Journal of Affective Disorders 295 (2021) 72–79

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

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

Janneke Gilden [a,*], Eline M.P. Poels [a], Simon Lambrichts [b], Annabel Vreeker [c], Marco P.M. Boks [d], Roel A. Ophoff [a], René S. Kahn [e], Astrid M. Kamperman [a,f], Veerle Bergink [a,e,g]

[a] Department of Psychiatry, Erasmus University Medical Center, 3000 CA Rotterdam, the Netherlands
[b] Academic Center for ECT and Neuromodulation (AcCENT), KU Leuven – University of Leuven, University Psychiatric Center KU Leuven, Kortenberg, Belgium
[c] Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Center, 3000 CA Rotterdam, the Netherlands
[d] Department of Psychiatry, Utrecht Medical Center, 3508 GA Utrecht, the Netherlands
[e] Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
[f] Epidemiological and Social Psychiatric Research Institute, Erasmus University Medical Center, Rotterdam, the Netherlands
[g] Department of obstetrics, gynecology and reproductive science, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

ARTICLE INFO

Keywords:
Bipolar disorder
Pregnancy
Postpartum period
Peripartum period
Recurrence
Lithium

ABSTRACT

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

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

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

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

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

1. Introduction

Bipolar I disorder is a severe chronic mood disorder characterized by episodes of mania, hypomania, and alternating or intertwining episodes of depression (Grande et al., 2016). It affects more than 2% of the world's population irrespective of nationality, ethnic origin, or socio-economic status (Alonso et al., 2011). In view of its recurrent nature, optimum long-term management is a preventive strategy that combines pharmacological, psychological, and lifestyle approaches from the first episode (Geddes and Miklowitz, 2013), with lithium being one of the most effective treatments of both manic and depressive episodes (Miura et al., 2014). The postpartum period has been identified as a high-risk period for women with bipolar disorder. There is strong, clear, and consistent evidence of a specific relationship between childbirth and the risk of a bipolar episode (Di Florio et al., 2013), with an overall recurrence risk of 37% (range 29-45%) (Wesseloo et al., 2016). In contrast to the postpartum period, information about the recurrence risk during pregnancy is limited and the wide variation in the reported rates

* Corresponding author at: Department of Psychiatry, Erasmus University Medical Center, Room Dp-1462, Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands.
E-mail address: j.gilden@erasmusmc.nl (J. Gilden).

https://doi.org/10.1016/j.jad.2021.08.006
Received 5 June 2021; Received in revised form 1 August 2021; Accepted 3 August 2021
Available online 8 August 2021

(4-73%) hampered previous efforts to do a meta-analysis (Salim et al., 2018; Stevens et al., 2019). In addition, very few studies have investigated the risk of a bipolar episode after miscarriage and induced abortion. This is remarkable since both miscarriage and induced abortion are common pregnancy outcomes. The risk of miscarriage among recognized pregnancies was 12.8% in a large Norwegian register based study (Magnus et al., 2019). Globally, about one in five pregnancies ended in induced abortion in 2008, corresponding with an abortion rate of 28 per 1000 women aged 15-44 years (Sedgh et al., 2012). In the Netherlands the abortion rate in 2016 was 3.3 times lower than the global abortion rate (8.5 per 1000 women aged 15-44 years) (Ministerie van Volksgezondheid Welzijn en Sport - Inspectie Gezondheidszorg en Jeugd, Januari 2018.) A clinical cohort study reported that the risk of a bipolar episode after miscarriage was 20.1% and after abortion this was 24.2% (Di Florio et al., 2015). Lastly, there is no study that provides an overview on episode risk both during pregnancy and after childbirth, miscarriage and induced abortion. This is a problem because women make decisions regarding family planning and prevention strategies based on their individual risk profile during the entire perinatal period. This is particularly relevant during pregnancy, when risk of fetal medication exposure should be weighed to both the episode risk during pregnancy and after delivery (Munk-Olsen et al., 2018; Patorno et al., 2017; Wesseloo et al., 2016). In this large clinical cohort we investigated the risk of a bipolar episode during the perinatal period in a sample of patients with bipolar I disorder. Additionally, we wanted to determine the effect of subsequent pregnancies on the episode risk and investigate the association between lithium use during pregnancy and episode risk.

2. Patients and methods

2.1. Study design

This retrospective cohort study was part of the Dutch Bipolar Cohort (DBC) study, a collaboration between the University of California - Los Angeles and the Dutch healthcare institutes University Medical Center Utrecht, GGZ Altrecht, GGZ inGeest, University Medical Center Groningen, Delta, Dimence, Parnassia (PsyQ) and Reinier van Arkel. The objective of the DBC study was to investigate genetic and phenotypic information of patients with bipolar disorder type I (BD-I), first-degree relatives and controls (van Bergen et al., 2019; Vreeker et al., 2016). Patients were recruited via clinicians, the Dutch patient association, pharmacies and advertisements. Inclusion criteria for all participants were 1) age 18 years or older 2) at least three Dutch-born grandparents 3) a good understanding of Dutch language. Patients with a somatic illness that could have influenced the diagnosis of BD were excluded (Vreeker et al., 2016). The study was approved by the accredited Dutch Medical Ethical Trial Committee (METC) and all participants gave written informed consent. Data collection took place between June 2011 and July 2015. A total of 1396 patients with bipolar disorder participated in the DBC study, of which 793 were women.

