnant or willing to become pregnant (Di Florio et al., 2017). Maternal SSRI use in early pregnancy may slightly increase the risk of major malformations overall, and cardiac malformations in particular, over the background risk (Alwan et al.,, 2016). As the risk of recurrence of a mood disorder during pregnancy also has negative effects on fetal health (Boden et al., 2012; Heller et al., 2017; Munk-Olsen et al., 2018; Pearlstein, 2015; Scrandis, 2017; Wald et al., 2016) a careful risk/benefit analysis will be needed.

Given the considerable clinical significance of the subject, it is surprising that there is a paucity of systematic data on the effect of pregnancy on the course of mood disorder. It is even more surprising that the number of studies addressing MDD is smaller than those on BD, given the relative prevalence of these disorders. Two recent reviews state that no firm conclusions can be drawn on the influence of pregnancy on recurrence rates in women with BD (Larsen and Saric, 2017; Salim et al., 2018). Larsen & Saric reviewed the risk of recurrence when discontinuing treatment with mood stabilizers and stated that there is no consensus about the risks of discontinuation of medication during pregnancy among women with BD. Their review included eight studies, but reported no overall recurrence rates comparing continuation or discontinuation of maintenance pharmacotherapy during pregnancy. Our findings provide additional information as they show a significant positive effect of maintenance pharmacotherapy on recurrence rate in women with BD. However, recent literature about the influence of pregnancy on the course of MDD is sparse. Indeed, Altshuler et al. (1998) already stated that little is known about risk for relapse in pregnant women with histories of depression who discontinue their antidepressants, in contrast to this well described risk in non-pregnant women.
Moreover, there are no contemporary prospective studies of medication-free women with BD or MDD addressing the effect of pregnancy on the natural course of BD or MDD.

It is of interest that the more recent publications are prospective studies in which pregnant BD and MDD patients were treated with medication and have higher recurrence rates than reported in two larger retrospective cohorts (Abdel-Hay et al, 2011; Di Florio et al., 2013; Newport et al., 2008; Viguera et al., 2011). Unfortunately, the medication status of the pregnant women in these two retrospective cohorts is not reported.

Our review has several limitations. We included studies with different designs: prospective or retrospective, and with or without medication. The course of MDD or BD was not assessed uniformly among studies. Furthermore, most of the studies were done in specialized perinatal clinics. Assuming there is more expertise in these clinics than elsewhere it is likely that women with a more severe illness are referred to these clinics. Also, not all studies on BD differentiated between BD I and BD II, whereas BD II has been indicated as a risk factor for recurrence of mood disorders during pregnancy (Viguera et al., 2007). Moreover, in most studies the medication status of the BD and MDD women was not available. Most of the studies only mentioned recurrence or no recurrence. And only some studies mentioned the polarity of the episodes in BD studies with depressive episodes more frequent than manic episodes. Although some studies used clinical interviews or formal assessment instruments, none of the studies used a daily mood-monitoring tool to assess the course of the mood disorder in more detail. Only some studies showed the timing of recurrence (first, second, or third trimester), but most did not. We found only one study comparing antidepressant continuation versus discontinuation in pregnant women with MDD (Cohen et al., 2006), while studies in women with BD only investigated continuation versus discontinuation of lithium and lamotrigine. Only some studies gave data on other risk factors for recurrence of a mood episode. Age of onset, illness duration, marital status, parity, history of mood episode in pregnancy might influence the recurrence rate (Di Florio et al., 2018; Viguera et al., 2011; Yonkers et al., 2011). These factors may confound the relationship between medication and recurrence rate of a mood disorder in pregnancy.

Despite these limitations our study has also several strengths: next to a thorough literature search and selection, we performed a quality assessment according to well-known quality assessment tools and have performed calculations of risk

measures.

Implications for practice
To reduce negative pregnancy outcomes and optimal outcomes of the offspring, from a psychiatric perspective the major goal in treatment of women with mood disorders is to preserve a euthymic state during pregnancy. Therefore it is important for clinicians to provide as early as possible, and preferably before pregnancy is planned information of an estimated risk of recurrence of mood disorder during pregnancy, whether or not to continue medication, and discuss the potential effect of the illness on the unborn child contrasting the possible negative effects of continuing medication on the unborn child. In case of a positive pregnancy wish the couple in close consultation with the clinician should then weigh the risks of continuing versus discontinuing medication in view of recurrence of the illness and negative outcomes on the fetus.

Recommendations for future research
Studies on recurrence rates of mood episodes during pregnancy should preferably make use of instruments that continuously assess mood during pregnancy, e.g. a daily mood monitoring tool such as the Life Chart Method (LCM)(Leverich et al., 2001), mood diaries, or at least monthly monitoring instruments. Especially registration with LCM facilitates a more detailed description of severity, duration and frequency of mood episodes.
Given the importance of the topic and the high prevalence of MDD among women, we recommend future research on medication in pregnant women with MDD or women with (a history of) MDD who plan to become pregnant. Large, multicenter, prospective studies are needed to answer the question whether continuation or discontinuation of antidepressants during pregnancy in women with MDD is recommendable. Unfortunately, randomized clinical trials are not feasible due to obvious ethical considerations.

CONCLUSION
There is limited evidence on the recurrence rate of BD and especially MDD during pregnancy. Whether pregnancy influences the course of mood disorders still remains an unanswered question. Still, our findings strongly suggest that continuing pharmacotherapy during pregnancy reduces the risk of recurrence of

mood episodes in women with BD or MDD significantly.
Clinicians should inform the pregnant woman and her partner about the complex risk/benefit analysis between teratogenic risks of medication versus risk of recurrence of mood disorders and create the opportunity for shared decision making consistent with individual needs and preferences.

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4

Chapter 4

The effect of sleep disturbance during pregnancy and perinatal period on postpartum psychopathology in women with bipolar disorder (study protocol)

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ABSTRACT

Background

Postpartum psychosis is a severe condition that usually requires hospital admission as result of the highly disturbed behaviour with potential risks for the mother and her newborn child. Women with bipolar disorder have a high risk of relapse related to childbirth, with up to 67% experiencing an episode in the postpartum period, including psychosis.

There is much evidence for a relationship between sleep disruption and mood disorders in the perinatal period. Sleep loss has been suggested as a final common pathway in the development of psychosis in vulnerable women, i.e., women with bipolar disorder or a history of psychosis after childbirth. Prospective studies monitoring sleep and mood are scarce.

The purpose of this study is to investigate the relationship between sleep disruption during pregnancy and the perinatal period and postpartum psychopathology in women with bipolar disorder.

Methods/Design

This is a prospective, observational, naturalistic, non-intervention study in pregnant women with an established diagnosis of bipolar disorder.

The period of observation will be from week 13 of pregnancy until 12 weeks postpartum.

Mood changes will be assessed using the LifeChart methodology throughout the whole study period. Sleep patterns will be assessed by a sleep diary and actigraphy in week 13 and week 26 of pregnancy and from two weeks before the expected delivery until four weeks after.

Data will be collected on demographics, diagnosis, medical history, clinical management, clinical, functional, and obstetrical outcomes. In the weeks mentioned before additional data on mood and life-events will be collected.

Primary outcomes are the occurrence of psychiatric symptoms during the first four weeks postpartum, and the number and type of any intervention started for impending psychiatric symptoms during the first four weeks postpartum.

Discussion
We hypothesize that sleep disturbances during pregnancy and the perinatal period is associated with increased postpartum psychopathology. If so, intervention strategies aimed to improve sleep patterns may decrease the risk for postpartum psychopathology in women with bipolar disorder or a history of postpartum psychosis. Early treatment of sleep disturbance could be a cost-effective method for the prevention of postpartum mood disorders.

This research protocol was approved by the Medical Ethics Review Committee of the VU University Medical Center (2012/3)

Keywords
Bipolar disorder, postpartum psychosis, sleep, pregnancy

BACKGROUND

Bipolar disorder is a severe recurrent psychiatric illness with an estimated lifetime prevalence of 1.5-2% [1,2]. The disorder typically begins in adolescence or early adulthood and is a lifelong condition characterized by high relapse rates, persistent subsyndromal morbidity and functional impairment, comorbid anxiety and substance use disorders, and premature mortality mainly due to suicide or somatic illness [3,4].
Treatment of women with bipolar disorder during pregnancy and in the postpartum period is a major challenge. Decisions must be made about whether or not to take psychiatric medication while pregnant and after delivery, weighing the risks for the mother and the (unborn) child. Especially the postpartum period is associated with an increased risk for the onset or exacerbation of bipolar disorder [5-7] and maternal death [8]. Viguera et al. [9], studying 479 pregnancies in 283 women with bipolar disorder, found that in 52% a mood episode occurred in the postpartum period. They did not investigate subsyndromal symptoms. Death caused by psychiatric illness (through severe self-neglect or suicide) is highest for women in the year following delivery [10,11]. In the first two weeks postpartum the risk of having an illness episode is highest: 25-30% despite ongoing medication, and up to 70% without medication [12,13].
Postpartum psychosis affects 1-2 per 1000 women in the postpartum period [5].

Women with bipolar disorder have a high risk of recurrence related to childbirth, with up to 67% experiencing a mood episode in the postpartum period [14,15]. The relative risk of hospital admission for bipolar disorder during the first month postpartum is 23 [16], which is four times higher than the relative risk for schizophrenia in that period. Women with bipolar disorder are at increased risk for developing postpartum psychosis as are women with a history of postpartum psychosis [15,17-19]. Other risk factors for postpartum psychosis include genetic predisposition, primiparity, medical complications during pregnancy or delivery, and psychological stress [5,20-24]. Symptoms of postpartum psychosis may occur within days after delivery [25].

Postpartum psychosis imposes a heavy burden on the woman, her spouse and their child(ren), and may have negative long-term consequences such as impaired mother-child bonding, child abuse, suicide, and infanticide [15,26-28].

Sleep disruption and mood disorders are highly associated. There is a significant temporal relationship between sleep disruption and mood changes, especially between loss of sleep and the occurrence of a hypomanic or manic episode [29]. Alterations in sleep often predict a worsening in clinical state, and in turn sleep worsens further during an illness episode [30]. Sleep reduction has been postulated as a final common pathway in the onset of mania [31]. A recent review suggests that sleep disturbances frequently precede the onset of bipolar disorder by years and could be a long-term risk factor for any kind of mood disorder [32]. Instability of the circadian system has been hypothesized as a core vulnerability for bipolar disorder and there is evidence that this vulnerability is also present in euthymic patients [1,18,33,34]. In patients with bipolar disorder short sleep duration (< 6 hours/day) was associated with more severe symptoms, and both short and long (> 9 hours/day) sleep duration were associated with poorer functioning and quality of life [35].

A systematic review by Ross et al. [36] indicated a significant interaction between sleep disruption and perinatal mood disorders. They suggest that preventing or treating sleep disturbance could be a cost-effective method for the prevention of postpartum mood episodes in women at risk. The authors stated that studies measuring both sleep and mood during the perinatal period will provide important information about causes, prevention and treatment of perinatal mood disorders. Only few studies assessed sleep disturbances in detail. One prospective study [37] found no difference in sleep-wake rhythm between women

with bipolar disorder and healthy women. However, that study was limited by the small sample size of 23 patients and 15 controls.
Women with subsequent postpartum psychosis may have had a longer duration of labour and were more likely to deliver at night than controls [23,38]. Sleep loss has been suggested as a final common pathway in the development of psychosis in vulnerable women [39]. Treatment guidelines [40-43] do not consider the possible importance of delivery during daytime. Furthermore, in clinical practice it is assumed that, in addition to sleep disruption, psychiatric symptoms during pregnancy are a risk factor for the subsequent development of postpartum psychopathology. To our knowledge this clinical impression has not been investigated prospectively.
In this article we describe a study protocol investigating the impact of altered sleep patterns during pregnancy and the perinatal period in women with bipolar disorder. We set out the following research questions to answer.
1. Do sleep disturbances during pregnancy and/or in the perinatal period predict postpartum psychopathology in women with an established diagnosis of bipolar disorder.?
2. Do (subsyndromal) symptoms of bipolar disorder during pregnancy and/or in the perinatal period predict postpartum psychopathology?
3. Is there an association between the use of psychotropic medication during pregnancy and the perinatal period and a decreased risk of postpartum psychopathology?
4. Do depressive symptoms during pregnancy and the postpartum period, as measured by the Edinburgh Postnatal Depression Scale, adequately predict any postpartum psychopathology in a population of pregnant women with bipolar disorder?

METHODS/DESIGN

Methods

This is a prospective, observational, naturalistic, non-intervention study. Pregnant women with an established diagnosis of bipolar disorder will be monitored prospectively during pregnancy and the postpartum period until 12 weeks after delivery. Treatment will be given as usual, i.e., as decided by the treating psychiatrist; and there will be no additional interventions as part of the study.

Study population

The study population consists of pregnant women with an established DSM-IV diagnosis of bipolar disorder as confirmed with a structured diagnostic interview. An estimation of the required number of participants (table 1) is based on various sources of information [44,45]. These sources provide a yearly estimate of 592 women with bipolar disorder receiving treatment in a mental health facility in the Netherlands who become pregnant.

Table 1. Estimated potential number of participants

Age	Prevalence of bipolar disorder [45]	Pregnancies/year [44]	Bipolar and pregnant/ year	Contacted mental health [45]	Potential participants in study/year
18-24	3.9%	17834	695		
25-35	1.0%	119944	1199		
35-44	0.5%	44391	221		
Total 18-44			2115	28%	592

Inclusion and exclusion criteria

Eligible participants are pregnant women, age ≥18 years, with less than 12 weeks of pregnancy (first trimester), and with a diagnosis of bipolar disorder type I (296.xx), II (296.89) or NOS (296.80) according to DSM-IV-TR. All participants are currently under outpatient psychiatric treatment. Women will be excluded if they (1) are unable to complete the survey; (2) do not give informed consent; (3) have a current severe substance abuse.

Sample size

We based the sample size calculation on a regression analysis of postpartum psychopathology on sleep disturbances and a group of five confounders. We have to make some assumptions (see Cohen, 1988, chapter 9), and suppose that the group of five covariates (A) predicts postpartum psychopathology (Y) to a level R2Y.A = 0.10. We further assume that sleep disturbance (B) has a medium effect size d = 0.5, which corresponds to a (semi partial) correlation r = 0.243 or, equivalently, to a squared multiple partial correlation R2YB.A = R2Y.A,B – R2Y.A = 0.06, which corresponds to the effect size index f2 = (R2Y.A,B – R2Y.A)/ (1 –

R2Y.A,B) = 0.071. Applying Table 9.4.2 (see Cohen, 1988, chapter 9) we find that under these assumptions we need n = 114 respondents.

Recruitment

The inclusion period will be 3 years. The need for a sample of 114 respondents implies that 38 respondents should be recruited yearly, corresponding to 6.4% (38/592) of the estimated potential number of participants in the Netherlands. Participants will be recruited from all over the Netherlands through psychiatrists, especially those who relate to the Dutch Foundation for Bipolar Disorders (KenBiS) or the Dutch Association for Psychiatry and Pregnancy (LKPZ), the Paediatrician, Obstetrician and Psychiatrist (POP)-outpatient clinics, and through the Dutch Patient Association for Bipolar Disorder (VMDB).

Measures

At inclusion demographic data, medical data en psychiatric history will be assessed. The Questionnaire for Bipolar Disorders (QBP), an extensive questionnaire addressing demographics and various aspects of bipolar illness history will be completed by the treating psychiatrist (part I) and the patient (part II) [46,47] (table 2).

The diagnosis of bipolar disorder will be confirmed with the MINI International Neuropsychiatric Interview [54]. Current symptomatic and functional status will be assessed with the Edinburgh Postnatal Depression Scale (EPDS) [48], the self-rated Quick Inventory of Depressive Symptomatology (QIDS-sr) [49], the Altman Self-Rating Mania Scale (ASRM) [50], and the Functioning Assessment Short Test (FAST-NL-P) [51].

The retrospective (last year before study entry) and prospective course of bipolar disorder will be assessed with a recently developed digital format of the LifeChart Methodology (LCM) [52].

During two separate weeks in pregnancy (week 13, 14, or 15 and week 26, 27, or 28) and from week 38 of pregnancy to week 4 postpartum patients will be asked to wear an actimeter and complete a sleep diary. On the first and the last day of week 13 and week 26 of pregnancy, weekly from week 38 of pregnancy until week 4 postpartum, and finally in week 12 postpartum the Edinburgh Postnatal Depression Scale (EPDS) and the Altman Self-Rating Mania Scale (ASRM) will be completed.

In week 13 (14 or 15), week 26 (27 or 28), and week 38 of pregnancy, and in week 4 and 12 postpartum all psychiatric and medical interventions (e.g. medication change, admission) and life-events of the preceding period will be recorded. During the whole study period (from inclusion to week 12 postpartum) any psychological or psychiatric intervention will be registered on an event form. Obstetric data will be collected from medical files in the first month postpartum. Apart from these diagnostic assessments, continuous mood charting, and periodic sleep monitoring, the study will not interfere with the ongoing treatment as decided by the treating psychiatrist since there are no therapeutic interventions as part of the protocol.
The following confounders and effect modificators will be assessed at baseline and during the study: marital status, age of onset of bipolar disorder, parity, number of previous mood episodes, and number of medications used during study period.

Table 2. Timeline and assessments potential number of participants

	Base line	Pregnancy, weeks							Postpartum, weeks				
T	T0	T1a	T1b	T2a	T2b	T3a	T3b	T3c	T3d	T3e	T3f	T4	T5
Pregnancy week		13-1	13-7	26-1	26-7	38	39	40	1	2	3	4	12
QBP-NL	x												
MINI	x												
FAST	x												
Medical history	x												
EPDS	x	x	x	x	x	x	x	x	x	x	x	x	x
QIDS	x	x	x	x	x	x	x	x	x	x	x	x	x
ASMR	x	x	x	x	x	x	x	x	x	x	x	x	x
Sleep diary actimetry		xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
Life events			x		x	x							x
Interventions			x		x	x							x
Obstetric data									x	x			
LifeChart	x	x	x	x	x	x	x	x	x	x	x	x	x
LifeChart retro 1 year	x												

Instruments

Questionnaire for Bipolar Disorder, Dutch Translation (QBP-NL)

The Questionnaire for Bipolar Disorder, Dutch translation is used to specify subtypes of bipolar disorder and its previous course fom onset until baseline. The QBP-NL was developed in a longitudinal study of the naturalistic course of bipolar disorder from the Stanley Foundation Bipolar Network and includes the demographics, psychiatric diagnosis and history, course of the illness characteristics, treatment history, factors influencing the onset and course of bipolar disorder, and family history of psychiatric disorders [46,47]. The questionnaire is divided into part A and B. The first part (21 questions) is completed by the clinician. The second part (40 questions) is completed by the patient.

Altman Self-Rating Mania Scale (ASRM)

The ASRM is a 5-item self-rating scale used in inpatient or outpatient settings to measure the severity of manic symptoms for clinical or research purposes [50]. It is compatible with DSM-IV criteria, and correlates significantly with Clinician-Administered Rating Scale for Mania (CARS-M), Young Mania Rating Scale (YMRS), and is sensitive to change.

