

# Perinatal Episodes Across the Mood Disorder Spectrum

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**Context:** Affective disorders are common in women, with many episodes having an onset in pregnancy or during the postpartum period.

**Objective:** To investigate the occurrence and timing of perinatal mood episodes in women with bipolar I disorder, bipolar II disorder, and recurrent major depression (RMD).

**Setting and Patients:** Women were recruited in our ongoing research on the genetic and nongenetic determinants of major affective disorders. Participants were interviewed and case notes were reviewed. Best-estimate diagnoses were made according to *DSM-IV* criteria. The 1785 parous women identified included 1212 women with bipolar disorder (980 with type I and 232 with type II) and 573 with RMD. Data were available on 3017 live births.

**Main Outcome Measures:** We report the lifetime occurrence of perinatal mood episodes, the rates of perinatal episodes per pregnancy/postpartum period, and the timing of the onset of episodes in relation to delivery.

**Results:** More than two-thirds of all diagnostic groups reported at least 1 lifetime episode of illness during pregnancy or the postpartum period. Women with bipolar I disorder reported an approximately 50% risk of a perinatal major affective episode per pregnancy/postpartum period. Risks were lower in women with RMD or bipolar II disorder, at approximately 40% per pregnancy/postpartum period. Mood episodes were significantly more common in the postpartum period in bipolar I disorder and RMD. Most perinatal episodes occurred within the first postpartum month, with mania or psychosis having an earlier onset than depression.

**Conclusions:** Although episodes of postpartum mood disorder are more common in bipolar I disorder and manic and psychotic presentations occur earlier in the postpartum period, perinatal episodes are highly prevalent across the mood disorder spectrum.

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**S**EX IS CLEARLY IMPORTANT in mood disorders. Unipolar depression is approximately twice as common in women than men and, despite an almost equal sex ratio for bipolar I disorder (BD-I), studies<sup>1</sup> report an increased risk in women of bipolar II, rapid cycling, and mixed episodes. Perhaps the major issue for women with mood disorder, however, is the impact of reproductive life events. In particular, there is strong, clear, and consistent evidence of a specific relationship between episodes of bipolar disorder and childbirth.<sup>2-4</sup>

In the traditional and simplistic view, there are 3 main postpartum mood episodes: maternity blues, postnatal depression, and postpartum (or puerperal) psychosis.<sup>5</sup> The term *postpartum psychosis*, although not used in current diagnostic

criteria, is widely accepted to describe the onset of a pleomorphic psychosis immediately after childbirth. Postpartum psychosis has been strongly and robustly related to bipolar disorder, both in epidemiologic<sup>6</sup> and clinical<sup>3</sup> samples. The eTable (<http://www.jamapsych.com>) summarizes current literature on rates of perinatal episodes (PNEs) in mood disorders. Although we know much about the very high risk of severe episodes of postpartum mood disorder occurring in women with BD-I, we know less about the burden of hypomanic and depressive PNEs in women with BD-I, bipolar II disorder (BD-II), and recurrent major depression (RMD).

This study moved beyond the rates of postpartum psychosis in BD-I to examine the occurrence of a wider range of PNEs (including manic/mixed episodes,

hypomania, psychotic depression, and nonpsychotic depression) in women with BD-I, BD-II, and RMD. We investigated the lifetime rates of perinatal mood episodes and the rates of episodes in relationship to each pregnancy. Finally, we looked at the timing of onset of PNEs. It has been argued that consideration should be given to different postpartum onset criteria for unipolar and bipolar illness.<sup>7</sup> We examined here whether empirical data support treating these disorders differently.

## METHODS

### RECRUITMENT

Participants were recruited in 2 clinical and genetic studies of mood disorders: RMD (March 1998 through December 2004)<sup>8,9</sup> and BD (September 1991 through December 2010).<sup>10</sup> Systematic recruitment identified participants through screening community mental health teams across the United Kingdom. Nonsystematic recruitment came via the media (television, press, radio, and Internet) and patient support organizations (eg, Depression Alliance and Bipolar UK). In the current analyses, 26% of the sample was recruited systematically. No significant differences emerged in rates of broadly defined PNEs between systematically and not systematically recruited women ( $\chi^2=0.56, P=.45$ ).

### INCLUSION CRITERIA

All participants were 18 years or older and provided written informed consent. Potential participants were excluded if they (1) had a lifetime diagnosis of intravenous drug dependency, (2) had experienced affective illness only as a result of alcohol or substance dependence, or (3) had experienced affective illness only secondary to medical illness or medication. The RMD study aimed to recruit a sample of participants with clear-cut unipolar depression. Thus, potential participants with RMD were excluded if they (1) had a first- or second-degree relative with a clear diagnosis of bipolar affective disorder, schizophrenia, schizotypal disorder, persistent delusional disorder, acute and transient psychotic disorders, or schizoaffective disorder or (2) had ever experienced mood-incongruent psychosis or psychosis outside of mood episodes. Participants were included in the current analyses if they (1) had a lifetime *DSM-IV* diagnosis of BD-I, BD-II, or RMD and (2) were parous, having given birth to at least 1 child.