2.2. Participants and aims

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

2.3. Data collection and procedures

For all patients, clinical bipolar I disorder diagnosis was confirmed at inclusion using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997), conducted by at least one well-trained independent rater of the DBC study (Houtepen et al., 2015). Other clinical features (i.e. age of onset, the total number of manic and depressive episodes, lifetime rapid cycling, family history of psychiatric illness and educational level) were also assessed at inclusion with the Dutch version of the Questionnaire for Bipolar Illness (QBP-NL, Dutch translation by Akkershuis, Groenesteyn, Nolen, 1997; an adaptation of the Enrolment Questionnaire as previously used in the Stanley Foundation Bipolar Network) and the SCID-I (First et al., 1997; Leverich et al., 2001; Suppes et al., 2001). For our primary and secondary outcome - occurrence of perinatal mood episodes during the first and subsequent pregnancies - data was collected retrospectively. Women were asked to report the date of birth of a living child, miscarriage or induced abortion and whether they experienced a manic episode (with or without prominent psychotic features) or depressive episode during pregnancy or the postpartum period. When the episode occurred after delivery of a living child, women were asked to specify the timing of onset (<4 weeks or 1-6 months after childbirth). For our third outcome – the association between lithium use and episode risk – we assessed medication use in two different ways: all participants were asked to 1) complete online questionnaires during inclusion and study assessment, including a list of current and lifetime medication use, and 2) complete a lithium satisfaction questionnaire including questions on current and past use of lithium. Detailed information regarding the timing and duration of use, was only available for lithium and was used to determine the prophylactic use of lithium during pregnancy as accurate as possible and to restrain misclassification (Abramovic et al., 2016). For the other types of medication, lifetime use could be determined, but data was not detailed enough to determine use during pregnancy. Lifetime medication use was defined as the exposure to medication in the period from the first episode until the assessment of pharmacological treatment during the DBC study. Data was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (von Elm et al., 2007).

2.4. Data-analysis

Data management and descriptive statistics were performed using Statistical Package for Social Sciences (SPSS) version 24.0. Comparisons of demographic and clinical variables between women who experienced a perinatal episode and those who did not, were completed by means of chi-squared or Fisher's exact test for categorical data; continuous variables were examined with two-sample t-tests or Mann-Whitney U tests. For our primary outcome, the risk of mood episodes during pregnancy, after live birth, miscarriage and induced abortion were determined. Episode risks related to the different pregnancy outcomes were compared using a chi-squared test. We report crude incidence risks and incidence risks adjusted for the occurrences of multiple pregnancies within the same women. Adjusted incidence risks were estimated using multilevel logistic regression models, for which we included women as level in our analyses to cluster the pregnancies. Self-reported phenomenology and timing of episodes was reported in a descriptive manner. In order to investigate whether the episode risk increased during the second perinatal period in women who experienced an episode in the first perinatal period, we calculated the odds ratio of a second perinatal episode. The association between lithium prophylaxis and the occurrence of an episode was examined in a subgroup of women who had a bipolar I disorder diagnosis *before* conception, using logistic regression

analysis. Analyses were conducted unadjusted, and repeated adjusting for possible confounders (age of onset, total number of episodes, family history of bipolar disorder, and multiple pregnancies within unique women) using a multivariable multilevel regression model. We report crude and adjusted odds ratios (cOR or aOR) with corresponding 95% confidence intervals. Statistical analyses were considered significant with an alpha of 0.05 (two-sided). We report absolute numbers and percentages.

3. Results

3.1. Demographic and clinical characteristics

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

Information regarding the lifetime use of mood stabilizers, antidepressants, antipsychotics and benzodiazepines was available for all 436 women. Lifetime mood stabilizer exposure was 87.2% (n=380) in our study population, with lithium being the most prescribed mood stabilizer. The majority of women (n=259) were also treated with antipsychotics (59.4%) at some point during their mood disorder, and to a lower extent with antidepressants (n=186, 42.7%). Benzodiazepines were prescribed to 252 of the 436 women (57.8%) as a pharmacological treatment during mood episodes.

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

3.2. Recurrence risk during all reproductive events

As shown in Fig. 1, the crude risk of an episode during pregnancy was 5.2% (48/919 pregnancies; adjusted risk: 5.6%). The risk of an episode after live birth was 34.4% (251/730 live births). When pregnancy resulted in a miscarriage, the episode risk was 15.2% (16/105 miscarriages), while the risk of an episode after induced abortion was 27.8% (10/36 abortions). The risk of a bipolar episode was significantly higher after a live birth compared to miscarriage (Chi2(1)=18.16; p<0.001)

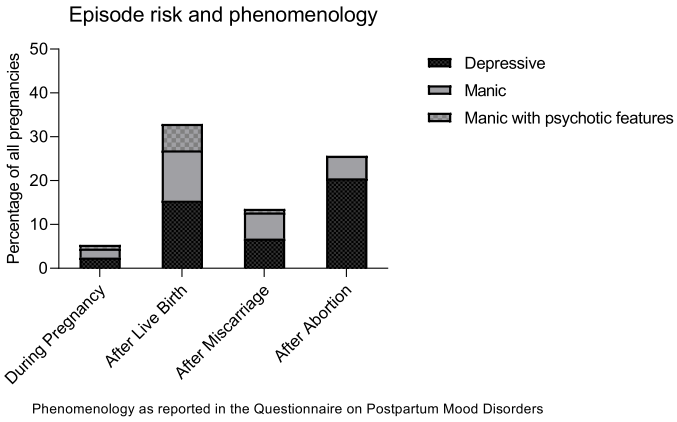

Fig. 1. Episode risk with subsequent pregnancies.

Table 1
Demographic and clinical characteristics.