Quick Inventory of Depressive Symptomatology (QIDS)

The 16-item Quick Inventory of Depressive Symptomatology (QIDS), a measure of depressive symptom severity derived from the 30-item Inventory of Depressive Symptomatology (IDS), is available in both self-report (QIDS-SR16) and clinician-rated (QIDS-C16) formats. The QIDS ratings include 16 items from the IDS-C-30 and the IDS-SR-30 to assess the nine DSM-IV core-criterion symptom domains during the past 7 days prior to assessment. Both the IDS and QIDS are easy to administer in either the clinician-rated (IDS-C30 and QIDS-C16) or patient self-report (IDS-SR30 and QIDS-SR16) versions. Both versions are sensitive to change, with medications, psychotherapy, or somatic treatments, making them useful for both research and clinical purposes. The psychometric properties of both the IDS and QIDS have been established in various study samples [49,53]. For the current study, the QIDS-SR is used.

Edinburgh Postnatal Depression Scale (EPDS)
The 10-question Edinburgh Postnatal Depression Scale (EPDS) is a valuable and efficient way of identifying patients at risk for perinatal depression. The EPDS is easy to administer and has proven to be an effective screening tool. The scale covers the previous week and a score above 13 indicates a depressive illness of varying severity. The EPDS score is not a diagnostic tool and a careful clinical assessment should be carried out to confirm the diagnosis of depression [48].

Functioning Assessment Short Test (FAST)
The Functioning Assessment Short Test (FAST) is a brief instrument designed to assess the main problems in functioning experienced by psychiatric patients, particularly bipolar patients. It comprises 24 items that assess impairment or disability in six specific areas of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time (59)

Mini-International Neuropsychiatric Interview (MINI)
The Mini-International Neuropsychiatric Interview (MINI) is a brief structured diagnostic interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the MINI. to the SCID-I for DSM-III-R and the CIDI for ICD-10. The results of these studies show that the MINI has acceptably high validation and reliability scores, but can be administered in less time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require a more extensive training [54].

Life Chart Methodology (LCM)
The Life Chart Methodology (LCM) provides a graphic representation of minor mood swings and major mood episodes and can be used retrospectively and prospectively [55]. A 1-year retrospective LCM gives an overview of the recent illness course (number, duration and severity of episodes), as well as treatment interventions (medication and psychosocial) and significant life events. A prospective LCM will be completed on a daily basis during the entire study period. Course of illness parameters (number, duration and severity of mood symptoms and mood episodes) and treatment interventions (ongoing or newly

initiated) can be rated and quantified from the LCM. The LCM will be completed via a web-based program.

Life events/Stress factors
Life events and stress factors will be assessed with sections of the QBP-NL.

Obstetric data
We developed a questionnaire with all items relevant to obstetric course, including delivery and health status of the newborn (see appendix)

Sleep diary
We developed a sleep diary that is largely consistent with The Expanded Consensus Sleep Diary for Evening (CSD-M) [56] of which a validated Dutch version is currently unavailable. Questions are grouped into morning and evening items. Participants are instructed to complete daytime items before going to bed, these items include activities, time and duration of naps, time of (sleep) medication, alcohol and caffeine use and experienced energy level (0-10). Evenings items are to be completed after getting out of bed and include time of going to bed, time of falling asleep, number and times of awakening, time of final awakening, time of getting out of bed, total hours of sleep and quality of sleep (0-10).

Actigraphy
Actigraphy provides objective, reliable data to measure sleep/wake patterns, circadian rhythms, and insomnia..Participants are asked to wear an actimeter (Motionwatch 8, CamNtech). The actimeter is worn around the wrist and measures movement. Data will be sampled in epochs of 60 seconds. Participants are instructed to press an event marker when going to sleep and after getting out of bed. Output of the associated software (MotionWare 1.0.9, CamNtech) includes: time in bed, assumed sleep, actual sleep time, actual wake time, sleep efficiency, and sleep latency.

Study endpoints
The first main study endpoint is the occurrence of psychiatric symptoms during the postpartum period, ranging from mild, subsyndromal symptoms (e.g., mild

anxiety, depressive or hypomanic symptoms) to syndromal bipolar disorder (depressive episode, hypomanic episode, manic episode, mixed episode), or psychosis (brief psychotic disorder, psychotic disorder NOS) according to DSM-IV-TR criteria.
The second main study endpoint will be the number and degree of psychiatric interventions (psychosocial, pharmacological, psychosocial or hospital admission) started during the postpartum period in addition to the ongoing treatment at the end of pregnancy, rated from level 0-6:
0. Treatment unchanged, no additional psychiatric intervention necessary.
1. Psychosocial or lifestyle intervention, but no additional psychiatric medication.
2. Dose adjustment (increase only) of any ongoing psychiatric medication.
3. New treatment with a benzodiazepine (hypnotic or anxiolytic).
4. New treatment with an antidepressant.
5. New treatment with a mood stabilizer or antipsychotic.
6. Hospitalisation for psychiatric reasons.

Statistical Analysis
The statistical analysis will include descriptive statistics of: (1) demographic variables; (2) variables measuring psychopathology; (3) variables evaluating sleep behaviour; (4) psychiatric symptoms during pregnancy; (5) psychiatric interventions during pregnancy; (6) psychiatric symptoms in the postpartum period; and (7) psychiatric interventions in the postpartum period.
The outcome variable of this study is postpartum psychopathology, as defined by psychiatric symptoms or newly started psychiatric interventions. To study to what extent postpartum psychopathology depends on sleep disturbances we will use different forms of regression analysis, since this technique allows controlling for specific variables such as demographic variables, illness history, depressive and manic symptoms. The specific form of regression analysis depends on the particular outcome measure: e.g. binary logistic regression for dichotomous outcomes and Poisson regression for count measures.
To analyse the longitudinal data we will use mixed effects models and survival models. These models allow studying the effect of sleep behaviour, the self-rated depression and mania scores and life events at different stages of the pregnancy on postpartum psychopathology.

Ethical Considerations

The study will be conducted with ethical principles that are consistent with the Declaration of Helsinki, amended by the 59th WMA General Assembly, Seoul, October 2008. This study protocol has been reviewed by the Scientific Committee of the EMGO Institute of VU University Medical Center in Amsterdam, The Netherlands, and has been approved by the Medical Ethical Committee of the VU University Medical Centre. Potential participants will obtain oral and written information about the study and will be asked to sign an informed consent form if they are willing to participate.

Discussion

This is, to our knowledge, the first prospective study that simultaneously collects data on mood fluctuations and sleep in a large group of pregnant women with bipolar disorder. It is a naturalistic, non-interventional study of pregnant women with a bipolar disorder or a history of postpartum psychosis. Besides collecting data about sleep and mood, we also collect obstetric data such as duration of labour and time of delivery. Retrospective studies showed that women with postpartum psychosis may have a longer duration of labour and may be more likely to deliver at night than controls. As far as we know there are no prospective studies addressing this subject. There may be an advantage to force deliveries during daytime in pregnant women with bipolar disorder, especially if they have shown risk factors for postpartum psychopathology earlier in pregnancy.
A better understanding of the impact of sleep disturbances during pregnancy and in the perinatal period on the occurrence of postpartum psychopathology could add evidence to such decisions and to the development of guidelines for prevention and treatment of postpartum psychosis in women at risk.

Competing interests

All authors declare that they have no competing interests in relationship to this study.

Authors' contributions

AS, PG and RK drafted this paper and it was modified by and approved by all other authors. All authors contributed to the design of the study protocol.

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5

Chapter 5

The effect of perinatal sleep on postpartum mood in women with bipolar disorder

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ABSTRACT

Background
Although it is well known that sleep patterns alter during pregnancy, evidence for the relation between peripartum sleep disturbance and postpartum recurrence of mood episodes in women with bipolar disorder (BD) is still scarce.

Methods
Observational study of 65 pregnant women with BD. Sleep data and mood symptoms were obtained in the last week of the first and second trimester of pregnancy, from week 38 of pregnancy until delivery, and from week 1 - 4 postpartum. Sleep was measured with actigraphy. Mood was assessed with the Altman Self-Rating Mania Scale, Quick Inventory of Depressive Symptomatology and Edinburgh Postnatal Depression Scale. Linear regression analysis was conducted, in which averaged mood outcomes measured in the postpartum period were regressed on the predictors sleep duration and sleep efficiency; adjusted for multiple confounders, including pre-partum mood, as mood and sleep are highly interrelated.

Limitations
Small sample, probably sample bias.

Results
Overall, sleep duration and sleep efficiency in trimesters 1, 2, and 3 do not predict mood-disturbance in the postpartum period. The strongest predictor for postpartum mood symptoms is mood symptoms in trimester 2 of pregnancy. In healthy sleepers who slept between 7 to 9 hours, poor sleep efficiency in the first week postpartum is predictive for hypomanic symptoms in the second week postpartum.

Conclusions
No association is found between objective sleep problems in pregnancy and postpartum mood symptoms in women with BD. In healthy sleepers, poor sleep efficiency in the first week postpartum is predictive of hypomanic symptoms in the second week postpartum.

Key words
Bipolar disorder, perinatal sleep, mood, pregnancy, postpartum

INTRODUCTION AND RATIONALE

It is well known that there is an increase in prevalence of mood disorders during pregnancy and postpartum (Brockington, 2004; Masters et al., 2022; Harris, 2016). A critical review indicated that there is a significant relationship between sleep disruption (especially short sleep duration) and mood disorders during pregnancy and the postpartum period (Ross et al., 2005).

Although there is a lack of knowledge of recurrence rates and risk factors for mood episodes during pregnancy and postpartum among women with Bipolar Disorder (BD), the current paucity of evidence indicates that the postpartum period is a time of considerable risk for recurrence of mood disorders in BD with an overall recurrence risk of 37%; a recurrence rate of 23% for women who used prophylactic medication and a recurrence rate of 66% for women who did not use prophylactic medication (Wesseloo et al., 2015). Although several factors have been identified that may increase the risk of postpartum recurrence like primiparity, discontinuation of medication, and dysregulation of the immune system (Bergink et al., 2013; Di Florio et al., 2014; Jones, Chandra, Dazzan, & Howard, 2014; Viguera et al., 2000), alterations in sleep may represent a final common pathway by which various risk factors lead to a mood episode, especially psychosis or mania, in women with BD (Ross, Murray, & Steiner, 2005; Sharma, 2003; Sharma & Mazmanian, 2003).

It is well established that sleep disruption can lead to recurrence of mood disorder episodes in non-pregnant patients with BD (Bauer et al., 2006; Jackson, Cavanagh, & Scott, 2003; Murray & Harvey, 2010; Wehr, Sack, & Rosenthal, 1987). Moreover, individuals with BD tend to have reduced sleep efficiency and increased night-time wakefulness in comparison to healthy controls (De Crescenzo, Economou, Sharpley, Gormez, & Quested, 2017). In a meta-analysis of nine independent studies, sleep latency and sleep duration were longer and wake after sleep onset and sleep efficiency were lower in women with BD compared to controls. (Geoffroy et al., 2015)].

Although there is still a lack of firm evidence, it can be assumed that there is a relationship between sleep disturbance during pregnancy and postpartum

mood recurrences in bipolar women, since pregnancy can alter sleep patterns. Indeed, 66%-94% of healthy pregnant women report alterations in sleep patterns and behavior from early pregnancy until at least three months postpartum (Hunter, Rychnovsky, & Yount, 2009; Mindell, Cook, & Nikolovski, 2015; Santiago, Nolledo, Kinzler, & Santiago, 2001). During the first trimester, total sleep time, daytime sleepiness, insomnia, and nocturnal awakenings increase, and overall sleep quality decreases. In the second trimester sleep appears to normalize (Karacan, Williams, Hursch, McCaulley, & Heine, 1969; Lee, 1998; Santiago et al., 2001; Suzuki, Dennerstein, Greenwood, Armstrong, & Satohisa, 1994). In the third trimester, nocturnal awakenings increase to 3-5 times per night, while insomnia and slow wave sleep decrease (Karacan et al., 1969; Lee, 1998; Santiago et al., 2001).

As sleep disorders are also a common symptom of mood disorders, it is important to investigate if sleep predicts postpartum mood independent of prepartum mood, especially because postpartum depressions often start prepartum (Dorheim, Bjorvatn, & Eberhard-Gran, 2014; Swanson, Kalmbach, Raglan, & O'Brien, 2020; Tham et al., 2016).

To the best of our knowledge, only two previous studies have examined the relationship between perinatal sleep and postpartum mood in patients with BD or postpartum psychosis (Bilszta, Meyer, & Buist, 2010; Sharma, Smith, & Khan, 2004). Sharma et al. conducted a retrospective study regarding sleep and postpartum psychosis in which sleep loss was operationalized as the time and duration of labor (Sharma et al., 2004). Women who were hospitalized for postpartum psychosis (n=21) were compared with a matched control group of healthy women (n=21). Women with postpartum psychosis had more nighttime deliveries and a significantly longer duration of delivery than women in the matched control group, suggesting that women with postpartum psychosis had more sleep disruption during the perinatal period. However, it should be noted that the study has some limitations including the use of a chart review, a small sample size, and no objective sleep patterns, nor self-reported sleep. In a second, prospective study of Bilszta et al, a pregnant group at high risk, i.e. women with a history of BD or postpartum psychosis (n=23) was compared to 15 pregnant healthy controls (Bilszta et al., 2010). No significant differences in sleep/wake patterns during pregnancy between these groups were found. Sleep parameters were assessed with sleep diaries and the Stanford Sleepiness Scale

and mood was assessed by the treating psychiatrist at the last fortnight of each trimester of pregnancy and in week 1, 4, and 8 postpartum. Altogether, despite the importance of the potential association between sleep disruption and mood disorders during the perinatal period, only two studies addressed this subject, with only one prospective study. None of these studies used objective sleep, while sleep registrations are typically more accurate in measuring sleep-wake parameters than subjective (i.e. self-reported sleep). In particular, patients with BD overestimate how long it takes them to fall asleep compared to patients with insomnia and subjects with good sleep, and they underestimate how much sleep they obtain overall by an average of 1.3 hours (Harvey, Schmidt, Scarna, Semler, & Goodwin, 2005).

The current study aims to examine in a prospective cohort of pregnant women with BD, the relationship between objective sleep quality during pregnancy and mood episode recurrences postpartum.

Based on the literature, it is hypothesized that sleep disturbance during the perinatal period predicts postpartum recurrence of mood symptoms in women with BD, also independent of prepartum mood.

METHODS

Design

The Sleepreg-BD study is a prospective multi-centre (n=22) cohort study throughout the Netherlands that investigates the effect of sleep disturbance in pregnancy on postpartum mood in women with BD. On different timepoints (baseline, week 13, week 26, week 38 and 39 of pregnancy, and week 1-4 postpartum). Participants were asked to complete mood questionnaires, the Life Chart Method (LCM, daily assessment of mood), a sleep diary, and wear an actigraphy watch (MotionWatch 8).

The Sleepreg-BD study was approved by the Medical Ethical Committee of the VU University Medical Centre, Amsterdam, the Netherlands (registration number 2012/3).

A detailed study protocol has been published previously (A. W. M. M. Stevens, Goossens, P.J.J., Hoogendoorn, A.W., Knoppert-van der Klein, E.A.M., Honig, A,, Kupka, R.W., 2014).

This study has been reported according to the STROBE-guidelines.(von Elm et al., 2007).

Study sample

The study sample consists of pregnant Dutch women with an established DSM-IV diagnosis of BD, who participated in the Sleepreg-BD study between July 2012 and Juni 2018.

Eligible participants were pregnant women, aged 18-40 years, diagnosed with BD, confirmed by the hypomanic and manic episode section of the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). We recruited participants at the near end of the first trimester after we concluded by practice that earlier recruitment may lead to drop-out of participants because of miscarriage. Once written informed consent had been obtained, participants provided demographic information. Exclusion criteria for analyses in the study were childbirth before 37 weeks of pregnancy, twins, and less than four consecutive days of sleep data.

In the Sleepreg-BD study 96 participants were enrolled. Of these participants 65 were included in the analyses. Reasons for exclusion were prematurity (n=7), no sleep data postpartum (n=8), only data on T0 (n=4), dropout after trimester 1 (n=3), dropout after trimester 2 (n=1), no sleep data at all (5), no data at all (n=2), or no QBP (n=1).

Assessment instruments

Actigraphy

Objective sleep parameters were measured using the MotionWatch 8 (MW8; CamNTech, Cambrigde, UK). The MW8 provides reliable, validated parameters of sleep, including sleep latency, total sleep duration, and sleep efficiency (Landry, Falck, Beets, & Liu-Ambrose, 2015). Participants wore the MW8 on their non-dominant wrist and data was collected in 60 second epoches. Sleep data were analyzed using the MotionWare PC software (CamNtech, Ltd). Research assistants also checked the analyzed data against participant's sleep diaries for discrepancies. Participants were asked to indicate when they went to bed and got out bed using the event marker button at the side of the MW8. The 'light out' and get up' times (i.e. bedtimes and waketimes) were obtained from the light recording function of the MW and verified by the MW event marker data and sleep diary data. The study variables are sleep duration and sleep efficiency. Participants were asked to wear the MW8 for the duration of 1 week in week 13, 26, 38, and 39 of pregnancy (if not yet delivered) and week 1-4 postpartum. A

minimum of four consecutive days of nights per week (including one weekend) were used for analysis. All participants met this criterium.

Questionnaire for Bipolar Illness, Dutch Translation (QBP-NL)
The QBP-NL is developed in a longitudinal study of the naturalistic course of BD from the Stanley Foundation Bipolar Network and includes demographics, psychiatric diagnosis and history, course of the illness characteristics, and family history of the study population (Leverich et al., 2001; Suppes et al., 2001).
The questionnaire is divided into part A and B. The first part (21 questions) is completed by the clinician. The second part (40 questions) is completed by the patient.

Altman Self-Rating Mania Scale (ASRM)
The ASRM is a 5-item self-rating mania scale and may be used in an inpatient or outpatient setting to screen for the presence of and/or severity of (hypo)manic symptoms for clinical or research purposes. Because it is compatible with DSM-IV criteria, and correlates significantly with Clinician-Administered Rating Scale for Mania (CARS-M), Young Mania Rating Scale (YMRS), it can be used effectively as a screening instrument to facilitate diagnostic assessment in patients with (hypo)manic symptoms or to measure the severity of manic symptoms (Altman, Hedeker, Peterson, & Davis, 1997). Mania subscale scores of greater than 5 on the ASRM resulted in values of 86% for sensitivity and 87% for specificity.

Quick Inventory of Depressive Symptomatology (QIDS)
The 16-item Quick Inventory of Depressive Symptomatology (QIDS), a measure of depressive symptom severity derived from the 30-item Inventory of Depressive Symptomatology (IDS), is available in both self-report (QIDS-SR16) and clinician-rated (QIDS-C16) formats. In this study the self-report version was used. The psychometric properties of the QIDS have both been established in various study samples (Rush et al., 2006; Rush et al., 2003)

Edinburgh Postnatal Depression Scale (EPDS)
The 10-question Edinburgh Postnatal Depression Scale (EPDS) establishes patients at risk for "perinatal" depression. The EPDS is easy to administer and has proven to be an effective screening tool. The scale measures self-reported

mood symptoms during the previous week (Cox, Holden, & Sagovsky, 1987). An EPDS score of ≥15 and ≥13 was used to identify probable cases of "antepartum depression" and "postpartum depression" respectively (Matthey, Henshaw, Elliott, & Barnett, 2006), based on validity studies which demonstrated specificity of 98% and sensitivity of 57% for antepartum depression, and specificity of 95–97% and sensitivity of 41–87% for postpartum depression (Gibson, McKenzie-McHarg, Shakespeare, Price, & Gray, 2009).
The two depression scales were used together to increase reliability. Whereas the EPDS is validated for pregnant and postpartum women, the QIDS is a general instrument for assessment of depressive symptoms.

