The Effect of Sleep Disturbance during Pregnancy and Perinatal Period on Postpartum Psychopathology in Women with Bipolar Disorder

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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 Life Chart 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 sub-syndromal 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 and maternal death [5-8]. 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 sub-syndromal 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 children, 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 (sub-syndromal) 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 who become pregnant. Women will be excluded if they (1) are unable to complete the survey; (2) do not give informed consent; (3) have a mood episode in 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?

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

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<td>18-24</td>
<td>3.9%</td>
<td>17834</td>
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<td>25-35</td>
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<td>2115</td>
<td>28%</td>
<td>592</td>
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Table 1: Estimated potential number of participants.
of five confounders. We have to make some assumptions (Cohen, 1988, chapter 9), and suppose that the group of five covariates (A) predicts postpartum psychopathology (Y) to a level $R^2_{Y.A} = 0.10$. 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 $R^2_{Y.B.A} = R^2_{Y.A,B} - R^2_{Y.A} = 0.06$, which corresponds to the effect size index $f^2 = (R^2_{Y.A,B} - R^2_{Y.A})/(1 - R^2_{Y.A,B}) = 0.071$. 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 are connected with 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 and 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.

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 form 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

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<td>T</td>
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<td>Life Chart retro 1 year</td>
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Table 2: Timeline and assessments.
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 (YMR-S), 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 or 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 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 (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, sub-syndromal 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 and 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.

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