		No episode		At least one episode during pregnancy or postpartum			
		N	%	N	%		
Women with BD1 diagnosis		195	44.7	241	55.3		
Pregnancies		571	62.1	348	37.9		
Demographic characteristics			Mean/N	SD/%	Mean/N	SD/%	Test
Educational level†							$Chi^2(1)=0.469$; p=0.493
	Lower and intermediate education		106	60.9	130	57.5	
	Higher education		68	39.1	96	42.5	
Clinical characteristics related to fertility			Mean/N	SD/%	Mean/N	SD/%	
Age at first pregnancy (years)†			27.0	4.9	28.0	4.6	T(381)=-.684; p=0.494
Pregnancy before illness onset			87	53.7	105	48.8	$Chi^2(1)=0.875$; p=0.349
Number of childbirths			1.8	1.0	1.8	0.9	T(434)=0.004; p=0.997
Clinical characteristics related to disorder							
Age at onset of illness† (years)			29.2	11.4	25.4	7.3	T(400)=4.172; p<0.001
Number of total bipolar episodes (median: IQR)							
	Manic†		3	1.5-5	3	2-6	Z=2.290; p=0.022
	Depressive†		4	2-7	4	2-8	Z=0.335; p=0.738
	Any†		7	4-13.25	8	5-16	Z=2.070; p=0.038
Rapid cycling†			35	20.5	48	21.9	$Chi^2(1)=0.121$; p=0.728
Family history							
	Bipolar disorder†		54	32.7	95	44.8	$Chi^2(1)=5.668$; p=0.017
	Depressive disorder†		99	59.6	114	53.8	$Chi^2(1)=1.320$; p=0.254
	Psychotic disorder†		35	21.5	57	26.5	$Chi^2(1)=1.278$; p=0.258
	Substance abuse†		41	25.2	60	28.0	$Chi^2(1)=0.392$; p=0.531

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

but not compared to induced abortion (Chi2(1)=0.34; p=0.439). For 23 women who experienced a perinatal episode, information on the onset was missing.

3.3. Phenomenology of episodes

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

3.4. Overall episode risk and timing of onset

The crude overall risk of a perinatal episode (both during pregnancy and postpartum) was 37.9% (348/919 pregnancies; adjusted risk: 39.9%). The crude risk of an episode during pregnancy was 5.2% (48/919 pregnancies; adjusted risk: 5.6%), while the crude risk was 30.1% (277/919; adjusted risk: 31.6%) postpartum (taking into account all pregnancy outcomes). Most episodes started within 4 weeks postpartum (crude risk 20.3%, 187/919 pregnancies), while episodes between 4 weeks and 6 months postpartum were less common (crude risk 9.8%, 90/919 pregnancies).

3.5. Bipolar episodes during and after subsequent pregnancies

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

3.6. Efficacy of lithium prophylaxis on recurrence risk during the perinatal period

Information on the use of lithium during pregnancy could be extracted for 462 pregnancies in 272 women with a diagnosis of bipolar I disorder *before* conception. In total, 18.8% of these pregnancies (87/462) were supported by lithium prophylaxis. Prophylactic lithium use during pregnancy was associated with a lower risk of a perinatal episode. The episode risk was 26.4% (23/87) in lithium supported pregnancies compared to 46.7% (175/375) in unsupported pregnancies (cOR=0.41; 95%CI 0.25-0.69; p=0.001). This association remained after adjusting for age of onset, total number of episodes, bipolar family history, and multiple pregnancies within unique women (aOR=0.47; 95%CI: 0.26-0.83; p=0.009). We also distinguished between the association of lithium prophylaxis on episodes during pregnancy and after delivery. For all the pregnancies in which information about the use of lithium and the timing of onset was available (n=449), 2.3% (2/86) of women with lithium use during pregnancy experienced an episode during pregnancy, compared to 8.0% (29/363) of women without lithium use (cOR=0.27; 95%CI:0.06-1.17; p=0.081). Similarly, 23.8% (20/84) of women with lithium use during pregnancy and postpartum experienced a postpartum episode, compared to 40.1% (134/334) of women without lithium use (cOR=0.47; 95%CI: 0.27-0.81; p=0.006). Women who had experienced an episode during pregnancy were censored in the analysis regarding postpartum recurrence risk.

4. Discussion

In this large retrospective cohort study, we found that women with bipolar disorder had a particularly high risk for developing an episode during the postpartum period (30.1% of pregnancies), which was six times the risk during pregnancy (5.2% of pregnancies). Especially, the early postpartum period (< 4 weeks) was a high-risk period for recurrence (20.3% of pregnancies). The risk for postpartum recurrence is consistent with previously published studies (Wesseloo et al., 2016) but the recurrence risk of 5.2% during pregnancy is rather low. Previous studies reported both low recurrence rates (Akdeniz et al., 2003; Di Florio et al., 2013; Grof et al., 2000) as well as quite high rates (Abd El-Hay et al., 2011; Newport et al., 2008; Viguera et al., 2007) during pregnancy among women with bipolar I disorder (range 4-73%). The higher risk in these latter studies could be a consequence of prospective study design (Abd El-Hay et al., 2011; Newport et al., 2008; Viguera et al., 2007), which is more sensitive to detecting less severe episodes compared to retrospective studies. In addition, some of these studies included mostly women from a tertiary referral hospital specializing in perinatal psychiatry (Viguera et al., 2007). These women likely had a more severe form of bipolar I disorder in comparison with the women in our study. Besides, some studies included women with bipolar II disorder in their study population (Akdeniz et al., 2003; Di Florio et al., 2013; Newport et al., 2008; Viguera et al., 2007), which has been found to be a predictor for an increased risk of recurrence during pregnancy when compared to women with bipolar I disorder (risk ratio 1.5, p<0.002) (Viguera et al., 2007).