Statistical analyses
Demographic (age, level of education and marital status) and clinical characteristics (age of onset of BD, parity, number of lifetime manic episodes, number of lifetime depressive episodes, and type of medication treatment) were summarized with descriptive statistics. Linear regression analysis was conducted, in which averaged mood outcomes measured with ASRM, QIDS, and EPDS in the postpartum period were regressed on the predictors: objective sleep duration and sleep efficiency. Trimester 2 was operationalized as the last week of the second trimester of pregnancy, so average mood scores and sleep data of that specific week were used in the analysis. Similarly, data from week 37 to week 41 of pregnancy were used for the third trimester. Data from the first seven days after childbirth were used to indicate a postpartum episode. The first calculated model was unadjusted, the second model was adjusted for parity, education level, and age of onset of BD. The third model was adjusted for the same variables as model 2, together with total mood scores in the last week of trimester 2 as assessed with the EPDS, ASRM, and QIDS to understand if sleep also predicts postpartum mood independent of sleep during pregnancy. Unstandardized beta's and p-values were calculated. All analyses were performed with IBM SPSS software version 27 (SPSS Inc., Chicago, IL, USA). Finally, we considered healthy versus short sleepers (in trimester 2) in the analyses. Based on the national sleep foundation recommendations (Hirshkowitz et al., 2015), healthy sleepers are defined as those who have seven up to nine hours sleep per day on average. Those women who slept less than seven hours per day were considered "short" sleepers. No women slept > 9 hours.

RESULTS

Patients were diagnosed with BD type I (n=37) or type II (n=28). No medication was used by 29 participants. Many participants were nullipara (n=40) and n=45 had a high level of education (table 1). Less than 1% discrepancies were found between the analyzed MW data, light recording function of the MW, event marker data of the MW, and sleep diary data.

Table 1. Sample characteristics of 65 pregnant women with BD

Demographic characteristics	
	Mean ± SD
Age	33.45±4.28
	No (%)
Level education	
- Low	4(6.2)
- Medium	15(23.1)
- High	45(69.2)
- Missing	1(1.5)
Marital status	
- Married, LAT	62(95.5)
- Single, divorced	2(3.0)
- Missing	1(1.5))
Clinical characteristics	
	Mean ± SD
Age of onset	23.06±5.78
	No (%)
Bipolar disorder 1	37(56,9)
Bipolar disorder 2	28(43,1)
Parity	
- Nullipara	40(61.5)
- Primipara	22(33.8)
- Multipara	3(4.6)
Manic episodes	
- None	1(1.5)
- 1	11(16.9)
- 2-4	27(41.5)
- 5-10	18(27.7)
- 11-20	4(6.2)
- > 20	3(4.6)
- Missing	1(1.5)
Depressive episodes	
- None	5(7.7)
- 1	5(7.7)
- 2-4	23(35.4)
- 5-10	18(27.7)
- 11-20	3(4.6)
- > 20	10(15.4)
- Missing	1(1.5)
Treatment	
- No medication	29(44.6)
- 1 mood stabilizer	18(27.7)
- Mood stabilizer and other psychofarmaca	1(1.5)
- Only other psychofarmaca	17(26.2)

Table 2. Sleep and mood characteristics

	Mean ± SD Range (minimum – maximum) N				
	Sleep efficiency, %	Objective sleep duraton, minutes	EPDS	QIDS	ASRM
Baseline			5.23 ± 5.34 0-24 65	6.08± 4.10 1 - 23 65	1.23 ± 1.70 0 - 8 65
Trimester 1[a]	78.21 ± 6.99 58.9 – 90.46 45	419.56 ± 54.15 322.71 - 541.29 45	5.43 ± 6.01 0 - 28 40	6.40 ± 4.51 1 - 24 40	1.05 ± 1.89 0 - 10 40
Trimester 2[b]	76.95 ± 8.52 40.25 - 91.35 59	408.95 ± 64.10 215.25 - 572.29 59	5.21 ± 5.80 0 - 27 58	5.71 ± 3.35 1 - 19 58	.98 ± 1.75 0 - 8 58
Trimester 3[c]	74.81 ± 7.86 48.64 - 84.91 38	412.18 ± 77.69 209.17 - 674.40 38	4.07 ± 4.64 0 - 25 50	6.11 ± 3.49 2 - 21 50	1.19 ± 1.99 0 - 10 50
Post partum[d]	75.01 ± 8.35 52.28 - 92.59 41	398.04 ± 64.15 269.90 - 561.59 41	6.78 ± 5.17 0 - 19 51	7.14 ±3.61 1 - 22 51	1.87 ± 3.06 0 - 16 51
Post partum week 1	71.92 ± 9.63 51.08 - 91.15 31	358.20 ± 62.07 241.25 - 456.00 31	6.73 ± 5.64 0 - 22 30	7.97 ± 3.94 2 - 16 30	2.37 ± 4.22 0 - 20 30
Post partum week 2	75.08 ± 10.45 38.27 - 92.63 39	387.10 ± 70.08 139.43 - 528.50 39	5.89 ± 5.54 0 - 22 35	6.94 ± 3.23 0 - 13 35	1.63 ± 2.08 0 - 7 35

Notes: a Last week first trimester of pregnancy, b Last week second trimester of pregnancy,
c Week 37-41 of pregnancy, d Week 1-4 postpartum. Data for actigraphic sleep variables were averaged over the recorded time.
QIDS = Quick Inventory of Depressive Symptomatology, EPDS = Edinburgh Postnatal Depression Scale, ASRM = Altman Self-Rating Mania Scale

Table 3. Relation between sleep and mood variables

	EPDS pp1-4			ASRM pp1-4			QIDS pp1-4		
Predictor	Model 1[a]	Model 2[b]	Model 3[c]	Model 1[a]	Model 2[b]	Model 3[c]	Model 1[a]	Model 2[b]	Model 3[c]
Mean obj sleep duration trim2[d] (n=43)									
B (unstandardized)	-.005	-.005	.008	.005	.005	.006	-.011	-.015	-.008
P	.723	.700	.432	.553	.559	.510	.264	.148	.259
Mean obj sleep duration trim3[e] (n= 30)									
B (unstandardized)	-.017	-.016	.004	.011	.013	.013	-.009	-.009	-.005
P	.187	.234	.061	.224	.154	.161	.252	.306	.559
Mean obj sleep duration pp1[f] (n=26)									
B (unstandardized)	-.005	.-007	-.001	.003	.005	.004	-.002	-.004	-.006
P	.752	.652	.963	.662	.458	.532	.847	.694	.503
Mean sleep efficiency trim2[d] (n= 43)									
B (unstandardized)	-0.75	-.0.57	.021	.001	.035	.0.38	-0.53	-.059	.015
P	.404	.579	.780	.989	.572	.551	.425	.419	.791
Mean sleep efficiency trim3[e] (n=30)									
B (unstandardized)	-.140	-.134	.017	.041	.078	.100	-.042	-0.41	-1.47E-5
P	.209	.265	.876	.606	.345	.264	.547	.590	1.000
Mean sleep efficiency pp1[f] (n=26)									
B (unstandardized)	-.019	-.067	-.020	.020	.043	.029	.011	-.011	-.041
P	.849	.594	.819	.624	.400	.536	.851	.892	.549

Notes: a not adjusted, b adjusted for parity, level of education, age of onset bipolar disorder, c adjusted for parity, level of education,
age of onset bipolar disorder, mood (EPDS/ASRM/QIDS) trimester 2/3, d Last week second trimester of pregnancy,
e Week 37-41 of pregnancy, f First week postpartum. Data for actigraphic sleep variables were averaged over the recorded time. QIDS = Quick Inventory of Depressive Symptomatology, EPDS = Edinburgh Postnatal Depression Scale, ASRM = Altman Self-Rating Mania Scale

Sleep parameters (measured using actigraphy) are shown in table 2. Sleep efficiency in trimester 3 (M=74.81 ± 7.86) was significantly lower than in trimester 2 (M = 76.95 ± 8.52), as was sleep efficiency in postpartum week 1 (M = 71.92 ± 9.63). Sleep duration in postpartum week 1 (M = 358.20± 62.07) was significantly lower than in trimester 3 (M = 412.18 ± 77.69).
Overall, sleep duration and sleep efficiency in trimesters 1, 2, and 3 did not predict mood disturbance in the postpartum period. Instead, our analyses showed that the strongest predictor for postpartum mood symptoms were having mood symptoms in trimester 2 of pregnancy (table 3).
Also in healthy sleepers or short sleepers, sleep duration and sleep efficiency were not associated with mood disturbance in the postpartum period (table 4 and 5).

Table 4. Relation between sleep and mood in healthy sleepers (=>420 min sleep/ night in the last week of trimester 2 of pregnancy)

	EPDS pp1-4			ASRM pp1-4			QIDS pp1-4		
Predictor	Model 1[a]	Model 2[b]	Model 3[c]	Model 1[a]	Model 2[b]	Model 3[c]	Model 1[a]	Model 2[b]	Model 3[c]
Mean obj sleep duration trim2[d] (n=17)									
B (unstandardized)	.021	.017	.017	-.034	-.041	.-0.21	-.008	-.003	-.012
P	.685	.770	.727	.500	.428	.691	.803	.916	.678
Mean obj sleep duration trim3[e] (n= 12)									
B (unstandardized)	-.009	-.010	.024	.009	.020	.019	-0.04	-.001	.006
P	.474	.484	.253	.560	.224	.259	.651	.957	.594
Mean obj sleep duration pp1[f] (n=8)									
B (unstandardized)	.025	.044	.098	.006	.017	.017	.010	.024	.037
P	.449	.368	.085	.519	.127	.232	.680	.427	.247
Mean sleep efficiency trim2[d] (n= 17)									
B (unstandardized)	-3.02	-2.88	-0.89	-.031	.044	.005	-.073	-.017	.124
P	.105	.170	.683	.869	.822	.981	.554	.890	.298
Mean sleep efficiency trim3[e] (n=12)									
B (unstandardized)	-.134	-.168	-.012	.074	.170	.182	-.037	-0.08	0.058
P	.258	.199	.951	.622	.279	.244	.637	.926	0.548
Mean sleep efficiency pp1[f] (n=8)									
B (unstandardized)	-.310	-.865	-.879	-.024	-.138	-.451	-.374	-.464	-.438
P	.437	.173	.303	.832	.474	.313	.165	.256	.499

Notes: a not adjusted, b adjusted for parity, level of education, age of onset bipolar disorder, c adjusted for parity, level of education, age of onset bipolar disorder, mood (EPDS/ASRM/QIDS) trimester 2/3, d Last week second trimester of pregnancy, e Week 37-41 of pregnancy, f First week postpartum.
Data for actigraphic sleep variables were averaged over the recorded time. QIDS = Quick Inventory of Depressive Symptomatology, EPDS = Edinburgh Postnatal Depression Scale, ASRM = Altman Self-Rating Mania Scale

Table 5. Relation sleep and mood in short sleepers (<420 min sleep/night in the last week of trimester 2 of pregnancy)

	EPDS pp1-4			ASRM pp1-4			QIDS pp1-4		
Predictor	Model 1[a]	Model 2[b]	Model 3[c]	Model 1[a]	Model 2[b]	Model 3[c]	Model 1[a]	Model 2[b]	Model 3[c]
Mean obj sleep duration trim2[d] (n=26)									
B (unstandardized)	-.021	-.015	.014	.002	.004	.009	-.027	-.035	-.009
P	.409	.608	.480	.801	.707	.415	.158	.106	.587
Mean obj sleep duration trim3[e] (n= 18)									
B (unstandardized)	-.045	-.047	-.046	.012	.013	.012	-.027	-.026	-.027
P	.109	.121	.039	.277	.272	.334	.129	.195	.104
Mean obj sleep duration pp1[f] (n=17)									
B (unstandardized)	-.010	-.013	-.010	.005	.009	.006	-.005	-.008	-.011
P	.607	.537	.436	.523	.363	.505	.692	.531	.305
Mean sleep efficiency trim2[d] (n= 26)									
B (unstandardized)	-.033	-028	.015	-.006	.002	.008	-.047	-.047	.003
P	.773	.845	.877	.887	.969	.878	.592	.661	.968
Mean sleep efficiency trim3[e] (n=18)									
B (unstandardized)	-.146	-.102	-.147	-.007	.011	-.074	-.050	-.048	-.057
P	.473	.661	.403	.931	.908	.511	.696	.747	.653
Mean sleep efficiency pp1[f] (n=17)									
B (unstandardized)	-.003	-.045	-.029	.037	.092	.065	-027	-.005	-.047
P	.978	.777	.762	.471	.190	.372	.697	.956	.578

Notes: a not adjusted, b adjusted for parity, level of education, age of onset bipolar disorder, c adjusted for parity, level of education, age of onset bipolar disorder, mood (EPDS/ASRM/QIDS) trimester 2/3, d Last week second trimester of pregnancy, e Week 37-41 of pregnancy, f First week postpartum. Data for actigraphic sleep variables were averaged over the recorded time. QIDS = Quick Inventory of Depressive Symptomatology, EPDS = Edinburgh Postnatal Depression Scale, ASRM = Altman Self-Rating Mania Scale

Sleep duration and sleep efficiency in postpartum week 1 predicted manic symptoms in postpartum week 2 in short sleepers when adjusted for parity, education, and age of onset of bipolar disorder, but this was no longer significant when also adjusting for ASRM score in the last week of trimester 2. In healthy sleepers, sleep efficiency in postpartum week 1 predicted the occurrence of manic symptoms in postpartum week 2. Sleep efficiency in postpartum week 1 predicted depressive symptoms (EPDS-score and QIDS-score) in postpartum week 2 in healthy sleepers but this was no longer significant when also adjusting for mood score in the last week of trimester 2 (table 6).

Table 6. Relation sleep in week 1 postpartum on mood in week 2 postpartum in healthy and short sleepers

	ASRM pp2[e]			EPDS pp2[e]			IDS pp2[e]		
Predictor	Model 1[a]	Model 2[b]	Model 3[c]	Model 1[a]	Model 2[b]	Model 3[c]	Model 1[a]	Model 2[b]	Model 3[c]
	Healthy Sleepers[f]								
Mean actual sleep pp1[d] (n=8)									
B (unstandardized)	0.000	.008	.007	.008	.010	.046	.015	.027	.042
P	.975	.582	.677	.813	.840	.557	.446	.395	.166
Mean sleep efficiency pp1[d] (n=8)									
B (unstandardized)	.013	-.242	-.616	-.309	-1.074	-1.090	-.432	-.693	-.770
P	.924	.222	.033	.459	.034	.103	.032	.044	.141
	Short Sleepers[g]								
Mean actual sleep pp1[d] (n=13)									
B (unstandardized)	.009	.011	.007	.008	.002	-.002	-.015	-.020	-.022
P	.392	.303	.460	.777	.966	.940	.377	.337	.214
Mean sleep efficiency pp1[d] (n=13)									
B (unstandardized)	.047	.147	.109	.107	.023	-.009	-.007	-.027	-.102
P	.434	.046	.155	.531	.929	.996	.949	.861	.467

Notes: a not adjusted, b adjusted for parity, level of education, age of onset bipolar disorder, c adjusted for parity, level of education, age of onset bipolar disorder, mood (ASRM/EPDS/QIDS) trimester 2/3, d first week postpartum, e second week postpartum, f 7-9 hours sleep, g <7 hours sleep

Data for actigraphic sleep variables were averaged over the recorded time. QIDS = Quick Inventory of Depressive Symptomatology, EPDS = Edinburgh Postnatal Depression Scale, ASRM = Altman Self-Rating Mania Scale

DISCUSSION

To the best of our knowledge, this is the first prospective longitudinal study examining the relationship between sleep and peripartum mood symptomatology using objective sleep data measured with actigraphy, and assessment of mood at different timepoints in pregnancy up to four weeks postpartum in women with BD.

Our findings did not show an association between sleep disturbance during pregnancy and postpartum mood symptomatology after adjusting for covariates. Our findings differ from the review of Ross et al. (2005), which indicated a significant relationship between sleep disruption and mood disorders during pregnancy and the postpartum period.

This discrepancy may be explained by the characteristics of our clinical sample. First, a considerable portion of the women dropped out during the study, especially after childbirth. A key reason, reported by women who dropped out, was that after childbirth, they were too busy and preoccupied to complete the questionnaires and wear the motionwatch. Some participants indicated that the study reminded them too much of their bipolar illness, deciding them to drop out of the study during pregnancy. This is not uncommon. Other studies with pregnant women with mood problems also showed recruitment difficulties or a

high drop-out rates (Heller, Hoogendoorn, Honig, Broekman, & van Straten, 2020; Perry et al., 2021; Rubin, 2018). Second, many participants in our sample used medication, most of them lithium. It is known that euthymic BD-I patients with lithium have better sleep efficiency and longer sleep duration than patients who do not use lithium (Geoffroy, Samalin, Llorca, Curis, & Bellivier, 2016). This may have influenced our findings.
In our sample, mood in trimester 2 of pregnancy was the strongest predictor of postpartum mood. Indeed, antenatal depression is known to be an important risk factor for non-psychotic postpartum depression in samples of women with unipolar major depression (Howard et al., 2014). A recent study found that the occurrence of mania or psychosis during pregnancy increased the risk of severe postpartum recurrence in women with BD, but no significant association was found between depression during pregnancy and postpartum mood episodes (Perry et al., 2021).
Another finding is that poor sleep efficiency in the first postpartum week in healthy sleepers predicted manic symptoms in the second week postpartum, but this did not apply to short sleepers. An explanation could be that women who are already used to short sleep during pregnancy are less affected by poor sleep efficiency in the first week postpartum. The relation between sleep disruption and hypomania has been reported before (Bauer et al., 2006; Murray & Harvey, 2010), but the association with poor sleep efficiency has to our knowledge not been studied.

Although it is known that sleep efficiency decreases during pregnancy until the first week postpartum (Garbazza et al., 2020; Lee, 1998), in this study we show that sleep efficiency postpartum seems to have more impact on postpartum psychopathology in BD patients than sleep duration. It may well be that sleep latency and WASO play a more profound role than sleep duration in predicting postpartum psychopathology in women with BD.

Strengths
Both sleep and mood were assessed at different timepoints during pregnancy and postpartum. This is important as sleep and mood are highly interrelated. Another strength is the assessment of objective sleep data by using actigraphy instead of self-reporting sleep questionnaires. Previous studies used a

retrospective design and/or only used self-reports of sleep, which has been shown to be less accurate in patients with BD due to reporting bias (Harvey et al., 2005).

Limitations

First, despite our efforts to increase number of women included in the study (by prolonging the study period by a few years and by approaching clinicians treating patients with a bipolar disorder), the anticipated number of participants (n=130) was not obtained. The drop-out rate was high, and many participants did not complete all measures. Obviously, pregnancy and the postpartum period create other priorities that may interfere with participation in research or distract participants from tasks associated with the study. Another limitation is the sampling bias, most of the patients in our study were highly educated and had a partner. Moreover, all women received adequate treatment mostly in specialized outpatient clinics and therefore may have been relatively stable, even when almost half of the sample did not use medication. Indeed, the mean EPDS, ASRM and QIDS scores we found throughout pregnancy and the postpartum period are far below the cut-off scores (EPDS > 12/13, QIDS > 13, ASRM > 5,) of depression and (hypo)mania (Levis et al., 2020; Meyer et al., 2020; Suris, Holder, Holliday, & Clem, 2016). Our sample was too small to investigate effects of various medication or psychotherapeutic interventions.