This study shows that the risk of a bipolar episode is highest after a live birth (34.4%) and lower after miscarriage (15.2%) and induced abortion (27.8%). These risks are comparable to the risks reported in a retrospective cohort study by Di Florio and colleagues, based on data gathered by interview and case-notes review (Di Florio et al., 2015). In addition, a Danish population-based cohort study showed that risk of readmission is similar before and after first-time first-trimester abortion, contrasting with a marked increase in risk of readmission postpartum (Munk-Olsen et al., 2012). Our results emphasize the importance of mental health care during reproductive events in this population and indicate that care should not solely focus on childbirth, but on all pregnancy outcomes. The end of pregnancy, including live childbirth, induced abortion or miscarriage, is evidently a very strong trigger for bipolar episodes and this likely has a biological base. The postpartum period is specifically characterized by sleep loss and sleep loss could be a trigger for the recurrence of mood episodes (Lewis et al., 2017). Interestingly though, in our study we also found induced abortion and miscarriage to be associated with a high recurrence risk even though induced abortion and miscarriage are not specifically characterized by sleep loss. This suggests that sleep loss by itself cannot fully explain the risk of recurrence of mood episodes. The risk of post-pregnancy episodes might be largely explained by the major physiological changes that occur with the transition from the state of pregnancy to a non-pregnant condition. After delivery or pregnancy termination the levels of sex hormones change, with rapid falls of estrogen postpartum (Galea et al., 2001). This may cause a change in mood regulation (Barth et al., 2015). Additionally, the immune system is triggered after live childbirth or termination which results in an overreaction, also called the 'rebound' phenomenon (Buyon, 1998; Calcagni and Elenkov, 2006; Confavreux et al., 1998; Haupl et al., 2008; Ruiz-Irastorza et al., 1996; Schramm

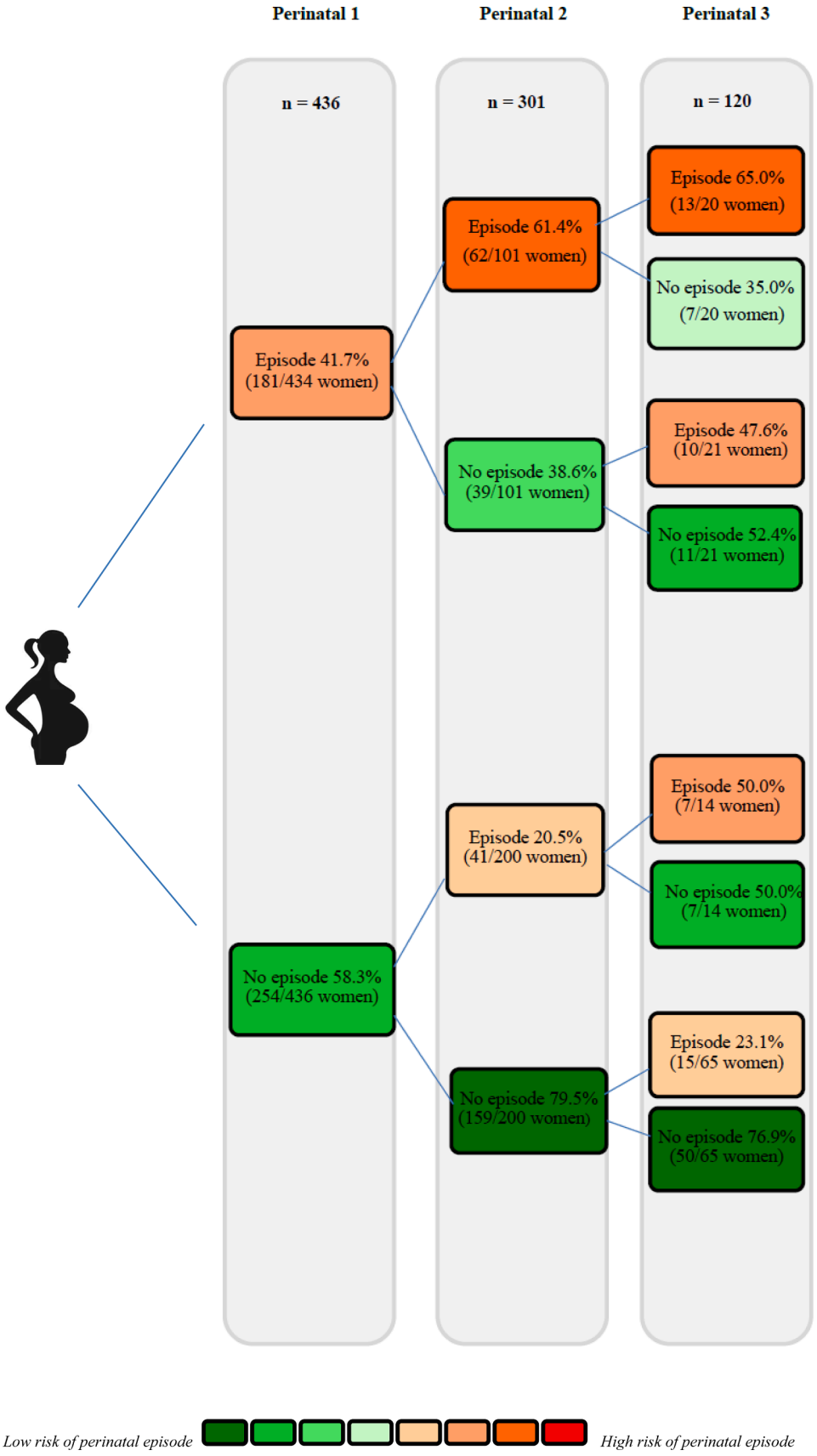

Fig. 2. describes the risk of any bipolar episode during the first perinatal period and subsequent perinatal periods. Perinatal 1 = first perinatal period, perinatal 2 = second perinatal period, perinatal 3 = third perinatal period.

et al., 2006; Sliwa et al., 2006; Weetman, 2010). In some women this results in exacerbation of pre-existing autoimmune disease or a first manifestation of an episode of autoimmune disease. The postpartum immune activation is postulated to produce the clinical manifestations of physical auto-immune diseases as rheumatoid arthritis, multiple sclerosis and thyroiditis and may play a central role in the pathogenesis of bipolar disorder (Drexhage et al., 2010). In addition to physical changes, psychological changes during the perinatal period may also play a role as a trigger for bipolar episodes. A systematic review found an increased risk of the onset of bipolar disorder within 6 months of stressful life events (Tsuchiya et al., 2003) and a more recently published meta-analysis found that patients experience more life events prior to bipolar episodes than during euthymic periods (Lex et al., 2017). Another large case-control study supported this association between life events and bipolar episodes, as it found that stressful life events, as suicide of a first-degree relative, but also divorce, marriage, disability or unemployment were associated with a first hospitalization for a manic episode (Kessing et al., 2004). Pregnancy, childbirth, miscarriage and induced abortion are all considered major life events.

Previous reports from the National Institute of Mental Health (NIMH), revealed that depression is the predominant affect of bipolar I disorder (Judd et al., 2003; Judd et al., 2002). Patients with these conditions experience depressive symptoms much more frequent than manic or hypomanic symptoms, with a ratio of 3:1 (Judd et al., 2003; Judd et al., 2002). Interestingly, in our study 51.4% of episodes during the perinatal period were of manic phenomenology (with or without prominent psychotic features), suggesting that manic episodes are more frequent during pregnancy or after childbirth than during other periods in life. In a retrospective cohort study by di Florio et al. information was gathered by semi-structured interview, questionnaires and case-note review from 887 women with bipolar disorder. The risk of perinatal recurrence was analyzed in women with bipolar I disorder and similar results to the current study were found (Di Florio et al., 2018). Of all women having an episode in the first perinatal period in that study, half of the women had an episode with manic phenomenology (Di Florio et al., 2018). A similar distribution of manic versus depressive bipolar episodes in the perinatal period was found in a meta-analysis of Wesseloo and colleague (Wesseloo et al., 2016). Our results emphasize the distinctive character of perinatal bipolar episodes.

Women who reported having suffered from an episode during the first perinatal period were significantly less likely to have a second pregnancy (55.5%), compared to 78.7% women with an uneventful first perinatal period. This is in line with a retrospective cohort study of Blackmore et al. in which clinical diagnostic interviews and medical case notes reviews were used to estimate that around half of those with postpartum psychosis in their first pregnancy had a subsequent pregnancy (Blackmore et al., 2013). Evidently, this may also influence the association between primiparity and perinatal bipolar episodes which has been described in previous studies (Di Florio et al., 2014). In our study, we showed that women who reported having experienced an episode related to their first perinatal period have an increased risk of an episode in a subsequent pregnancy (61.4%). In contrast, the risk was lower (20.5%), but not absent, after a first uneventful perinatal period. This pattern was further amplified over subsequent pregnancies. Similar results have been found by di Florio et al. (2018) (Di Florio et al., 2018), who described that rates were significantly higher in women with previous perinatal psychiatric history (55%), but women without such episodes were still at risk of developing perinatal illness (31%). These findings are particularly important for clinicians and patients, because these risks influence family planning and prevention strategies during the perinatal period.

A meta-analysis (Wesseloo et al., 2016) reported previously that lithium prophylaxis during pregnancy is important for maintaining mood stability during pregnancy and after delivery in women with bipolar I disorder. The association between lithium prophylaxis and lower episode risk found in this study confirms these findings but should be interpreted with caution due to several methodological limitations. Moreover, in general, the benefits of the protective effect of lithium prophylaxis during pregnancy should be weighed against the risk of congenital malformations con (Munk-Olsen et al., 2018; Patorno et al., 2017) and an increased risk of miscarriage (Poels et al., 2020). Prophylactic medication immediately after delivery is recommended in clinical practice, given the high recurrence risk postpartum. Ideally, women with bipolar I disorder of reproductive age have access to specialized women's mental health care facilities in order to weigh both risk and benefits of medication, with a reproductive psychiatrist.

4.1. Methodological considerations

A few limitations need to be considered when interpreting the results of this study. Data was collected retrospectively at one point in time, with information on childbearing history and related mood episodes being assessed through a self-report questionnaire. This means that data on this matter may have been subject to recall bias. It would have been preferable if perinatal episodes were confirmed by parallel interview of partners or family members. We do, however, not expect that recall bias had a major impact on our results as it has been shown that perinatal illness is a remarkable event for mothers, and therefore its severity and duration seem to be recalled accurately (Cox et al., 1984).