Conclusions

Sleep problems during pregnancy did not predict postpartum mood symptoms in women with BD, also not when adjusted for pre-partum mood. In fact, pre-partum mood during the second trimester of pregnancy turned out to be the strongest predictor for mood symptoms in the postpartum period in women with BD. However, in healthy sleepers, poor sleep efficiency in the first week postpartum is predictive for manic symptoms in the second week postpartum.

Clinical implications

Good sleep in BD patients is especially important in the first week postpartum. To optimize this, it should be considered that the partner or a family member provide the feedings to the baby during the night (by using formula feedings or expressed milk). As we found that mood symptoms in in the second trimester

of pregnancy are the strongest predictor of mood postpartum, treatment of mood symptoms during pregnancy is most important to prevent postpartum recurrences.

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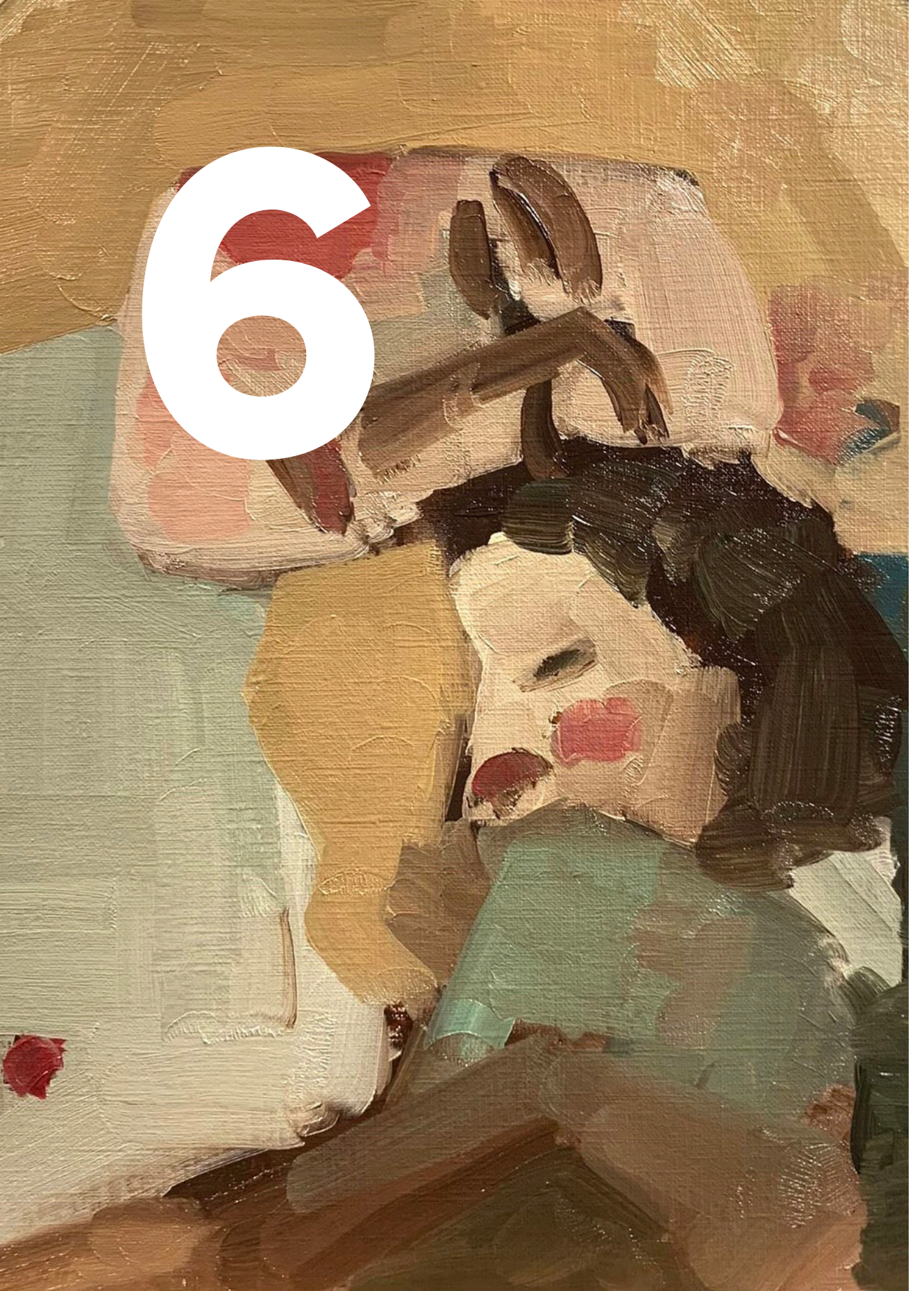
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Chapter 6

The course of bipolar disorder in pregnant versus non-pregnant women

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ABSTRACT

Background and Rationale

Although it has been suggested that pregnancy may influence the course of bipolar disorder (BD), studies show contradictory results. Until now, no studies included a finegrained validated method to report mood symptoms on a daily basis, such as the lifechart method (LCM). The aim of the present study is to investigate the course of BD during pregnancy by comparing LCM scores of pregnant and non-pregnant women.

Methods

Study design: Comparison of LCM scores of two prospective observational BD cohort studies, a cohort of pregnant women (n=34) and a cohort of non-pregnant women of childbearing age (n=52). Main study parameters are: (1) proportions of symptomatic and non-symptomatic days; (2) symptom severity, frequency, and duration of episodes; (3) state sequences, longitudinal variation of symptom severity scores.

Results

No differences in clinical course variables (symptomatic days, average severity scores, frequency, and duration of episodes in BD were found between pregnant and non-pregnant women. With a combination of State Sequence Analysis (SSA) and cluster analysis on the sequences of daily mood scores three comparable clusters were found in both samples: euthymic, moderately ill and severely ill. The distribution differences between pregnant and non-pregnant women were significant, with a majority of the pregnant women (68%) belonging to the moderately ill cluster and a majority of the non-pregnant women (46%) to the euthymic cluster. In pregnant women the average daily variation in mood symptoms as assessed with Shannon's entropy was less than in non-pregnant women (respectively 0.43 versus 0.56).

Conclusions

Although the use of daily mood scores revealed no difference in overall course of BD in pregnant versus non-pregnant women, more pregnant than non-pregnant women belonged to the moderately ill cluster, and during pregnancy the

variation in mood state was less than in non-pregnant women. Further research is necessary to clarify these findings.

Key words
bipolar disorder, course, pregnancy, life chart method

INTRODUCTION AND RATIONALE

Bipolar disorder (BD) is a recurrent mental illness characterized by depressive, hypomanic, and/or manic episodes separated by euthymic intervals and usually manifests in young adulthood (1). The lifetime prevalence ranges from 1.3% to 2.4% (2, 3).
Patients with BD show considerable illness-related morbidity (4, 5) and the disorder significantly influences their wellbeing and social, occupational, and general functioning (6-8).
In clinical practice, women with BD often ask their physician about the impact of pregnancy on the course of their illness. However, research into the relation between pregnancy and course of BD is scarce. Unlike repeated findings that the postpartum period has a negative influence on the course of BD, with a risk of relapse of 35% (9), the impact of pregnancy itself on the course BD is still uncertain, and various studies have reported conflicting results (10, 11).

While some population-based studies suggest that pregnancy could be protective with low rates of new onset and relapse during this period (12, 13), clinical studies provide conflicting findings. Most of the older studies are retrospective, and most of the prospective studies report high recurrence rates in women who discontinue mood stabilizers (14).
In a retrospective study (15), clinical data were pooled of 2252 pregnancies of women with BD and unipolar depression. Rates of affective episodes and risk factors were identified during pregnancy and the postpartum period. Among women with BD, 23% had illness episodes during pregnancy, compared to 4.6% of women with unipolar depression. Risk factors were younger age at illness onset, previous postpartum episodes, shorter duration of illness, having fewer children, and not being married.
Freeman et al. (2002) interviewed 30 women with BD after pregnancy with a

structured clinical interview, and found that 15 (50%) reported no change or fewer mood symptoms during pregnancy, while the other half reported more symptoms. The experience of worsening of mood symptoms during pregnancy also predicted postpartum recurrence (16). A limitation of this study is that the assessment was retrospective and thus prone to recall bias.
Grof et al. (2000) found a protective effect of pregnancy on the frequency and duration of mood episodes in a sample of 28 women with BD (with 56 pregnancies), who had become pregnant prior to receiving successful lithium prophylactic treatment (17). Retrospectively, they compared illness severity during the 9 months of pregnancy with the 9 months before pregnancy intra-individually. The recurrence risk during pregnancy was markedly lower and recurrences of mood episodes were significantly shorter during pregnancy in comparison to pre-pregnancy.
In a recent review of the influence of pregnancy on the course of BD we concluded that despite the importance of the topic there is a paucity of evidence on recurrence rates of mood episodes during pregnancy among women with BD (18). Another review also stated that the literature cannot answer the question of how pregnancy affects the course of BD, but merely informs us about the effect of discontinuation of medication in pregnancy (19). Retrospective studies are more sensitive to recall bias and results are therefore less reliable, while prospective studies focused mainly on the effect of discontinuation of medication and hardly on the relation between pregnancy and course of illness.
Moreover, none of these studies used a detailed mood monitoring method to assess course of illness during pregnancy. The LifeChart Method (LCM) (20, 21) is a prospective assessment of fluctuations and severity in mood on a daily basis, resulting in more precision, with less risk for recall bias as compared with retrospective self reported data that were collected in most studies (22).
The aim of the present study is to prospectively investigate the relationship between pregnancy and the course of BD.

METHODS

LCM-data of two observational, prospective cohort studies were used to compare the course of BD in pregnant versus non-pregnant women.

2.1. Study samples

The research samples were (1) pregnant Dutch women with an established DSM-IV diagnosis of BD, who participated in the Sleepreg-BD study between 2012 and 2018 (n=34), and (2) non-pregnant Dutch women of childbearing age with an established DSM-IV diagnosis of BD, who participated in The Stanley Foundation Bipolar Treatment Outcome Network study between 1995 and 2000 (n=52).

The Sleepreg-BD study was a multi-site study in the Netherlands investigating the effect of sleep disturbance in pregnancy and the perinatal period on postpartum psychopathology in Dutch women with BD (23). Pregnant women, aged 18-45 year, with a diagnosis of BD were asked to fill in the LCM from week 13 of pregnancy till 12 weeks postpartum. To avoid including women whose pregnancy ended prematurely, we recruted pregnant women at the end of the first trimester of pregnancy. To investigate the illness course during pregnancy, for this study LCM postpartum scores were not included in the analysis. The LCM was completed by 46 women, of these 34 met the inclusion criterion of at least 60 days of LCM reports.

The Stanley Foundation Bipolar Network (SFBN) was a multi-site research program coordinated at the National Institute of Mental Health (NIMH), with four clinical centers in the USA, two in Germany and one in the Netherlands, as described in detail elsewhere (20, 24). Its main aim was to evaluate the long-term illness course and define longitudinal illness patterns, and to investigate the effectiveness of conventional and novel pharmacological treatments in a large group of patients with BD. The SFBN database consisted of over 900 patients, including n=174 from the Netherlands. For this current study we included data of the 52 non-pregnant women, age 18-45 year, and included in the Netherlands, who had completed at least one full year of LCM. Since the pregnant women delivered a maximum of 272 daily severity scores, we selected the 272 completed last lifechart ratings from the first year of prospective follow-up of the SFBN women for comparison with the Dutch women of the Sleepreg-BD study.

2.2. Assessment instruments and outcome variables

Patient and clinician questionnaires:

The Stanley Foundation Bipolar Treatment Outcome Network designed two questionnaires to collect basic demographic and clinical data from both patients and clinicians. These questionnaires (Questionnaire for Bipolar disorder, QBP)

generate a comprehensive overview of the characteristics of participants as well as illness and treatment history (20, 25), and were translated into Dutch.

QBP reports of medication use were transformed into categories (0: no medication; 1: one mood stabilizer; 2: more than one mood stabilizer; 3: mood stabilizer and other psychotropic medications; 4: only other psychotropic medications).

LCM

The LCM provides a graphic representation of minor mood swings and major mood episodes, and can be used both retrospectively and prospectively (21, 26). The impact of daily mood symptoms on functioning is rated on a 5-point scale (0=no dysfunction or euthymia, 1 = mild, 2 = low moderate, 3 = high moderate, 4 = severe dysfunction). Since severity is rated for two poles: mania and depression, this results in nine different ratings. Patients of both cohort studies were asked to complete a prospective LCM on a daily basis during the entire study period. Illness course variables could be calculated, thus allowing longitudinal assessment of illness patterns (27-29). Relevant variables were: number, duration, and severity of mood symptoms and mood episodes, and proportion of time ill during the observation period. A validation study reported high correlations between LCM ratings and ratings on the Young Mania Rating Scale (YMRS) ($r = 0.656$, $p < 0.001$) and the Inventory of Depressive Symptomatology-Clinician (IDS-C) ($r = 0.875$, $p < 0.001$) (21). Draisma et al. (2015) found a Spearman's Rho of 0.61 between LCM depression scores and Clinical Global Impression (CGI-BD) rated depression, and a Rho of .63 between LCM mania scores and CGI-C rated mania in a sample of Dutch patients with BD (n=137), denoting a strong association between LCM ratings and CGI scores (22).

Thus, main study parameters where threefold: (1) demographical variables at baseline: age, marital status, educational level and work status at baseline; (2) clinical variables at baseline consisting of diagnosis, illness duration, age of onset, number of lifetime manic and depressive episodes, number of hospitalizations, use of medication, lifetime alcohol/drugs abuse, number of serious suicide attempts; and (3) LCM derived clinical variables such as proportion of time ill or impaired, number of days with scores not equal to five (i.e. the euthymic state),

average illness severity scores, average duration of episodes, and frequency of episodes.

2.3 Statistical analysis

Analyses were done in four steps: (1) demographic and clinical characteristics of the pregnant and non-pregnant samples were compared with descriptive statistics; (2) complete series of illness states – the LCM mood scores – were analyzed and typified for the two samples with the use of state sequence analysis (SSA); (3) cluster analysis was performed on the state sequences; and (4) two regression analyses were done, one on clusters with a set of predictors and another on variation in daily states with the same set of predictors.

The set of predictors were illness duration, marital status, work status, educational level, use of medication (15, 30).

Differences in demographical and clinical variables were analyzed with descriptive statistics, using t-tests for continuous variables and chi square tests for categorical variables. Descriptive analyses were performed in SPSS version 27. Missing lifechart scores of the 34 pregnant women within the observation period (less than 0.3% of the data) were imputed through intrapolation of the surrounding daily scores.

Complete series of illness states as expressed in fluctuations of daily severity scores of the pregnant and non-pregnant women were analysed with SSA (31, 32). The time series of a maximum of 272 daily severity scores resulted in so-called sequences of successive states. The goal of SSA is to describe complete sequences of events as trajectories of subjects though possible states. It is a non-parametric approach with no assumptions regarding underlying processes and aimed at description of sequences as a whole (33).

Dissimilarities between state sequences were calculated with a dissimilarity measure based on the number of operations necessary to translate a specific sequence into another. The similarities and differences were based on optimal matching techniques. Subsequently, clustering methods were applied to build similar types of sequences (34). By clustering sequences, groups were formed that were as homogenous as possible within the group and as different as possible from other groups. In the analysis, hierarchical clustering was applied using Ward's linkage on the distance matrix. The clustering procedures resulted

in a typology of sequence courses. Sequences within a cluster had the lowest dissimilarity scores with each other, and between clusters dissimilarity was optimal. Distributions of women over the clusters found in the sample of pregnant women (n=34) were subsequently compared to those found in the non-pregnant women (n=52).
Shannon entropy, an indicator of diversity of states (~severity scores) within sequences was calculated for all day. Entropy can vary between 0 (all sequences in the same state at time T), to 1 (maximum diversity at time T).
Multinomial regression of clusters on the predictors was performed. In the same vain regression of entropy on this set of covariates was applied.
The package TraMineR (version 2.2-0.1) within R-software was used for sequence analysis.

RESULTS

First, descriptive statistics with respect to the comparisons of sample characteristics are presented in tables 1-3. Next the distribution of states over days is presented in an index plot for all women in figure 1. Cluster solutions for both samples are also presented graphically as index plots in figure 2. Mean time spent in a cluster is given in figure 3. Results of multinomial regression of clusters in the combined set of samples on predictors are provided in table 4. Finally, results of regression of entropy on the same set of predictors are presented.

Table 1. Demographic characteristics of non-pregnant and pregnant women with BD recruited from two study cohorts from the Netherlands.

	Non-pregnant (n=52)	Pregnant (n=34)	Test statistic
Age Mean (SD)			
Years	35.2 (6.3)	34.1 (3.9)	T= -0.95 p=0.35
Marital status n (%)			
Married/cohabitating	24 (46.2)	33 (97.1)	
Widowed/separated	3 (5.8)	0 (0)	
Single	25 (48.1)	1 (2.9)	χ^2 = 23.2 p<0.01
Educational level n (%)			
Low (some high school or less)	1 (1.9)	1 (3.0)	
Middle (high school-2 year college)	43 (82.7)	8 (24.2)	
High (graduate of professional school)	8 (15.4)	24 (72.7)	χ^2 = 29.2 p<0.01
Work n (%)			
Regular work, school or household	29 (59.2)	26 (78.8)	
Other work	19 (38.8)	2 (6.1)	
Unable to work	1 (2.0)	5 (15.2)	χ^2 = 14.0 p <0.01

Table 2. Lifetime clinical characteristics of non-pregnant and pregnant women with BD recruited from two study cohorts from The Netherlands

Clinical characteristics	Non-pregnant (n=52)	Pregnant (n=34)	Test statistic
Diagnosis, n (%)			
Bipolar I	38 (76.0)	19 (59.4)	χ^2=2.541 p=0.11
Bipolar II	12 (24.0)	13 (40.6)	
Illness duration			
Mean duration in years (SD)	15.4 (7.29)	14.6 (6.18)	T= -5.02 p=0.62
Less than 5 years	3 (5.8)	3 (9.1)	
5-9 years	9(17.3)	3 (9.1)	
10-19 years	21 (40.4)	17 (51.5)	
20-29 years	19 (36.5)	10 (30.3)	χ^2=2.071 p=0.56
Age of onset (mean. SD)	19.9 (5.93)	19.5 (5.23)	T= -0.31 p=0.76
No. of depressive episodes, n (%)			
0	0 (0)	3 (9.1)	
1 episode	6 (11.5)	1 (3.0)	
2-4 episodes	16 (30.8)	16 (48.5)	
5-10 episodes	13 (25.0)	7 (21.2)	
11-20 episodes	5 (9.6)	4 (12.1)	
>20 episodes	12 (23.1)	2 (6.1)	χ^2=11.977 p=0.04
No. of manic episodes, n (%)			
0	0	1 (3.0)	
1 episode	4 (7.7)	6 (18.2)	
2-4 episodes	20 (38.5)	19 (57.6)	
5-10 episodes	16 (30.8)	4 (12.1)	
11-20 episodes	7 (13.5)	1 (3.0)	
>20 episodes	5 (9.6)	2 (6.1)	χ^2=10.699 p=0.06
Hospitalizations, mean (SD)	4.1 (5.8)	1.4 (1.7)	T= -2.627 p=0.01
Medication, n (%)			
Without medication	0 (0.0)	8(23.5)	
1 Mood stabilizer	23 (44.2)	8 (23.5)	
>1 Mood stablizers	20 (38.5)	0 (0.0)	
Moodstabilizer and other medication	9 (17.3)	8 (23.5)	
Other medication only	0 (0.0)	10 (29.4)	χ^2=43.453 p<0.01
Substance abuse/dependence, n (%)			
Alcohol	9 (17.3)	3 (9.1)	χ^2=1.124 p=0.29
Drugs	7 (13.5)	7 (21.5)	χ^2=0.881 p=0.35
Serious suicide attempts			
None	36 (69.2)	28 (84.8)	
One or more	16(30.8)	5 (15.2)	χ^2=2.547 p=0.10

Table 3. Clinical lifechart results of non-pregnant and pregnant women with BD recruited from two study cohorts from The Netherlands.