Second, assumptions on lithium use during pregnancy may have been inaccurate due to the fact that it was assessed through self-report, with the duration of lithium use not always being described as precisely as hoped for. Additionally, we did not have information on dosing and blood levels of lithium during pregnancy. However, in this study two different assessments of lithium use were combined to determine the use of current and past medication as accurate as possible and restrain misclassification (Abramovic et al., 2016). Information on the use of other mood stabilizing medication during pregnancy was unfortunately collected in less detail and therefore we could not investigate the association with other medication and episode risk. To our knowledge, there is no single other study that has been able to provide this information. Third, since lithium may have been predominantly prescribed in women with more severe previous bipolar episodes, confounding by indication is possible. This would most likely have led to an underestimation of the protective effect of lithium. Another limitation is that selection bias toward those willing to participate in a study is always possible (Rothman, 2002). Together with the finding that most women in the sample are Caucasian, this may affect the generalizability of our results to all women with bipolar I disorder in the childbearing age, even though there was a large variety in treatment settings and great variety in socioeconomic status in our sample. Our data did not allow us to compare perinatal recurrence risks to recurrence risk in a similar period of time in women of reproductive age who are not pregnant or postpartum. Interestingly, inpatient admission risks during pregnancy have been studied in a population based study, and the authors found a decreased risk for inpatient admission during pregnancy compared to a year after delivery (RR 0.53, 95%CI 0.-0.7) (Munk-Olsen et al., 2006), but this study investigated all new inpatient admissions, not specifically bipolar episodes.

5. Conclusions

This study shows that women with bipolar I disorder are at high risk of a bipolar episode after childbirth, miscarriage and induced abortion, but not during pregnancy. Consistent with previous studies, the risk is especially high in the first four weeks postpartum. This pattern is known from autoimmune disorders such as autoimmune thyroiditis, rheumatoid arthritis and multiple sclerosis. Future prospective studies should focus on the underlying biology of this remarkable flair pattern. After a first perinatal episode, the risk of a recurrent episode increases with subsequent pregnancies. Our data supports the need for preventive strategies immediately after delivery, given the high recurrence risk

within 4 weeks postpartum. Women with bipolar I disorder should be informed about all risks associated with pregnancy, preferably before conception. Together with their treating physician women should weigh the benefits and risks of mood stabilizing therapy during pregnancy and develop an individualized plan to prevent episodes following delivery. Future studies are needed on the effect of all mood stabilizing medication during pregnancy on the recurrence risk in the perinatal period.

Author statement

EP, JG, SL and VB devised the study concept. AK wrote the initial analysis plan with input from all authors and performed the data analysis. AK and JG contributed to creation of the tables and figures. AK, EP, JG, SL and VB wrote the initial draft of the manuscript. Supervision was performed by VB. All authors contributed to interpretation of the data, writing, editing and approval of the final version.

Funding

This work is supported by NWO, VENI and Clinical fellowship to VB. This work is supported by the National Institute of Mental Health (Grant number: R01MH 090 553) to RO and RK.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declaration of Competing Interest

All authors report no financial relationships with commercial interests.

Acknowledgments

The authors like to thank the women who participated in this study.

References

Abd El-Hay, M.A., El Sawy, H.F., Badawy, A.A., 2011. P01-204-predictors of recurrence of bipolar disorder during pregnancy and postpartum period in a sample of Egyptian women. Eur. Psychiatry 26, 205.

Abramovic, L., Boks, M.P., Vreeker, A., Bouter, D.C., Kruiper, C., Verkooijen, S., van Bergen, A.H., Ophoff, R.A., Kahn, R.S., van Haren, N.E., 2016. The association of antipsychotic medication and lithium with brain measures in patients with bipolar disorder. Eur. Neuropsychopharmacol.: J. Eur. Coll. Neuropsychopharmacol. 26, 1741–1751.

Akdeniz, F., Vahip, S., Pirildar, S., Vahip, I., Doganer, I., Bulut, I., 2003. Risk factors associated with childbearing-related episodes in women with bipolar disorder. Psychopathology 36, 234–238.

Alonso, J., Petukhova, M., Vilagut, G., Chatterji, S., Heeringa, S., Ustun, T.B., Alhamzawi, A.O., Viana, M.C., Angermeyer, M., Bromet, E., Bruffaerts, R., de Girolamo, G., Florescu, S., Gureje, O., Haro, J.M., Hinkov, H., Hu, C.Y., Karam, E.G., Kovess, V., Levinson, D., Medina-Mora, M.E., Nakamura, Y., Ormel, J., Posada-Villa, J., Sagar, R., Scott, K.M., Tsang, A., Williams, D.R., Kessler, R.C., 2011. Days out of role due to common physical and mental conditions: results from the WHO World Mental Health surveys. Mol. Psychiatry 16, 1234–1246.

Barth, C., Villringer, A., Sacher, J., 2015. Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. Front. Neurosci. 9, 37.

Blackmore, E.R., Rubinow, D.R., O'Connor, T.G., Liu, X., Tang, W., Craddock, N., Jones, I., 2013. Reproductive outcomes and risk of subsequent illness in women diagnosed with postpartum psychosis. Bipolar Disord. 15, 394–404.

Buyon, J.P., 1998. The effects of pregnancy on autoimmune diseases. J. Leukoc. Biol. 63, 281–287.

Calcagni, E., Elenkov, I., 2006. Stress system activity, innate and T helper cytokines, and susceptibility to immune-related diseases. Ann. N. Y. Acad. Sci. 1069, 62–76.

Confavreux, C., Hutchinson, M., Hours, M.M., Cortinovis-Tourniaire, P., Moreau, T., 1998. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. N. Engl. J. Med. 339, 285–291.