Averages (SD)*	Non-pregnant (n=52)	Pregnant (n=34)	Test statistic T	p
No. depressive episodes*	3.43 (11.95)	0.55 (0.94)	1.40	0.16
No. manic episodes*	0.35 (0.68)	0.38 (1.35)	- 0.14	0.89
No. hypomanic episodes*	1.10 (2.95)	1.29 (1.59)	- 0.40	0.69
No. manic days*	14.06 (36.53)	8.90 (20.81)	0.75	0.46
No. hypomanic days*	16.19 (23.12)	18.83 (33.25)	- 0.43	0.66
No. depressive days*	71.85 (76.07)	56.78 (80.20)	0.88	0.38
No. days ill (depressed, manic, hypomanic)*	102.10 (84.53)	84.51 (93.17)	0.91	0.37
Average mania score	0.39 (1.01)	0.23 (0.54)	0.85	0.40
Average depression score	0.45 (0.58)	0.34 (0.55)	0.88	0.38

* corrected for the number of observations

No age differences were present between the samples. Pregnant women were significantly more often married, attained higher educational levels and were more often unable to work (Table 1). Pregnant women had less previous hospitalisations and used less medication than the non-pregnant group (Table 2). Of the pregnant women three women used antidepressant medication without a mood stabilizer, while in the non-pregnant group none of the women used an antidepressant without a mood stabiliser. No significant differences were found regarding lifetime illness duration, age of onset, lifetime number of experienced manic or depressive episodes, lifetime substance abuse or dependence, and number of attempted suicides.

Comparison of the course of BD in both samples showed no significant differences in LCM variables (table 3) regarding episodes or number of ill days during the observation episode.

Sequence Analysis results

Distributions of proportions of severity scores per day were plotted for the whole observation periods in an index plot (Figure 1).

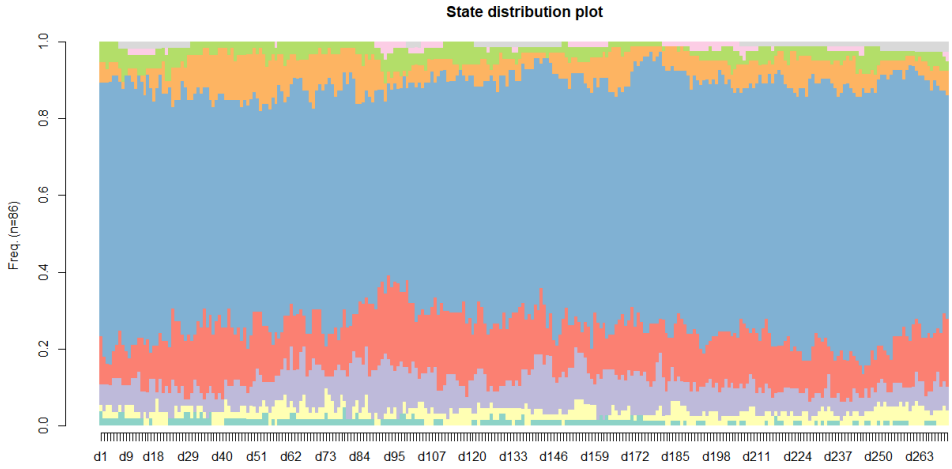


Figure 1 shows that most time of women with BD was spent in the euthymic state. This state covered the largest surface per day during the whole observation period. The percentage of women in this state was the highest, followed by 'mildly depressed' and 'mildly manic'.

Figure 2 gives the graphic results of a cluster analysis with three clusters for the separate samples.

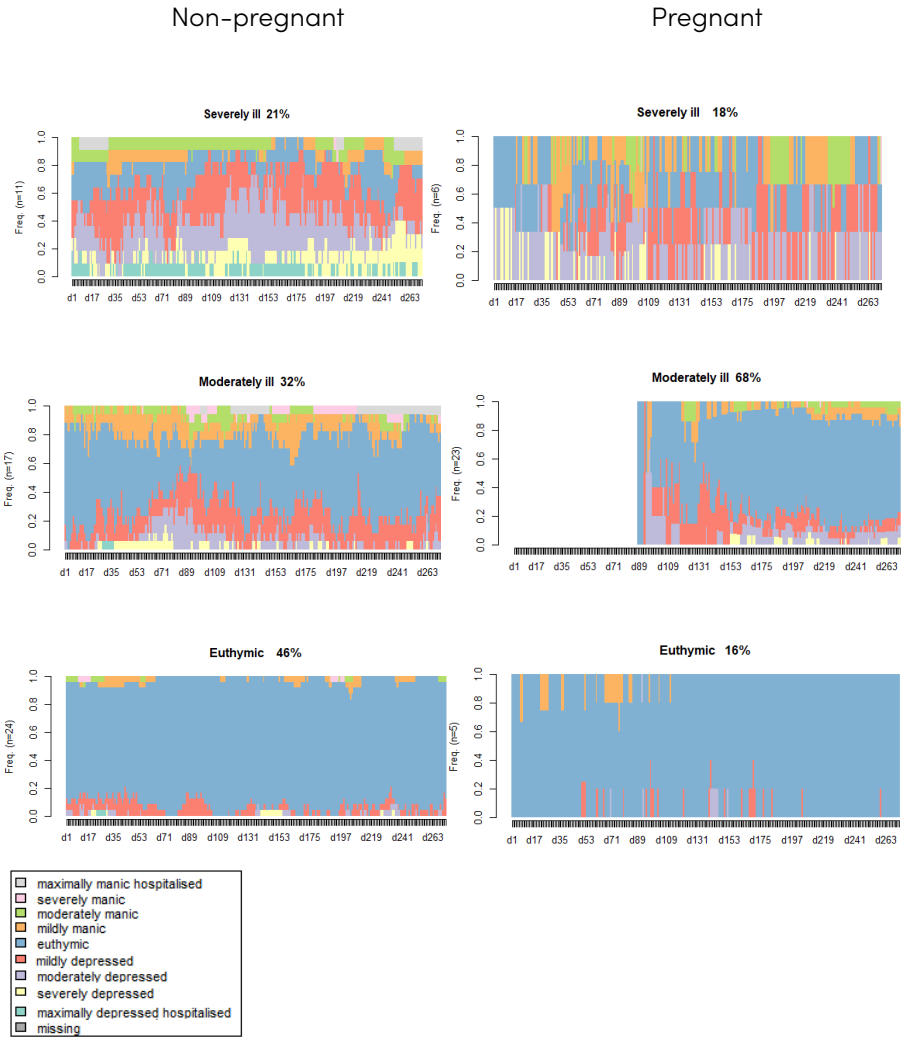
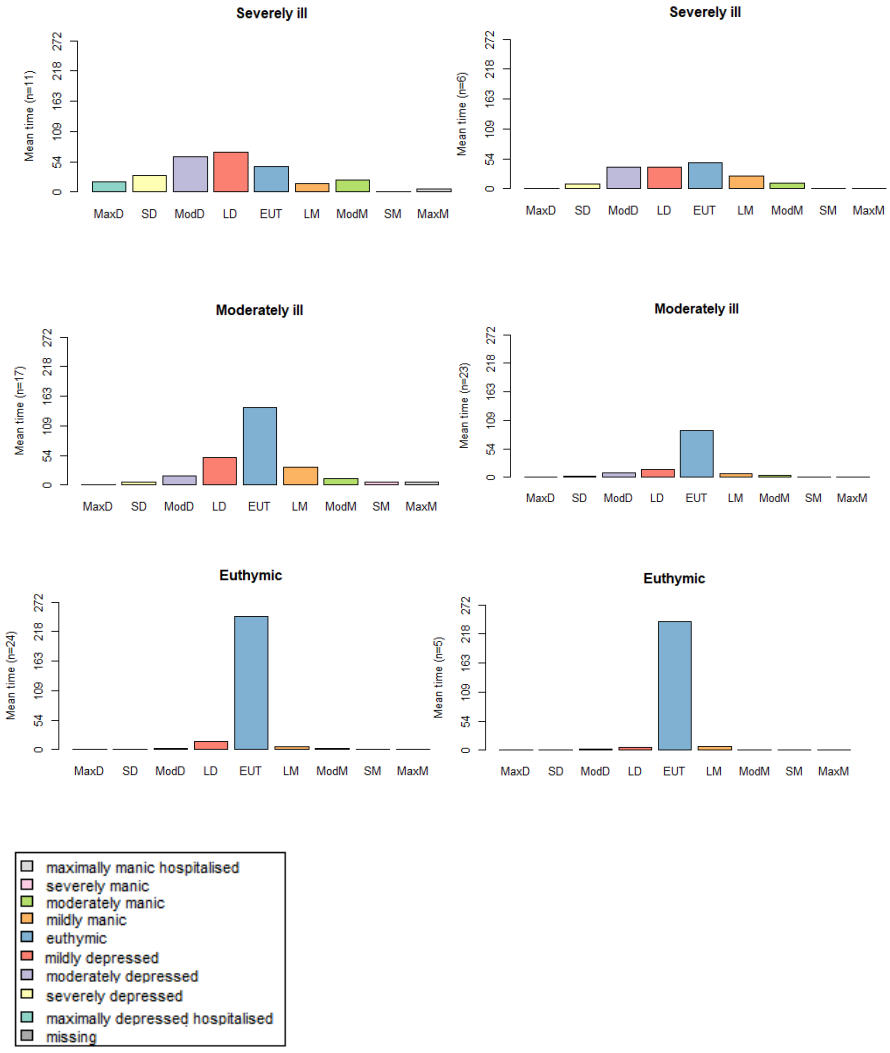


Figure 2. Index plots of three cluster solution for the pregnant sample and non-pregnant sample; X-axis: time in days (d1 means dey 1), Y axis: proportions women distributed over states in cluster.

Women in the clusters 'severely ill' of both samples showed sequences with mainly severe and moderate depressive or manic days and few euthymic states. The second set of clusters, 'moderately ill' contained state sequences with some illness, days with mild to moderately ill days with respect to both mania as well as depression. Finally, clusters 'euthymic' were typified by sequences with mainly euthymic days, the main area of these clusters were taken up by euthymic states. This three cluster solution shows that the severely ill cluster in the non-pregnant sample consisted of 21% (11 / 52) of the participants and in the pregnant sample 18% (6 / 34) of the participants. The euthymic cluster in the pregnant sample consisted of 16% (5 / 34) the women, whereas this euthymic cluster in the non-pregnant sample was larger, consisting of 46% (24 / 52) of the women. The majority of the pregnant women were clustered as 'moderately ill': the percentage in this cluster is twice as high as the percentage of non-pregnant women in this cluster (68% and 32%, respectively). These distribution differences between samples were significant: χ^2= 48.02, df = 2, p-value <0.001.

Number of days spent in each of the nine states obviously differed over the three clusters. Evidently, more days were spent in the euthymic state in the euthymic cluster as compared to the other clusters. Interestingly, daily scores were not normally distributed over mania and depression. There was a tendency that more days were rated as depressed (left side of the cluster figures) than manic (right side of the figures) (Figure 3).

Figure 3. Mean time (in days) spent in each state for three clusters, pregnant women on the left, non-pregnant women on the right



The level of entropy of scores, i.e., the diversity of states on each day for both samples, for the non-pregnant women were higher (average 0.56) than for the pregnant women (average 0.43).

In multinomial regression the dependent variable (cluster) has three different categorical values. Regression of the three clusters on three demographic variables (educational level, marital status and work) and two clinical variables (medication, illness duration) showed only one significant relation, namely between educational level: the odds of going from cluster 1 (severely ill) to cluster 2 (moderately ill). Thus, the higher the level of education, the higher the odds of going from severely ill to moderately ill (Table 4).

Table 4. Multinomial regression of clusters on a selection of predictors (n=86). Odds ratio's and standard errors. Base outcome (reference category) cluster 1: severely ill. **p<0.01

	Odds ratio (Std. Error)	
	Cluster 2 (moderately ill)	Cluster 3 (euthymic)
Educational level	6.71 (0.67)**	1.64 (0.57)
Marital status	1.3e-06 (245.87)	1.2e-00 (0.48)
Work	1.59 (0.57)	1.14 (0.49)
Medication	1.06 (0.25)	0.87 (0.26)
Illness duration	0.75 (0.41)	1.29 (0.32)
Pseudo R^2	0.19	

Subsequently, the results of regression of entropy (n=86) on the same set of predictors is shown (Table 5).

Table 5. Regressing Entropy on a selection of covariates (n=86)

Variable	Beta	Std. error	*t* value	Pr. (>|t|)
Intercept	0.594	0.214	2.779	0.007**
Educational level	- 0.134	0.054	-2.481	0.016*
Marital status	- 0.002	0.053	-0.039	0.969
Work	- 0.015	0.046	-0.332	0.741
Medication	0.025	0.023	1.080	0.283
Illness duration	0.011	0.032	0.339	0.736

The only covariate that produced a significant effect in regression of entropy on predictors was educational level. This suggests that the lower the educational level, the more instability occurred in the course of BD.

DISCUSSION

While previous prospective studies have investigated risk of, and/or time to, recurrence of mood episodes during pregnancy in BD (35, 36), this is the first study comparing fine-graded prospective illness course with the lifechart method (LCM) in pregnant and non-pregnant women with BD. No differences were found in illness severity variables, such as number of days ill, including days depressed, hypomanic, or manic, or average severity scores. However, with a cluster analysis of LCM data within both samples to reveal longitudinal illness patterns, within the study period, more pregnant women were moderately ill, whereas more non-pregnant women were euthymic.

In addition, pregnant women showed less variation of mood states than non-pregnant women. Women with a higher educational level in both samples were more likely to belong to a cluster moderately ill than to a cluster severely ill. An explanation for the relation between educational level and less mood instability could be that more adequate psycho-education is obtained by higher educated women.

Constructing typologies/groups, according to temporal data, of patients with BD has been done by other investigators. Post et al. (2003) determined the severity of illness in the first 258 outpatients in the SFBN who had one year of prospective LCM ratings (4). Their typologies contain groups of patients who remained severely and almost continuously ill (26.4%), intermittently ill (40.7%), or minimally ill (32.9%) over the course of that year. The patterns of the ratings were visually assigned to the three groups by two independent investigators. Nowadays, with the application of state sequence analysis, clustering methods can be used to build similar types of illness course and so defining groups that are as homogenous as possible on the one hand and as different as possible from other groups on the other. This clustering method does not depend on subjective clinician ratings, but can be applied automatically using algorithms, enhancing reliability.

A possible explanation for the difference between our two samples, especially the higher proportion of euthymic days in non-pregnant women versus pregnant

women, could be that more non-pregnant women used psychotropic medication during the observation period. The use of medication prevents recurrences in pregnant and non-pregnant women (18, 37-39). In more detail, in our study 23.5% of pregnant women used no medication at all, compared to none (0%) of the non-pregnant women, whereas 38.5% of the non-pregnant women used more than one mood stabilizer compared to none of the pregnant women. Although the use of antidepressant medication without a mood stabilizer is not recommended in bipolar disorder because of the risk of mood instability and switch to mania (40), three pregnant women but none of the non-pregnant women used an antidepressant without a mood stabilizer.

All women in both samples received psychiatric treatment and most of the pregnant women had pre-pregnancy consultations. It is possible that women with a more severe BD, who would not stop medication because of fear for recurrence, decided not to attempt to conceive, which could explain why the number of medications used in the pregnant women in our study was relatively low.

In general, women with a childwish are recommended to be stabilized for a period of at least six months before becoming pregnant (41). In a study of 70 women with BD, 45% who sought consultation for treatment options and risks during pregnancy had been advised to avoid pregnancy by a health care professional before consultation (42). After the consultation 37% chose to avoid pregnancy with the most commonly reported reason being fears of adverse effect of medication on the development of the fetus (56%) or concerns of genetic transmission of BD to offspring (22%).

There still is a paucity of systematic data on the effects of pregnancy on the course of BD. In our study, with use of daily mood monitoring, no differences were found in the course of BD in pregnant versus non-pregnant women. Comparing trajectories may be a better way to study the effect of pregnancy on the course of BD. A major challenge would be to investigate the role of pregnancy on the 'naturalistic' (i.e. untreated) course of BD, since it is recommended to prescribe some form of preventive medication in patients with BD also during pregnancy (43).

Our study has several strengths. It is the first study comparing prospective daily mood ratings in a sample of pregnant and non-pregnant women with BD. The samples did not differ in demographic characteristics such as nationality and

age, nor in clinical variables such as type of diagnosis (BD I or II), illness duration, age of onset, lifetime number of manic and depressive episodes, lifetime substance abuse, and serious suicide attempts. Also, this is the first study using SSA and clustering methods on LCM data to reveal different clusters of illness course.
However, there are also several limitations. Since the design consists of two cohorts from different studies, and cases were not assigned at random or via case control procedures, the comparability of both samples remains uncertain. The pregnant women had a higher educational level and were more often married than the non-pregnant women. The use of medication differed between the two cohorts, with a potential impact on the course of BD. Also, LCM data from pregnant women were reported from week 12 of pregnancy untill giving birth, hence data on the first trimester are not included.

CONCLUSION

No differences in average values of clinical course variables in BD were found among pregnant women compared to non-pregnant women. The application of SSA to reveal patterns in the overall course in the observational period did show differences in proportions of pregnant versus non-pregnant women distributed over three clusters of sequences. More pregnant women showed a moderately ill pattern of daily mood scores whereas more non-pregnant women showed a euthymic pattern. One explanation is that more non-pregnant women used (more) psychotropic medications than pregnant women, which may have a protective effect. Pregnant women showed less variation in mood than non-pregnant women.
To answer the question whether pregnancy influences the course of BD, ideally we need large, prospective case-control studies comparing pregnant and non-pregnant women. Another option is to compare within individuals the course of BD during pregnancy and during the year before.

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7

Chapter 7

Postpartum mania in a man with bipolar disorder

Case report and a review of the role of sleep of loss

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ABSTRACT

Background

In contrast to postpartum mood episodes in women with bipolar disorder, little is known about the risk of recurrence risk in bipolar men who just became father.

Case report

We present the case of a male patient with bipolar disorder who had a manic episode immediately after becoming father. His spouse had a normal pregnancy and delivery started during daytime and lasted until the early morning hours. The patient subsequently developed a manic episode, which had a major impact on the family.

Conclusions

There is a well-known correlation between sleep loss and the occurrence of a manic episode. The study of psychopathology in the postpartum period in relation to sleep disturbance refers mainly to women. Disturbance of sleep patterns in the days around childbirth and the weeks thereafter may also negatively impact the course of bipolar disorder in the father. When the spouse of a male bipolar patient becomes pregnant, preventive strategies for the postpartum period should be planned in advance.

INTRODUCTION

The postpartum period is strongly associated with a highly increased risk for recurrence of mood episodes in women with bipolar disorder (1). Moreover, women not previously diagnosed may experience their first mood episode soon after childbirth. In contrast to the vast literature on the impact of pregnancy on the course of bipolar disorder in women, little attention is given to the male patient with bipolar disorder who is to become a father. However, it is likely that pregnancy of the spouse, childbirth, and the post-partum period will have a major impact on the life of the male bipolar patient and may put him at an increased risk for depressive and especially manic recurrences. Apart from emotional factors, altered sleep patterns may play a major role in destabilisation of mood disorder. We present a case of a male patient who suffered from a manic episode following childbirth and give an overview of the existing literature.