Cox, J.L., Rooney, A., Thomas, P.F., Wrate, R.W., 1984. How accurately do mothers recall postnatal depression? Further data from a 3 year follow-up study. J. Psychosomatic Obstetr. Gynecol. 3, 185–189.

Di Florio, A., Forty, L., Gordon-Smith, K., Heron, J., Jones, L., Craddock, N., Jones, I., 2013. Perinatal episodes across the mood disorder spectrum. JAMA Psychiatry 70, 168–175.

Di Florio, A., Gordon-Smith, K., Forty, L., Kosorok, M.R., Fraser, C., Perry, A., Bethell, A., Craddock, N., Jones, L., Jones, I., 2018. Stratification of the risk of bipolar disorder recurrences in pregnancy and postpartum. Br. J. Psychiatry: J. Ment. Sci. 213, 542–547.

Di Florio, A., Jones, L., Forty, L., Gordon-Smith, K., Blackmore, E.R., Heron, J., Craddock, N., Jones, I., 2014. Mood disorders and parity - a clue to the aetiology of the postpartum trigger. J. Affect. Disord. 152-154, 334–339.

Di Florio, A., Jones, L., Forty, L., Gordon-Smith, K., Craddock, N., Jones, I., 2015. Bipolar disorder, miscarriage, and termination. Bipolar Disord. 17, 102–105.

Drexhage, R.C., Knijff, E.M., Padmos, R.C., Heul-Nieuwenhuijzen, L., Beumer, W., Versnel, M.A., Drexhage, H.A., 2010. The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder. Expert. Rev. Neurother. 10, 59–76.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1997. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I). Biometric Research Department, New York.

Galea, L.A., Wide, J.K., Barr, A.M., 2001. Estradiol alleviates depressive-like symptoms in a novel animal model of post-partum depression. Behav. Brain Res. 122, 1–9.

Geddes, J.R., Miklowitz, D.J., 2013. Treatment of bipolar disorder. Lancet 381, 1672–1682.

Grande, I., Berk, M., Birmaher, B., Vieta, E., 2016. Bipolar disorder. Lancet 387, 1561–1572.

Grof, P., Robbins, W., Alda, M., Berghoefer, A., Vojtechovsky, M., Nilsson, A., Robertson, C., 2000. Protective effect of pregnancy in women with lithium-responsive bipolar disorder. J. Affect. Disord. 61, 31–39.

Haupl, T., Ostensen, M., Grutzkau, A., Burmester, G.R., Villiger, P.M., 2008. Interaction between rheumatoid arthritis and pregnancy: correlation of molecular data with clinical disease activity measures. Rheumatology (Oxford), 47 Suppl 3, iii19-22.

Houtepen, L.C., Boks, M.P., Kahn, R.S., Joels, M., Vinkers, C.H., 2015. Antipsychotic use is associated with a blunted cortisol stress response: a study in euthymic bipolar disorder patients and their unaffected siblings. Eur. Neuropsychopharmacol.: J. Eur. Coll. Neuropsychopharmacol. 25, 77–84.

Judd, L.L., Akiskal, H.S., Schettler, P.J., Coryell, W., Endicott, J., Maser, J.D., Solomon, D.A., Leon, A.C., Keller, M.B., 2003. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch. Gen. Psychiatry 60, 261–269.

Judd, L.L., Akiskal, H.S., Schettler, P.J., Endicott, J., Maser, J., Solomon, D.A., Leon, A.C., Rice, J.A., Keller, M.B., 2002. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch. Gen. Psychiatry 59, 530–537.

Kessing, L.V., Agerbo, E., Mortensen, P.B., 2004. Major stressful life events and other risk factors for first admission with mania. Bipolar Disord. 6, 122–129.

Leverich, G.S., Nolen, W.A., Rush, A.J., McElroy, S.L., Keck, P.E., Denicoff, K.D., Suppes, T., Altshuler, L.L., Kupka, R., Kramlinger, K.G., Post, R.M., 2001. The Stanley Foundation Bipolar Treatment Outcome Network. I. Longitudinal methodology. J. Affect. Disord. 67, 33–44.

Lewis, K.S., Gordon-Smith, K., Forty, L., Di Florio, A., Craddock, N., Jones, L., Jones, I., 2017. Sleep loss as a trigger of mood episodes in bipolar disorder: individual differences based on diagnostic subtype and gender. Br. J. Psychiatry: J. Ment. Sci. 211, 169–174.

Lex, C., Bäzner, E., Meyer, T.D., 2017. Does stress play a significant role in bipolar disorder? A meta-analysis. J. Affect. Disord. 208, 298–308.

Magnus, M.C., Wilcox, A.J., Morken, N.-H., Weinberg, C.R., Håberg, S.E., 2019. Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. BMJ 364, l869.

30 Ministerie van Volksgezondheid Welzijn en Sport - Inspectie Gezondheidszorg en Jeugd, Januari 2018. Jaarrapportage 2016 van de wet afbreking zwangerschap, Utrecht.

Miura, T., Noma, H., Furukawa, T.A., Mitsuyasu, H., Tanaka, S., Stockton, S., Salanti, G., Motomura, K., Shimano-Katsuki, S., Leucht, S., Cipriani, A., Geddes, J.R., Kanba, S., 2014. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry 1, 351–359.

Munk-Olsen, T., Laursen, T.M., Pedersen, C.B., Lidegaard, O., Mortensen, P.B., 2012. First-time first-trimester induced abortion and risk of readmission to a psychiatric hospital in women with a history of treated mental disorder. Arch. Gen. Psychiatry 69, 159–165.

Munk-Olsen, T., Laursen, T.M., Pedersen, C.B., Mors, O., Mortensen, P.B., 2006. New parents and mental disordersa population-based register study. JAMA 296, 2582–2589.

Munk-Olsen, T., Liu, X., Viktorin, A., Brown, H.K., Di Florio, A., D'Onofrio, B.M., Gomes, T., Howard, L.M., Khalifeh, H., Krohn, H., Larsson, H., Lichtenstein, P., Taylor, C.L., Van Kamp, I., Wesseloo, R., Meltzer-Brody, S., Vigod, S.N., Bergink, V., 2018. Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies. Lancet Psychiatry.

Newport, D.J., Stowe, Z.N., Viguera, A.C., Calamaras, M.R., Juric, S., Knight, B., Pennell, P.B., Baldessarini, R.J., 2008. Lamotrigine in bipolar disorder: efficacy during pregnancy. Bipolar Disord. 10, 432–436.

Patorno, E., Huybrechts, K.F., Hernandez-Diaz, S., 2017. Lithium use in pregnancy and the risk of cardiac malformations. N. Engl. J. Med. 377, 893–894.

Poels, E.M.P., Kamperman, A.M., Vreeker, A., Gilden, J., Boks, M.P., Kahn, R.S., Ophoff, R.A., Bergink, V., 2020. Lithium use during pregnancy and the risk of miscarriage. J. Clin. Med. 9.

Rothman, K.J., 2002. Epidemiology: An Introduction. Oxford University Press.

Ruiz-Irastorza, G., Lima, F., Alves, J., Khamashta, M.A., Simpson, J., Hughes, G.R., Buchanan, N.M., 1996. Increased rate of lupus flare during pregnancy and the puerperium: a prospective study of 78 pregnancies. Br. J. Rheumatol. 35, 133–138.
Salim, M., Sharma, V., Anderson, K.K., 2018. Recurrence of bipolar disorder during pregnancy: a systematic review. Arch. Womens Ment. Health 21, 475–479.
Schramm, C., Herkel, J., Beuers, U., Kanzler, S., Galle, P.R., Lohse, A.W., 2006. Pregnancy in autoimmune hepatitis: outcome and risk factors. Am. J. Gastroenterol. 101, 556–560.
Sedgh, G., Singh, S., Shah, I.H., Ahman, E., Henshaw, S.K., Bankole, A., 2012. Induced abortion: incidence and trends worldwide from 1995 to 2008. Lancet 379, 625–632.
Sliwa, K., Fett, J., Elkayam, U., 2006. Peripartum cardiomyopathy. Lancet 368, 687–693.
Stevens, A., Goossens, P.J.J., Knoppert-van der Klein, E.A.M., Draisma, S., Honig, A., Kupka, R.W., 2019. Risk of recurrence of mood disorders during pregnancy and the impact of medication: A systematic review. J. Affect. Disord. 249, 96–103.
Suppes, T., Leverich, G.S., Keck, P.E., Nolen, W.A., Denicoff, K.D., Altshuler, L.L., McElroy, S.L., Rush, A.J., Kupka, R., Frye, M.A., Bickel, M., Post, R.M., 2001. The Stanley Foundation Bipolar Treatment Outcome Network. II. Demographics and illness characteristics of the first 261 patients. J. Affect. Disord. 67, 45–59.
Tsuchiya, K.J., Byrne, M., Mortensen, P.B., 2003. Risk factors in relation to an emergence of bipolar disorder: a systematic review. Bipolar Disord. 5, 231–242.
van Bergen, A.H., Verkooijen, S., Vreeker, A., Abramovic, L., Hillegers, M.H., Spijker, A. T., Hoencamp, E., Regeer, E.J., Knapen, S.E., Riemersma-van der Lek, R.F., Schoevers, R., Stevens, A.W., Schulte, P.F.J., Vonk, R., Hoekstra, R., van Beveren, N. J., Kupka, R.W., Sommer, I.E.C., Ophoff, R.A., Kahn, R.S., Boks, M.P.M., 2019. The characteristics of psychotic features in bipolar disorder. Psychol. Med. 49, 2036–2048.
Viguera, A.C., Whitfield, T., Baldessarini, R.J., Newport, D.J., Stowe, Z., Reminick, A., Zurick, A., Cohen, L.S., 2007. Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. Am. J. Psychiatry 164, 1817–1824 quiz 1923.
von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C., Vandenbroucke, J.P., Initiative, S., 2007. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 370, 1453–1457.
Vreeker, A., Boks, M.P., Abramovic, L., Verkooijen, S., van Bergen, A.H., Hillegers, M.H., Spijker, A.T., Hoencamp, E., Regeer, E.J., Lek, Riemersma-Van der, R.F., Stevens, A. W., Schulte, P.F., Vonk, R., Hoekstra, R., van Beveren, N.J., Kupka, R.W., Brouwer, R.M., Bearden, C.E., MacCabe, J.H., Ophoff, R.A., 2016. High educational performance is a distinctive feature of bipolar disorder: a study on cognition in bipolar disorder, schizophrenia patients, relatives and controls. Psychol. Med. 46, 807–818.
Weetman, A.P., 2010. Immunity, thyroid function and pregnancy: molecular mechanisms. Nat. Rev. Endocrinol. 6, 311–318.
Wesseloo, R., Kamperman, A.M., Munk-Olsen, T., Pop, V.J., Kushner, S.A., Bergink, V., 2016. Risk of Postpartum Relapse in Bipolar Disorder and Postpartum Psychosis: A Systematic Review and Meta-Analysis. Am. J. Psychiatry 173, 117–127.