Case report

Mr. A. is a 32-year-old married and unemployed craftsman, previously diagnosed with bipolar I disorder. He had his first depressive episode at age 25. Following a second depression at age 28 he suffered from a first manic episode. In total he had four episodes; his last episode was three years ago, and since then he had remained stable on lithium prophylaxis. His wife has a challenging job at a housing broker and had her first pregnancy. The couple had made the usual preparations, both materially and emotionally. They had informed the therapist of Mr. A about the pregnancy. Since no problems were expected, no special arrangements for the period surrounding childbirth were made. It was agreed that 3 months after delivery his wife would return to her work and the patient would stay at home and take care of the child. They anticipated a positive effect on Mr. A, assuming that the responsibilities for the baby would improve his daytime structure.

The delivery lasted for about 24 hours, started at 06:00 am, and the baby was born at 04:00 am the other day. The baby had an irregular sleep rhythm, and in the first nights she cried a lot. As a consequence, Mr A's sleep was disrupted; he was awake every time the baby cried and had problems falling asleep afterwards. After five days and nights in which he had just slept for about four hours a night, he became increasingly excited. He wanted to go out in the middle

of the night to tell his friends about his happiness having a baby. Although well-informed about his bipolar illness, he and his wife did not recognize that these feelings and behaviours could be the first manifestations of a manic episode. Twelve days after childbirth mr. A. was hospitalized for acute mania. It took several months before he was recovered and able to take care of his daughter.

DISCUSSION

The literature on postpartum psychopathology refers almost exclusively to women.

(1). Paternal "postpartum" mood disorders have attracted far less attention and some studies suggest that these are relatively rare (2). However, a recent meta-analysis reported that the prevalence of paternal depression in the period between the first trimester of pregnancy and the first-year post-partum is estimated at 10%, with higher rates of 25% during the 3- to 6-month post-partum period (3).

Goodman (4) reviewed 20 studies of postpartum paternal depression. The incidence of paternal depression ranged from 1,2% to 25,5% in community samples, and from 24% to 50% among men whose partners were experiencing postpartum depression. Maternal depression was the strongest predictor of paternal depression during the postpartum period.

It was not reported whether these men experienced a first onset of depression during the postpartum period or whether they had a recurrence of a previously diagnosed mental disorder.

Wee et al (5) reviewed the literature on correlates between ante- and postnatal depression in fathers and found that having a depressed partner was the most common risk factor. They pointed out however that there were significant methodological limitations to these studies.

Ramchandani et al (6) found in a population-based study that 4 % of the fathers were depressed in the first 8 weeks after childbirth, and that this had a negative impact on the emotional development of these children.

Bipolar disorder (i.e., the occurrence of mania, hypomania, and mixed states next to depression) is rarely addressed in the current research on paternal perinatal psychopathology. In a longitudinal follow-up study of fathers of newborn children (born in a Braziian hospital from April 2007 through May 2008), the prevalence

of paternal depressive, manic, and hypomanic episodes at the second month postpartum was 4.5%, 3.4%, and 3.3%, respectively, and at 12 months postpartum was 4.3%, 3.5%, and 0.9%, respectively (7). There was no clear relationship between mood episodes during pregnancy and those postpartum.
Davenport et al (8) studied 40 men with bipolar disorder admitted to a research unit during a nine-year period. Twenty-one of them experienced an affective episode during the pregnancy of their spouse or in the first year postpartum. Compared to those who had no affective episode in that period they had an earlier onset of the bipolar disorder and the experience of parental loss in youth.
There is a significant temporal relationship between sleep disruption and mood change, especially between loss of sleep and the occurrence of a hypomanic or manic episode (9). Alterations in sleep often predict a worsening in clinical state, and in turn sleep worsens further during an episode (10). Wehr et al (11) hypothesized that sleep reduction could be the final common pathway to mania.
Instability of the circadian system has been hypothesized as a core vulnerability for bipolar disorder and there is evidence that this is also present in euthymic patients (12-15).
Ankers and Jones (16) found differences in circadian activity and sleep patterns between individuals at behavioral high-risk for hypomania and age-matched controls, suggesting that these differences are not simply the consequences of existing bipolar disorder.

Studies of postpartum depression, mania, or psychosis in relationship to sleep disturbances refer mainly to women. Ross et al (17) reviewed the association between sleep and perinatal mood disorders. There is some evidence that women with subsequent postpartum psychosis had a longer duration of labour and were more likely to deliver at night than controls (18,19). Sleep loss has been suggested as a final common pathway in the development of psychosis in vulnerable women (20). Although these studies only included women, it is likely that sleep loss and disruption of social rhythm in the perinatal period is a risk factor for vulnerable men as well (21).
Becoming father can cause significant psychological stress because of e.g. a changed relationship with the spouse, new responsibilities for a child and financial consequences. In early literature also psychodynamic factors are mentioned (8).

In our case report several risk factors coincided: the major life event of becoming father for the first time, sleep loss due to a long and night-tjme delivery, and sleep deprivation due to the irregular sleep pattern of the newborn. The patient's bipolar disorder had been fairly stable and all attention was directed towards his spouse and the baby. The impact of becoming father and the disruption of social and circadian rhythm and sleep pattern surrounding and following childbirth were not sufficiently anticipated. Increased emotionality, excitement, and feelings of intense happiness may well have been regarded as appropriate in the turmoil of having a first child, resulting in signs of impending mania being dismissed. The relationship between sleep loss and the onset of symptoms appears very strong. Although there was no overt ambivalence, whether the agreement between patient and his spouse that he would take care the primary caregiver role for the baby played a role in the aetiology of the manic period is unknown. In the case of women with bipolar disorder it is customary to make a prevention plan for the entire period of pregnancy and postpartum. We strongly advise to do the same for the male bipolar patient whose spouse becomes pregnant.

CONCLUSION

The postpartum period is recognized as a time of high risk of recurrence for women with bipolar disorder. However, male patients with bipolar disorder who become father may also have an increased risk for recurrences of mood episodes during the perinatal and post-partum period. Although the underlying pathophysiology may differ from bipolar women, sleep deprivation and disrupted social and circadian rhythm may be a shared risk factor for manic episodes in particular. It is important to discuss these issues during pregnancy of the spouse and plan preventive strategies optimizing sleep regulation and anticipate treatment options for sleep disorder and early signs of recurrence. Becoming a parent should be regarded as a major and positive life event that unfortunately may carry a considerable risk of mood instability for both women and men with bipolar disorder.

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8

Chapter 8

Summary and general discussion

The aim of this thesis was to study the course of bipolar disorder (BD) in pregnant women and the influence of sleep during pregnancy and the peripartum period on the development of postpartum mood symptoms. Importantly, we also wanted to explore considerations of women with BD about family planning and pregnancy.
The aim of the thesis emerged from my daily clinical practice. As a clinician I often get questions of patients about how pregnancy and the postpartum period affect the course of their illness. At the same time, I became interested about how women with BD themselves think about family planning, use of medication, and support by professionals during pregnancy and the postpartum period. Another theme that intrigued me was the effect of perinatal sleep disturbance on postpartum psychopathology. Although much has been written about BD and pregnancy, after systematic reviewing the literature I was surprised that only two studies specifically addressed perinatal sleep disturbance and postpartum psychosis (J. L. Bilszta et al., 2010; Sharma et al., 2004) and felt more work was needed to close this knowledge gap.

Bipolar disorder is an often severe mental illness with an estimated lifetime prevalence ranging from 1.3% tot 2.4% (de Graaf et al., 2012). Pregnancy and especially the postpartum period are vulnerable periods for women with BD. Women with BD have a high risk of recurrence of mood disorders and psychosis in the postpartum period (Wesseloo et al., 2016). This has huge consequences, not only for the mother and her family, but importantly these psychiatric symptoms can also affect the development of the child.

This chapter provides a summary of our findings, a reflection on the strengths and limitations and methodological considerations of the studies, and finally recommendations for clinical practice and future research.

Main findings

1. *What are thoughts and considerations of women with bipolar disorder about family planning and pregnancy?*

In chapter 2 we investigated experiences and considerations of women with BD about if and when they wanted to get pregnant. A qualitative study of 15

childless women with BD I revealed that they worried about heritability of BD, had questions about medication use during pregnancy, and were fearful of recurrence of a mood episode during pregnancy or postpartum. In addition, these women feared to be incompetent as a mother during future mood episodes and mentioned that support of their partner, social network, and mental health providers is essential. A timely, open, and thorough discussion with their mental health professionals about family planning was desired and initiating this was perceived as a shared responsibility.

2. *What is the impact of medication on the course of bipolar disorder in pregnant women?*

In chapter 3 we present the results of a systematic review about the impact of continuing maintenance medication on the recurrence of mood disorders during pregnancy. One of the conclusions is that the 22 included studies reported a wide range in the recurrence rate of BD (0% to 73%) and major depressive disorder (1% to 75%). Another conclusion is that maintenance pharmacotherapy during pregnancy in women with mood disorders significantly reduced the risk of recurrence (66% in BD and 54% in major depressive disorder).

3. *What is the effect of perinatal sleep disturbance on postpartum mood in women with bipolar disorder?*

The study protocol of the Sleepreg-bd study is described **in chapter 4**. Mood and sleep was monitored during weeks 26, 38, 39, and 40 of pregnancy, the first four weeks postpartum, and finally in week 12 postpartum. Assessments consisted of self-report questionnaires and objective (actigraphy) and subjective (diary) sleep measures.

In chapter 5 the results of the Sleepreg-bd study are presented. We did not find an association between objective sleep disturbance in the perinatal period on postpartum mood symptoms in women with BD. In healthy sleepers, i.e., women who slept 7-9 hours/day, poor sleep efficiency in the first week postpartum was predictive of hypomanic mood symptoms in the second week postpartum. The strongest predictor for postpartum mood symptoms was having mood symptoms in the second trimester of pregnancy.

4. Does the course of bipolar disorder differ in pregnant women versus non-pregnant women?

We compared the course of BD in a cohort of 34 Dutch pregnant women from the Sleepreg-bd study to the course of BD in a cohort of 52 Dutch non-pregnant women who participated in the Stanley Foundation Bipolar Network (SFBN) Naturalistic Follow-Up Study (Leverich et al., 2001) using scores of the Lifechart Method (LCM) in chapter 6. Our findings showed no differences in several clinical BD course variables (symptomatic days, average severity scores, frequency, and duration of episodes) between pregnant and non-pregnant women. Looking beyond these parameters, with a combination of State Sequence Analysis (SSA) and cluster analysis on the sequences of daily mood scores on the LCM we discovered three comparable clusters: a euthymic, a moderately ill, and a severe ill cluster. The distribution differences between pregnant and non-pregnant women were significant, with a majority of the pregnant women (68%) belonging to the moderately ill cluster and a majority of the non-pregnant women (46%) to the euthymic cluster. The average daily variation in mood symptoms as assessed with Shannon's entropy in pregnant women was less than in non-pregnant women (respectively 0.43 versus 0.56). In conclusion, although no differences were found in overall course of BD in pregnant women versus non-pregnant women, more pregnant than non-pregnant women with BD belonged to the moderately ill cluster, and during pregnancy the variation in mood state in pregnant women with BD was less than in non-pregnant women with BD.

5. What about men?

In chapter 7 we present the case of a man with BD who had a manic episode immediately after the birth of his child. Although a single case study cannot answer the question whether sleep is one of the causes of a manic episode, we argued that in this case several risk factors coincided: sleep loss due to a long, night-time delivery, subsequent sleep deprivation due to the irregular sleep pattern of the baby, and the major life event of becoming a father. This case study underscores the need to also pay attention to men with BD who become fathers.

General discussion

Part 1: What can be recommended to professionals when a woman with bipolar disorder expresses a child wish?

In our qualitative study we found that women expect early consultation with professionals for support and for getting specific information about heritability of the illness and the safety of medication use during and immediately after pregnancy.
As women consider it important to receive treatment/support from their trusted professionals (chapter 2) treatment and support during pregnancy and the postpartum period thus can best be provided by professionals known to them, with the possibility of consultation at the POP-clinic.
In the Netherlands women with BD (or other psychiatric disorders) can get a preconception advice by the "Psychiatric-Obstetric-Pediatric (POP)"-clinic. The POP outpatient clinic consists of a multidisciplinary team that provide the woman and her partner an integral medical advice from the psychiatric, obstetric, and pediatric perspective.
Interestingly, currently there is no guideline how POP-clinics in the Netherlands should be organized. And as a consequence there are 3 different POP models described (Paarlberg et al,, 2015). In the first model the patient sees one professional, mostly a gynecologist, who brings the case into a multidisciplinary discussion, where the treatment advice is determined and after that discussed with the patient by one professional and the advice is sent to all involved professionals. In the second model, the patient has a consultation with the multidisciplinary team (a gynecologist, a psychiatrist, and a pediatrician) in which among other issues the use of medication during pregnancy and lactation is discussed and the patient can ask questions to the team. The treatment is not taken over by the POP-clinic but remains with the own (mental health) professional. In the third model, the treatment of the women during pregnancy and postpartum period is completely transferred to the POP-clinic.
Model two best reflects the desire of women to continue treatment with their trusted professional.
Decision-making is often difficult for women with BD. In a qualitative study the factors influencing the decision-making regarding pregnancy and childbirth in

women with BD were investigated (Dolman et al., 2016). Women in that study reported that accessing information to be able to make informed decisions generally was very difficult. They felt that professionals lack the knowledge to answer their questions adequately and that they were reluctant to refer them to a POP outpatient clinic as they may have doubts whether the women could fulfil a mother role in the future. Although we have not investigated this, in our study none of the women mentioned this explicitly.
These results show the importance of shared decision making, in which information is given by professionals (if necessary, with the aid of a POP-clinic) and discussion for possible and best suited options is explored with the woman and if possible, her partner. In the end the woman and her partner can make a well-informed decision whether to continue of discontinue prophylactic medication.
Development of patient decision aids (PDAs) is a first step forward, but in the field of psychotropic medication these are still scarce and limited in sorts of medication (Broughton et al., 2021; Hussain-Shamsy et al., 2022).

Women with BD also have concerns about their capability of being a good enough mother (Anke et al., 2019). The women in our study expressed the same concerns, especially if they would have a mood episode. Attention to this subject should therefore be part of the treatment and if necessary, referral to an infant mental health specialist, if possible, may be considered.

We recommend making an individualized treatment plan, that includes whether or not to use medication, addressing early signs of recurrence of mood symptoms, and what to do in case these emerge. In addition, there is a need that more practical issues, such as wishes regarding childbirth, are openly discussed. Clinical experience indicate that women feel more secure if practical matters have been carefully considered beforehand.
This individualized treatment plan should be known to all professionals with whom the woman will deal during pregnancy and the postpartum period (i.e., gynecologist, obstetrician, pediatrician, midwife, maternity nurse, general practitioner). This can be summarized in a so called "Pregnancy Plan".
We have been involved with the development of a "Pregnancy Plan" in collaboration with experts-by-experience (pregnant women with BD), at our

Centre of Bipolar Disorders, a specialized outpatient clinic for patients with BD in the eastern part of the Netherlands. An example of such a plan is included at the end of this chapter.

Part 2: Course of bipolar disorder in pregnant women

Despite the importance of the topic, a paucity of studies is available about the impact of pregnancy on the course of BD (McAllister-Williams et al., 2017). Apart from our review three other reviews address the topic ((Larsen & Saric, 2017; Salim et al., 2018; Sharma & Pope, 2012). These reviews all contain less than 20 studies; the review of Larsen et al. about the risk of recurrence when discontinuing treatment with mood stabilizers contains 8 studies; Salim et al reviewed 11 studies investigating the impact of pregnancy on the course of BD and Sharma et al reviewed 8 studies on this topic. Our review included 14 studies on the influence of pregnancy on the course of BD.
To the best of our knowledge no prospective study has been done investigating the course of BD in pregnant women compared to non-pregnant women. Our study is the first comparing both groups. A limitation is that the comparison is based on two different studies (the SFBN-study and the Sleepreg-bd-study) and that cases were not assigned via case control procedures or at random. Consequently, the comparability of both samples remains somewhat uncertain. Although we did not find differences in clinical course variables, we discerned three comparable clusters in both samples.

Apparently pregnant women report more mood symptoms than non-pregnant women. A possible explanation for this difference, especially the higher proportion of euthymic days in non-pregnant women versus pregnant women, could be that more non-pregnant women used psychotropic medication during the observation period. Another reason could be that pregnant women experience more discomfort such as nausea, other pregnancy ailments, and disturbed sleep. Use of medication prevents recurrences in pregnant and non-pregnant women with BD (Geddes & Miklowitz, 2013; Kishi et al., 2020; Larsen & Saric, 2017; Stevens et al., 2019). In our study 23.5% of pregnant women used no medication at all, as compared to none (0%) of the non-pregnant women. None of the pregnant women used more than one mood stabilizer, while more than

one mood stabilizer was used by 38.5% of non-pregnant women. An explanation why the number of medications used by pregnant women in our study was so low might be that women who would not stop medication because of fear of recurrence, decided not to attempt to conceive. Another explanation might be that women with medication during pregnancy decided not to participate in the study.

Part 3: Impact of perinatal sleep on postpartum mood disorders

Although clinical experience learns us that sleep disturbance is a risk factor for postpartum psychosis, only two studies addressed this topic, one retrospective study (Sharma et al., 2004) and one prospective study (J. L. C. Bilszta et al., 2010). More studies have been done on the impact of perinatal sleep disturbance on postpartum depressive episodes, indicating that self-reported perinatal sleep disturbance is associated with postpartum depressive episodes or depressive symptoms (Bei et al., 2015; Marques et al., 2011; Okun et al., 2009).
In our prospective study we found no association between objective sleep problems in pregnancy and postpartum mood symptoms in women with BD. It may be that no such association exists. Nevertheless, possible reasons for not finding an association between objective sleep disturbance in pregnancy and postpartum mood symptoms are the considerable dropout rate in the study, the use of medication in pregnancy and postpartum period, and the occurrence of few mood symptoms during pregnancy and postpartum period in our sample. Our sample turned out to be a healthy sample with few women who used prophylactic medication during pregnancy. In the Netherlands, it is recommended that women with BD should use prophylactic medication directly postpartum, minimally as 'if necessary' medication in case of mood symptoms or sleep disturbance. Unfortunately, in our study we did not have data of the actual use of medication postpartum.
Sleep disturbance is both a risk factor and a symptom of a (postpartum) mood episode. A systematic review even suggests that sleep disturbance frequently precedes BD by several years and the results of a study in 771 healthy subjects support the assumption of disturbed sleep as a possible predisposing factor for BD (Hensch et al., 2019; Ritter et al., 2011). It is difficult to differentiate whether sleep disturbance is a risk factor for or an early symptom of a mood episode.

In our study we found that in women who slept 7-9 hours/day in the second trimester of pregnancy (so called healthy sleepers), poor sleep efficiency in the first week postpartum was predictive of hypomanic mood symptoms in the second week postpartum. Whether this can be seen as a risk factor or as an early symptom of a (hypo)manic mood episode is difficult to decide. Still, from a clinical perspective this is less interesting, in both cases the recommendation would be to treat the sleep disturbance. Sleep medication can be given initially; if necessary, when signs of (hypo)mania emerge, antipsychotics can be added.
Although we primarily studied the impact of perinatal sleep on postpartum mood symptoms, we found that having mood symptoms in the second trimester of pregnancy was the strongest predictor of postpartum mood symptoms. In women with major depressive disorder (MDD) antenatal depression is known to be an important risk factor for postpartum depression (Howard et al., 2014; Robertson et al., 2004). A recent study reported that a mood episode in pregnancy was a risk factor for lack of improvement in women with BD who were jointly hospitalized with their infant for a postpartum mood episode (Lasica et al., 2022).

Part 4: What are the challenges of research in women with bipolar disorder during pregnancy?

Many articles are written about pregnancy, the perinatal period, and/or the postpartum period in women with BD, but most of them are descriptive, assessing risk factors or general management of BD based on clinical practice (Jones et al., 2014; Sharma et al., 2020) or are studies or reviews on medication (Clark, 2020; Poels et al., 2018). Reviews state that more research is needed (Sharma & Sharma, 2017; Thomson & Sharma, 2018). A systematic review on sleep and postpartum mental disorders concluded that among 31 studies the quality of one study was strong, 13 were moderate and 17 were weak, and the authors recommended high-quality research (Lawson et al., 2015)
We met several problems investigating the impact of pregnancy on the course of BD or to study the impact of sleep disturbance on mood symptoms in the postpartum period, two topics of this thesis.
To investigate the impact of pregnancy on the (natural) course of BD a large cohort of pregnant and matched non-pregnant women with BD is needed and

moreover, if we really want to establish the impact of pregnancy on the course of bipolar disorder participants should not use prophylactic medication. Nowadays, this would be unethical knowing most women with BD benefit from prophylactic medication, also in pregnancy. In our review we calculated a risk reduction of 66% in favor of continuing medication during pregnancy. Although our review has several limitations (inclusion of studies with different designs, prospective or retrospective, and with or without medication; most studies were done in specialized clinics with the risk of bias to more ill participants), it strongly suggests that continuing prophylactic pharmacotherapy during pregnancy reduces the risk of recurrence of mood episodes in women with BD.
Apart from the abovementioned it turned out to be difficult to recruit pregnant participants. In a systematic review on facilitators and barriers to pregnant women's participation in research the conclusion is that pregnant women report mostly altruistic and personal reasons for their participation in research. Inconveniences, such as time requirements, risks for mother and/or child, randomization, seem to be evaluated in the same way as by non-pregnant research subjects, often resulting in refusal to participate (van der Zande et al., 2018). In our study on the impact of perinatal sleep disturbance on postpartum mood symptoms, we recognize facilitators. Most women who participated in our study started because of altruistic reasons. They found it important to know more about the impact of sleep on postpartum mood, not only for themselves, but also for other women with BD who want to become pregnant in future. Women who refused to participate in the study mentioned that participation required too much time or they were afraid that the study would draw too much attention to their sleep or mood, which could make them uncertain. This may have caused a sample bias, as it is striking that most participants in our sample did not use any medication during pregnancy.

We also encountered some logistic problems that may have influenced the recruitment. We started the Sleepreg-bd study in collaboration with the Dutch Foundation of Bipolar Disorder (KenBiS), a national knowledge network in which many mental health care institutions participate. Other nationwide studies have shown that this network is very helpful in including participants (van Bergen et al., 2019; van Zaane et al., 2014). We estimated we had to enroll 130 participants. In the same period, another study started in the Netherlands, the NP3-study,

which aimed at inclusion roughly the same type of participants as we needed for our study. Fortunately, we agreed to a common recruitment of women with BD for both studies. Nevertheless, despite all our efforts to increase the number of participants (by prolonging the study period by two years, giving mouse pads to professionals who are working with women with BD as daily reminder of the study, giving presentations about the topic and the study), it turned out to be difficult to enroll enough participants and we did not obtain the target number of participants.

Another problem was that the dropout rate of women who had started the study was rather high. We included 105 participants in the study, but only 65 participants delivered complete data to be analyzed. Reasons for incomplete data were prematurity of the child, no sleep data at all, or no sleep data postpartum. There are several reasons for drop-out, such as pregnancy complications, and severe mood problems postpartum. Next to these more objective reasons, also subjective reasons were mentioned: women told us that by participating in the study they were confronted repeatedly with possible mood symptoms or possible sleep disturbance. Assessments were done at the end of the first and second trimester of pregnancy and from 2 weeks before delivery to 4 weeks after delivery, hence during pregnancy and the postpartum period women had to complete (mood) questionnaires, wear a MotionWatch and complete sleep diaries. Adherence to the study was in some cases ambivalent, some women did not want to wear the MotionWatch, other had difficulty with completing the sleep diary.
Remarkably, it turned out that relatively many dropped out in the period around delivery. In exit interviews these women told us that after the birth of their baby other things became more important than participating in the study. In a way, this can be seen as a healthy attitude, what is more important, getting used to a family or expanding family or participating in research?

Possibly, one of the main problems of the high dropout rate has been that, despite much contact via email or telephone (participants got a reminder to complete questionnaires, wear the MotionWatch, use the sleep diary and fill in the LifeChartMethod), there was no face-to-face contact between participants and researchers. We think one of the strengths of the SFBN-study is that participants

were seen monthly during the entire study by their own psychiatrist (Leverich et al., 2001; Post et al., 2001). This probably motivated participants to continue in the study. Despite the recruitment issues and limitation of dropouts, to the best of our knowledge, we have studied the largest prospective cohort of pregnant women with BD until now, assessing sleep and mood variables during pregnancy and the postpartum period.

Another challenge for investigating women with BD are external factors such as the healthcare system. The treatment of women with BD in the Netherlands is, in general, of good quality. As a consequence, relatively few symptoms and recurrences occur in the postpartum period, much less than found in other studies. Although this is something to be proud of and important for our patients, it makes finding significant results in this group more challenging. Indeed, in a country where care and treatment of women with BD is good, a large number of participants are needed to study postpartum psychopathology. In our study only three women had to be hospitalized in the postpartum period because of a postpartum mood episode. Of these three women, two had a delivery of more than 24 hours. We analyzed the data regarding duration and time of delivery, but, in contrast to Sharma, we could not replicate their finding of a relation between a long duration or night-time delivery and increased risk for mood symptoms in the postpartum period (Sharma et al., 2004). To make the matter even more complicated, sleep in late pregnancy predicts length of labor and type of delivery; pregnant women who slept less than 6 hours per night had longer deliveries and more caesarian sections than women who slept more than 6 hours per night in the ninth month of pregnancy (Lee & Gay, 2004). This suggests that shortened sleep in late pregnancy lengthens the duration of labor, which subsequently increases the risk for a mood episode.

In conclusion: pregnancy and especially the postpartum period are vulnerable periods in women with BD (Perry et al., 2021). Investigating the impact of pregnancy on the natural course of BD would be unethical because we know that prophylactic medication positively influences the course of BD, also in pregnant women. Studying the impact of perinatal sleep disturbance on postpartum mood symptoms/episodes requires a prospective design in a period of huge changes in the life of the participant (and her partner) with problems for recruitment and risk

of dropouts.

We have the following recommendations for future studies based on our experiences.
First, it may be better to use a questionnaire to assess subjective sleep, such as the Pittsburg Sleep Quality Index (PSQI), because it is probably more easy to use for participants than to complete a sleep diary every day (Buysse et al., 1989). At the time the protocol of the study was made it was decided to use a sleep diary, as it is more specific than the PSQI, a daily monitoring instead of retrospective assessing sleep in the month prior to complete the PSQI.
Second, using both subjective and objective measures may be too much an effort. In the first period of the study, we wanted to stick to the protocol, but since we would lose participants, we decided that if women did not want to use both sleep assessment-instruments (sleep diary for subjective sleep, or MotionWatch for objective sleep), they remained included if they used only one of them. As a consequence, fewer participants recorded both objective and subjective experiences. It is still an option with the data we have, to analyze whether a distinction exists between the impact of objective and subjective sleep data on postpartum mood symptoms. In an exploratory study perceived daily sleep quality was worse than sleep quality measured by wrist actigraphy in women with a mental disorder (Van Ravesteyn et al., 2014).
Third, the risk of dropouts may be reduced when there is face to face contact with the participant, preferably interweaving the study in the treatment.
Finally, prospective studies are also needed to investigate the natural course of BD in pregnant women and to study prospective studies the impact of sleep disturbance during pregnancy on postpartum psychopathology. For this we need (inter)national collaboration.

Part 5: What about men

Last but not least, although the literature on postpartum psychopathology in BD refers almost exclusively to women, men with BD can also have a recurrence after the birth of a child. Whether the life event of becoming a father, sleep disturbance, or other issues are a risk factor is still unknown. Studies on postpartum mood symptoms in men with BD are very scarce, we found no studies published since

2015. The emotional burden of fatherhood is mentioned as risk factor (Davenport & Adland, 1982), while a case report suggested psychodynamic factors as risk factor without designating the 48-hour lack of sleep that particular individual experienced (Davenport & Adland, 1982; Shahani, 2012). Two recent meta-analyses revealed several risk factors for postpartum depression in men: parental mental illness, maternal depression, and several psychosocial factors. Neither of these meta-analyses revealed sleep disturbance as a risk factor (Ansari et al., 2021; Wang et al., 2021).

Although in recent years no studies have been published on this subject, in clinical practice attention to men with BD becoming a father is growing. One way or the other, men with BD may also experience sleep disturbance after the birth of their child and thereby have an increased risk for having a mood episode or mood symptoms after becoming a father, so it is important to pay attention to men with BD after the birth of a child.

Clinical findings

- During and immediately after pregnancy we found only limited psychopathology much which may be a reflection of good healthcare for women with BD, especially in this period (chapter 5).
- Mood symptoms in, especially in the second trimester of pregnancy is a profound risk factor for a mood episode postpartum (chapter 5).
- Pregnancy is not protective against mood symptoms (chapter 6).
- Continuing prophylactic pharmacotherapy during pregnancy reduces the risk of recurrence of mood episodes in women with BD (chapter 3).
- Women with BD who consider family planning, worry about the heritability of BD, medication issues, and the risk of recurrence of a mood episode during pregnancy or postpartum (chapter 2).
- Women with BD fear to be incompetent as a mother and need support of partner, family/friends and professionals known to them (chapter 2).
- Men with BD may also be vulnerable for a mood episode after becoming father (chapter 7).

Clinical recommendations

- Inform women with BD, preferably before pregnancy, about the risk/benefit analysis between teratogenic risks of medication versus the risk of recurrence of mood disorders during pregnancy and the postpartum period and create the opportunity for shared decision making regarding the individuals needs and preferences.
- Referral to a POP-clinic may be necessary, but, according to the preference of women with BD, good cooperation with well-known professionals is essential.
- Make an individualized pregnancy relapse prevention plan that includes mental health issues as well as practical issues.
- Treat mood symptoms during pregnancy to prevent mood symptoms postpartum.
- Attention to mothering should be part of the treatment if a woman with BD has one or more children.

Research recommendations

- Prospective studies are needed to investigate the impact of sleep disturbance during pregnancy on postpartum psychopathology, which can only succeed by international research collaboration.
- Prospective studies are also needed to investigate the natural course of BD in pregnant women. Medication-free pregnant women with BD are needed and this also necessitates international collaboration.
- The burden of having BD in pregnant women is huge, and it is important to consider "subject burden", especially when the study covers a long period of time. A possibility might be to opt for questionnaires once a month instead of daily monitoring (depending on the aim of the study).
- Prevent drop-out of participants by keeping contact and seeing them regularly face-to-face.

Pregnancy relapse prevention plan

Patient's name:
Birthdate:
Phone:
Address:
City:
Due date:

Practitioner's name:
Phone:

Stress factors:	**Protective factors:**
- Fear attachment problems - Stress at work - *Fear of delivery* - *Fear for recurrence* - *Doubts about parental skills* - *Family problems* - *Fear of relapse* - *Memories of traumatic past* - *Other…*	- *Resting by taking a walk, a shower or reading a book* - Talking with partner - *Talking with a friend on the phone* - *Contact with practitioner* - *Relaxation techniques* - *Other…*

hase	**Overview of behaviors/risks**	**Possible actions/by whom**
pregnancy	*Discuss with partner/psychiatrist/nurse specialist* 1. *Preparing nursery and baby gear* 2. *Child's check-ups* 3. *Make arrangements with family* 4. *Sleep pattern during delivery* 5. *Preparations for delivery (at home/hospital)* 6. *Other preparations for delivery* 7. *Substance use* 8. *Possibility of the 'Pregnant, now what?' intervention* 9. *Medication* 10. *Other….*	*Examples of possible actions/agreements* 1. *Finished except for furnishing, to be done in week 30* 2. *Determine sex, in order to anticipate. I'd like an experienced obstetrician assigned to me* 3. *I would have a clear agreement with in-laws concerning e.g. frequency of visits after delivery* 4. *When sleep is less than 6 hrs./night consider sleep medication and discuss with …* 5. *Midwife-led hospital birth, I'm sufficient informed about procedures etc.* 6. *….* 7. *Monitoring with partner and practitioner but quitting is successful* 8. *Not participating unless stress during pregnancy becomes too much (I decide when)* 9. *No medication use during pregnancy* 10. *….*
Childbirth	*Discuss with partner/psychiatrist/nurse specialist* 1. *Who is/is not present during delivery* 2. *Presence of hospital staff* 3. *Induced labor?* 4. *Hospital care: staff* 5. *Hospital care: environment* 6. *'Bevalplan'* 7. *Other…*	*Examples of possible outcomes* 1. *Partner only* 2. *Only required staff, no interns etc.* 3. *Decide in consultation with gynecologist, based on sleep patterns during pregnancy, if labor is to be induced* 4. *Continuity of staff as far as possible, staff introductions at start of shifts* 5. *A quiet environment, preferably a single room* 6. *The 'bevalplan' is made with the midwife.* 7. *….*
Post partum	*Discuss with partner/psychiatrist/nurse specialist* 1. *Postpartum period: who visits when and for how long?* 2. *Breastfeeding* 3. *Taking care of newborn* 4. *Additional counseling for monitoring purposes* 5. *Child attachment* 6. *Extended maternity care* 7. *Signals indicating things are not well:* a. *Lack of feelings for child* b. *Eager to hand over child* c. *Feelings of depression* d. *Not sleeping well* e. *Suspiciousness* f. *Anxiety*	*Examples of possible actions/agreements* 1. *Agreements with immediate family on frequency and length of visits and maximum amount of visitors. I want the first 14 day no appointments. If we are feeling well than some short visits of immediate family in the second week.* 2. *No, starting medication immediately after giving birth* 3. *When I don't feel capable myself, … will take over. We can fall back on …* 4. *Once every three weeks for the first three months postpartum* 5. *When I, or my partner, notice attachment problems, we will start the parents/child intervention* 6. *Yes, I will apply for extension myself* 7. *Actions;* a. *By myself*
	g. *More prominent presence of traumas* h. *Secluded and quiet* 8. *Medication*	b. *By the sign. others* c. *When to call your professional* 8. *Prophylactic medication*

Important numbers:

- **GP**:
- **Midwife:**
- **Hospital;**
- **Significant others:**

Who has access to the plan

Patient	[X]	GP	[X]
practitioner	[X]	Hospital	[X]
significant others	[X]	IHT	[X]
Midwife	[X]		

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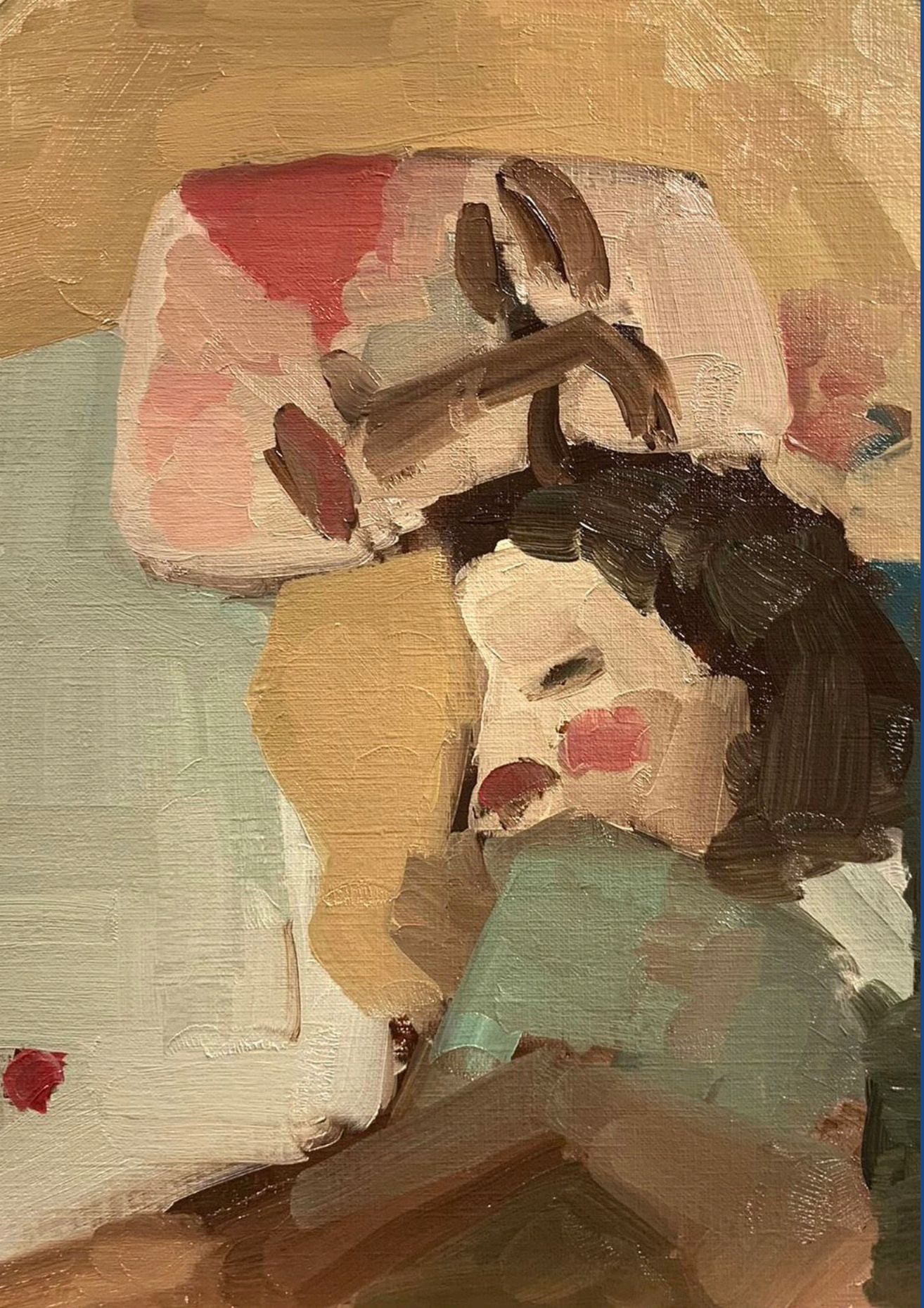

Appendix

Nederlandse samenvatting

De bipolaire stoornis, eerder manisch-depressieve stoornis genoemd, is een psychiatrische aandoening die gekenmerkt wordt door depressieve en (hypo) manische episoden, afgewisseld met perioden van een neutrale (euthyme) stemming, en vaak in de adolescentie of jonge volwassenheid voor het eerst manifest wordt. Bij veel vrouwelijke patiënten is de bipolaire stoornis dan ook al aanwezig in de vruchtbare levensfase. Een zwangerschap en het krijgen van een kind zijn voor iedere vrouw (en op een iets andere manier ook voor een man) enerverende gebeurtenissen en voor vrouwen met een bipolaire stoornis in het bijzonder. De periode van zwangerschap en de drie maanden na de geboorte van de baby (de postpartumperiode) zijn extra uitdagend, waarbij de kans op een stemmingsepisode vooral in de periode na de geboorte van de baby fors verhoogd is. Dat betreft vooral de kans op het krijgen van een kraambedpsychose (postpartum psychose). Een postpartum psychose is een zeer ernstig ziektebeeld die vaak leidt tot een psychiatrische opname van de moeder en een enorme impact op het jonge gezin heeft. Als een opname noodzakelijk blijkt, dan wordt gestreefd om moeder en kind samen op te nemen op een moeder-baby unit. In de algemene bevolking komt een postpartum psychose zelden voor, bij 1 tot 2 van 1000 geboorten, maar bij vrouwen met een bipolaire stoornis is dat veel vaker. Het gebruik van preventieve medicatie in de periode na de bevalling verlaagt het risico op het krijgen van een stemmingsepisode van 66% naar 23%.

Het doel van dit proefschrift is om de invloed van zwangerschap op het beloop van de bipolaire stoornis te onderzoeken en meer specifiek of slaapproblemen tijdens de zwangerschap en rondom de bevalling een risicofactor zijn voor stemmingssymptomen in de postpartum periode bij vrouwen met een bipolaire stoornis. Een ander doel is te achterhalen welke ideeën en zorgen vrouwen met een bipolaire stoornis hebben met betrekking tot gezinsplanning en zwangerschap,

In **hoofdstuk 2** laten we de resultaten van een kwalitatief onderzoek zien, waarin we 15 vrouwen met een bipolaire stoornis hebben gevraagd wat hun gedachten en overwegingen waren rondom gezinsplanning en het krijgen van een kind. De belangrijkste bevindingen zijn dat zij vragen hebben over het gebruik van medicatie tijdens de zwangerschap en de postpartumperiode en over de

erfelijkheid van de bipolaire stoornis. Daarnaast maken zij zich zorgen of zij wel een goede moeder kunnen zijn en vinden zij het belangrijk om juist in deze fase behandeld te worden door een voor hen bekende en vertrouwde behandelaar.

In **hoofdstuk 3** beschrijven we een literatuuroverzicht waarin we hebben gekeken of zwangerschap het beloop van een bipolaire stoornis en een ernstige depressieve stoornis beïnvloedt. Lang bestond de mythe dat een zwangerschap gunstig was voor vrouwen met een bipolaire stoornis omdat er tijdens een zwangerschap minder manische of depressieve episodes zouden voorkomen. Onze systematische review kon dit echter niet bevestigen. We hebben 22 studies naar het vóórkomen van een stemmingsepisode tijdens de zwangerschap bestudeerd (14 studies betroffen de bipolaire stoornis, acht de depressieve stoornis en twee beide). Dit bleek te variëren van 0% tot 73% bij de bipolaire stoornis en van 1%-75%, bij de depressieve stoornis. Daarnaast vonden we dat het gebruik van onderhoudsmedicatie tijdens de zwangerschap de kans op een stemmingsepisode vermindert van 71% naar 24% bij vrouwen met een bipolaire stoornis en van 68% naar 31% bij vrouwen met een ernstige depressie in de voorgeschiedenis.
Het gebruik van medicatie tijdens de zwangerschap kan nadelige gevolgen hebben voor de foetus, maar ook het krijgen van een stemmingsepisode kan negatieve gevolgen hebben op de ontwikkeling van het kind. Zo geeft een depressie of een manie bij de zwangere vrouw stress voor de foetus met hierdoor een grotere kans op latere emotionele en gedragsproblemen bij het opgroeiende kind. Ook zal een zwangere vrouw als zij tijdens de zwangerschap een manie of depressie doormaakt vaak een hogere dosering medicatie moeten nemen dan wanneer bij voorbaat profylactische medicatie zou zijn voorgeschreven. Bovendien heeft een depressie of psychose in de postpartumperiode vaak een negatieve invloed op de hechting tussen moeder en kind en de socio-emotionele ontwikkeling van het kind. Kortom, het is belangrijk om in de beslissing om al dan niet preventieve medicatie te gebruiken tijdens de zwangerschap mee te nemen dat het gebruik van deze medicatie de kans op een depressie of manie tijdens de zwangerschap fors vermindert, zoals onze review aantoont, en dat dit in veel gevallen zal opwegen tegen de risico's voor het (ongeboren) kind.

Hoofdstuk 4 beschrijft het protocol van de Sleepreg-bd studie naar de

invloed van slaapproblemen in de zwangerschap en rondom de bevalling op stemmingssymptomen na de bevalling. In deze studie zijn op verschillende meetmomenten, zowel tijdens de zwangerschap als na de bevalling, slaap en stemmingssymptomen in kaart gebracht. Slaap werd subjectief gemeten met slaapdagboeken en objectief met een Motionwatch, een horloge dat slapen en waken registreert. De stemming werd bijgehouden met vragenlijsten en de LifeChart methode, een stemmingsgrafiek waarmee dagelijks de stemming wordt bijgehouden.

In **hoofdstuk 5** worden de resultaten van het onderzoek naar de invloed van slaap tijdens de zwangerschap op ontregeling van de stemming na de bevalling beschreven. We vonden geen verband tussen objectieve slaapproblemen in de perinatale periode op stemmingssymptomen bij de moeder na de geboorte van het kind. Wel bleek dat bij gezonde slapers (vrouwen die 7 tot 9 uur per nacht slapen) aan het einde van het tweede trimester van de zwangerschap een slechte slaapefficiency (percentage van de tijd dat men in bed ligt daadwerkelijk slaapt) in de eerste week na de bevalling voorspellend was voor manische symptomen in de tweede week na de bevalling. Aanbevolen wordt dan ook om bij vrouwen die na de bevalling slecht slapen te zorgen dat het slapen verbetert om een manie te voorkomen. Ook zagen we dat het hebben van stemmingssymptomen in het tweede trimester van de zwangerschap de belangrijkste voorspeller is voor het krijgen van stemmingssymptomen na de bevalling. Met andere woorden, als een vrouw tijdens de zwangerschap stemmingsproblemen vertoont is het zinvol om deze goed te behandelen, ook om problemen na de bevalling te voorkomen.

In **hoofdstuk 6** laten we een studie zien waarbij we 34 zwangere vrouwen met een bipolaire stoornis (uit onze eigen studie) vergeleken met 52 niet-zwangere vrouwen met een bipolaire stoornis (uit een eerder in Nederland uitgevoerde studie). We vonden geen verschil in klinische variabelen zoals frequentie of duur van de stemmingsepisoden, en evenmin zagen we een verschil in aantal dagen met stemmingssymptomen. We zagen in beide groepen drie verschillende beloopsclusters: een cluster met normale (euthyme) stemming), een matig ziek cluster en een ernstig ziek cluster. De zwangere vrouwen zaten vooral in het matig zieke cluster (68%) en de meeste niet-zwangere vrouwen zaten in het

euthyme cluster (46%). Opvallend was dat de zwangere vrouwen minder vaak medicatie gebruikten dan de niet-zwangere vrouwen, mogelijk een verklaring waarom meer zwangere vrouwen in het matig zieke cluster zaten.

In **hoofdstuk 7** bespreken we de casus van een man met een bipolaire stoornis, die manisch werd nadat hij vader was geworden, waarbij we de rol van slaapproblemen bespreken die mogelijk deze manie mede hebben veroorzaakt. Hoewel in de klinische praktijk (en in wetenschappelijk onderzoek) de aandacht vooral gaat naar vrouwen met een bipolaire stoornis rondom zwangerschap, bevalling en kraambed, is het ook van belang om extra aandacht te geven aan mannen met een bipolaire stoornis die binnenkort vader gaan worden.

In de discussie (**hoofdstuk 8**) hebben we onder meer aandacht besteed aan de vraag of het mogelijk is om te onderzoeken in hoeverre het beloop van de bipolaire stoornis beïnvloed wordt door zwangerschap. Wij denken dat dit tegenwoordig eigenlijk niet meer in strikte zin te onderzoeken is. Om dit te onderzoeken zou men een grote groep zwangere vrouwen met een bipolaire stoornis moeten vergelijken met een grote groep niet-zwangere vrouwen met een bipolaire stoornis en beide groepen zouden geen medicatie mogen gebruiken of, als wel, vergelijkbare preventieve medicatie. Een dergelijk onderzoek is echter ethisch niet te verantwoorden en ook praktisch niet uitvoerbaar.
Ook hebben we gemerkt dat het niet eenvoudig is om gedegen onderzoek te doen bij onze doelgroep van zwangere vrouwen met een bipolaire stoornis. Het werven van participanten bleek moeilijker dan verwacht en ook was het aantal drop-outs hoog, waardoor uiteindelijk het beoogde aantal participanten niet is gehaald. Desondanks is de Sleepreg-bd studie, voor zover wij hebben kunnen nagaan, het grootste prospectieve cohort van zwangere vrouwen met een bipolaire stoornis, waarin zowel de slaap als de stemming systematisch werd gemeten gedurende de zwangerschap en de postpartumperiode.
We zagen in onze Sleepreg-bd studie opvallend veel minder stemmingssymptomen en stemmingsepisodes in de postpartumperiode dan in de literatuur staat beschreven. Hoewel we het niet met zekerheid kunnen zeggen, is dit mogelijk toe te schrijven aan de goede gezondheidszorg voor deze patienten in Nederland. Zwangere vrouwen met een bipolaire stoornis worden vaak naar een POP-poli verwezen, waar door een team van een kinderarts, een

gynaecoloog en een psychiater een advies wordt gegeven over de behandeling gedurende zwangerschap en postpartumperiode, en soms de behandeling tijdelijk wordt overgenomen. Tevens wordt geadviseerd om een individueel zwangerschapsplan te maken, waarin wordt beschreven welke acties wanneer genomen zouden moeten worden, zowel op mentaal gebied als op praktisch gebied.

Verdere prospectieve onderzoeken zijn nodig om de impact van slaap tijdens de zwangerschap op postpartum stemming te kunnen bestuderen. Het is wenselijk om dit in een internationaal onderzoeksconsortium uit te voeren. Ten eerste omdat zwangere vrouwen met een bipolaire stoornis moeilijk te rekruteren zijn. Ten tweede omdat we ook geïnteresseerd zijn in het natuurlijk beloop van de bipolaire stoornis tijdens de zwangerschap en hiervoor voldoende vrouwen geworven moeten worden die tijdens de zwangerschap (of hoe dan ook) geen medicatie gebruiken.

De belangrijke bevindingen van het onderzoek in dit proefschrift zijn:

- Zwangerschap beschermt niet tegen stemmingssymptomen bij vrouwen met een bipolaire stoornis;
- Het gebruik van profylactische medicatie tijdens de zwangerschap vermindert het risico op stemmingsepisodes;
- Slaapproblemen in de eerste week na de bevalling zijn een voorspeller van manie in de tweede week na de bevalling;
- Stemmingssymptomen tijdens de zwangerschap zijn een belangrijke voorspeller voor stemmingssymptomen in de postpartumperiode en moeten dus snel en adequaat behandeld worden;
- Vrouwen met een bipolaire stoornis hebben vooral vragen over het al dan niet blijven gebruiken van medicatie tijdens de zwangerschap en over de erfelijkheid van de bipolaire stoornis. Daarnaast geven zij aan in de periode van zwangerschap en postpartum in behandeling te willen blijven bij de hen bekende behandelaar en maken zij zich zorgen of zij wel een goede moeder zullen zijn;
- Ook mannen met een bipolaire stoornis wier vrouw binnenkort zal bevallen verdienen extra aandacht vanwege een risico op ontregeling van de stemming na de geboorte van het kind.

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Curriculum vitae

Anja Stevens is geboren op 13 juli 1963 in Voorhout. Na het behalen van het VWO-diploma aan College Leeuwenhorst, startte zij de studie Geneeskunde in Leiden. Van 1991 tot 1996 deed zij de specialisatie psychiatrie aan het Haags Leids Opleidings Consortium Psychiatrie. Een groot deel van de opleiding volgde zij in PC Bloemendaal (nu Parnassia Groep) en haar keuzestage deed ze op de Jelgersmapolikliniek en de afdeling eetstoornissen in de Jelgersmakliniek.

Na een korte periode bij RIAGG Rivierenland (nu onderdeel van Pro Persona) gewerkt te hebben, kwam Anja bij Adhesie (nu Dimence Groep) te werken. Aanvankelijk in Almelo en vanaf 2002 in Deventer. Zij werkte destijds op de afdeling ziekenhuispsychiatrie en startte in 2002 een 'bipolaire poli' in Deventer. Uiteindelijk mondde deze uit in een specialistisch centrum bipolaire stoornissen (SCBS), welke in 2012 het predikaat TOPGGz kreeg. Tot 2019 heeft Anja als hoofd bij het SCBS gewerkt, waarbij zij naast patiëntenzorg ook onderzoek deed, onderwijs gaf en lezingen gaf op (inter)nationale congressen.
Van juni 2019 tot december 2000 heeft Anja met veel plezier bij Transfore gewerkt, het forensisch onderdeel van de Dimence Groep.

Anja is van 2009 tot 2020 secretaris van het Kenniscentrum Bipolaire Stoornissen (KenBiS), van 2010 tot 2017 algemeen bestuurslid van het Landelijk Kenniscentrum Psychiatrie en Zwangerschap (LKPZ) en van 2014 tot 2020 penningmeester geweest bij de Stichting Mind2Care . Daarnaast is zij van 2009 tot 2011 plaatsvervangend opleider en gedurende een half jaar A-opleider psychiatrie geweest van Dimence.

Vanwege de toekomstplannen van Anja is zij sinds 2020 ZZP-er en werkt(e) op verschillende plekken, onder meer bij het psychiatrisch centrum van de PI Zwolle en de bipolaire poli van Pro Persona in Ede. Sinds 2022 zeilt Anja met haar man in de zomermaanden op de Middellandse Zee.

Anja heeft in de periode 2008-2009 een onderzoeksvoorstel in concept geschreven, welke onder begeleiding van promotor Ralph Kupka en copromotoren Birit Broekman, Stasja Draisma en Peter Goossens tot een definitief onderzoek is gekomen.

Anja is getrouwd met Peter en heeft twee dochters, Susanne en Sabine.

Dankwoord

Na heel veel jaren, niemand weet meer helemaal precies hoeveel, mag ik het dankwoord schrijven van mijn proefschrift. Graag wil ik iedereen bedanken die heeft bijgedragen aan de totstandkoming van dit proefschrift.

Allereerst dank aan de deelneemsters aan het onderzoek. In de toch al wat stressvolle periode van zwangerschap en bevalling werd jullie gevraagd vragenlijsten in te vullen, slaaplogboeken bij te houden, een motionwatch te dragen en een interview te geven. Velen deden dit secuur en met zorg. Dank hiervoor. Zonder jullie zou dit onderzoek er niet geweest zijn.

Zonder de directie van destijds Adhesie (een van de voorlopers van de Dimence Groep) zou ik nooit gepromoveerd zijn. Ooit zei Roelof ten Doesschate (directeur Adhesie) dat ik zou moeten promoveren, destijds mompelde ik: "ik wil best wel onderzoek doen, maar het doel is niet te promoveren; mocht het ooit zover komen dat ik genoeg artikelen heb, ja, dan zal ik promoveren". Sybren Bangma (voorzitter Raad van Bestuur, Dimence Groep) heeft mij, en het Specialistisch Centrum Bipolaire Stoornissen (SCBS), altijd enorm gesteund, vooral door een enorm vertrouwen in mij/ons uit te stralen en mij/ons met wijze raad terzijde te staan.

Ralph Kupka, toen jij hoogleraar werd benaderde je me met het voorstel mijn promotor te worden, via via had je gehoord dat ik een onderzoeksvoorstel in mijn la had liggen. Wat ben ik blij dat jij mijn promotor bent. Je hebt een kritisch opbouwende houding en houdt me scherp. Heel fijn dat je bij Kenniscentrum Bipolaire Stoornissen (KenBiS) altijd weer aandacht vroeg voor mijn onderzoek, waardoor ik weer deelneemsters kon includeren. Waar ik af en toe ergens met gestrekt been in kan gaan en geduld niet een kernkwaliteit van mij is, kun jij meer achteroverleunend rustig blijven en bereiken wat nodig is. Je onvolprezen kennis over de bipolaire stoornis kent nauwelijks grenzen. Daarnaast ben je een aimabel mens, met wie ik op meerdere fronten heb samengewerkt. Dat we, buiten de bipolaire stoornis, ook gezamenlijke andere interesses hebben, bleek toen we elkaar per toeval tegenkwamen in de wijk Georgetown in Washington op een vrij moment tijdens het ISBD-congres. Voor mij ben je van onschatbare waarde geweest.

Stasja Draisma, de eerlijkheid gebiedt te zeggen dat we even aan elkaar hebben moeten wennen, de oudere PhD student van ver buiten Amsterdam, die ook nog eens niet altijd ja en amen zei, maar uiteindelijk is dat helemaal goed gekomen. We hebben vele beeldbelafspraken gehad tijdens de coronaperiode, waarin je me enthousiasmeerde "R" te gebruiken om de data te analyseren en daarin heb je helemaal gelijk gekregen.

Peter Goossens, voor mij was het logisch dat jij copromotor zou worden, we werkten samen binnen het (latere) SCBS en jij was degene die verstand had van onderzoek binnen het aandachtsgebied bipolaire stoornissen. Je hebt me erg geholpen met de kwalitatieve studie en met veel plezier denk ik terug aan het maken van de review, waarbij we boeiende discussies hadden om consensus te krijgen over welke artikelen wel of niet te includeren in de review en analyse.

Birit Broekman, hoewel jij pas halverwege het traject mijn copromotor bent geworden, ben jij voor mij heel belangrijk geweest. Je bent altijd positief en constructief en op momenten, waarbij ik bijna het bijltje erbij neer wilde gooien, wist jij me weer te motiveren door te gaan, gewoon door op het juiste moment de juiste dingen te zeggen en vertrouwen uit te stralen. Daarnaast was je feedback snel en 'to the point' en constructief. Dank daarvoor.

Adriaan Honig, wat vond ik jouw rustige constructieve reacties fijn. Je hebt je promotorschap neergelegd om Birit een plek te kunnen geven, desondanks ben je in de onderzoeksgroep gebleven. Ik heb veel waardering voor je wijze waarop je me gesteund hebt.

Elise Knoppert-van der Klein, ik ken jou al sinds mijn coschappen op de Jelgersmapoli. Hoewel ik het keuzecoschap 'cognitieve therapie' liep en we maar zijdelings met elkaar te maken hadden op de Jelgersmapoli, bleek al snel dat we een klik hadden. Dezelfde interesse voor de bipolaire stoornis en zwangerschapsgerelateerde psychiatrie. In de loop der jaren hebben we veel contact gehad en ook samengewerkt op dit gebied en hebben we, naast natuurlijk wetenschappelijk verantwoord bezig zijn, veel lol gehad. Minstens zo belangrijk binnen dit werkveld.

Ik wil ook graag mijn andere co-auteurs bedanken: Martijn van de Klis, Thea Daggenvoorde en Elaine Tham. Dank voor jullie inzet en betrokkenheid. Zonder Martijn van de Klis en Thea Daggenvoorde zou de kwalitatieve studie naar gedachten en overwegingen van vrouwen met een bipolaire stoornis over gezinsplanning er niet zijn geweest en Elaine Tham is van onmisbare waarde geweest in de analyses van de studie naar de invloed van slaap op postpartum stemmingsproblemen.

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