Some participants in our studies were recruited specifically because of a history of severe postpartum illness. Including these women would inflate the rates of postpartum episodes, since, by definition, they were ill at this time. We therefore excluded women from the current analysis who were recruited on the basis of having a postpartum episode.

Because we were interested in mood disorder episodes in the reproductive years, women were excluded if they reported an age at onset in the postmenopausal period. A cutoff age of 50 years was set, according to the mean European age at menopause.<sup>11</sup> This study received all necessary multiregion and local research ethics committee approvals.

### ASSESSMENTS

Participants were interviewed using the Schedules for Clinical Assessment in Neuropsychiatry,<sup>12</sup> and psychiatric case notes were reviewed for 78% of participants. Best-estimate lifetime diagnoses were made according to *DSM-IV*,<sup>13</sup> and key clinical variables, such as age at onset and number of episodes, were rated.

In cases with some doubt, diagnostic and clinical ratings were made by at least 2 members of the research team blinded to each other's rating. Interrater reliability was assessed in a formal exercise using a randomly selected 20 cases. Mean  $\kappa$  statistics were 0.85 for *DSM-IV* diagnoses and ranged between 0.81 and 0.99 for other key clinical categorical variables; mean intraclass correlation coefficients were between 0.91 and 0.97 for key clinical continuous variables. All team members involved in the interview, rating, and diagnostic procedures were research psychologists or psychiatrists (A.D.F., L.F., K.G.-S., J.H., L.J., N.C., and I.J.).

### PERINATAL EPISODES

Because of our long-standing interest in PNEs of mood disorders, information was obtained from all participants about the lifetime occurrence of pregnancy and postpartum episodes. Participants recruited more recently were also asked pregnancy-by-pregnancy questions about the relationship of episodes of illness to childbirth. We were therefore able to report lifetime rates of postpartum episodes in the whole sample (N=1785) and rates per delivery in most women (n=1441).

### LIFETIME RATINGS

For lifetime ratings, we used 3 overlapping and hierarchical definitions:

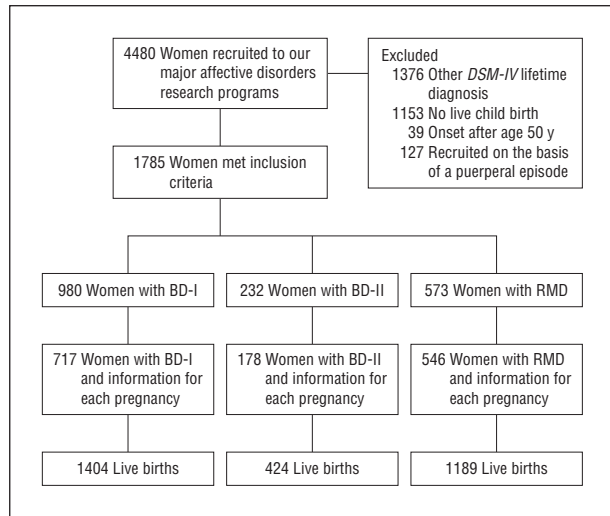
1. *Narrow*: an episode of any of the following that has an onset within 6 weeks of delivery: (a) mania with or without psychotic features, (b) hypomania, (c) a mixed episode, or (d) psychotic depression.
2. *Intermediate*: women meeting the narrow criteria plus those with an episode of nonpsychotic major depression with onset within 6 weeks of delivery.
3. *Broad*: women meeting either the narrow or intermediate criteria plus those with a history of an episode of any major mood disorder with onset in pregnancy or within 6 months of delivery.

Women were rated on a lifetime basis into the narrowest category that applied for any of their pregnancies. The 6-week onset cutoff is consistent with previous studies; includes the *DSM-IV* and *International Statistical Classification of Diseases, 10th Revision* definitions of the postpartum period; and was chosen as a compromise between very narrow (onset within 1 or 2 weeks) and wide (onset within 6 months) possible definitions of postpartum episodes.

### INDIVIDUAL PERINATAL PERIODS

For women with pregnancy-by-pregnancy information, we rated the following episodes according to *DSM-IV* criteria: mania/mixed episode, hypomania, major depression with psychotic symptoms, and nonpsychotic major depression.

Currently, there is no consensus on the time frame that should be used to label episodes as occurring in relation to childbirth. Episodes within 4 weeks of childbirth can be recorded via the postpartum-onset specifier in *DSM-IV*,<sup>13</sup> but this may be too narrow for depressive episodes.<sup>6,14</sup> In common usage, episodes occurring within 6 or even 12 months of delivery are considered to be post partum. We therefore used the widest possible definition of postpartum episode and conducted a 2-step analysis: first we reported all episodes that occurred during pregnancy and within 12 months of childbirth. The rates of deliveries affected by mood episodes were then analyzed with use of survival curves to address the time of onset.



**Figure 1.** Flowchart of the sample selection and assessment process. BD-I indicates bipolar I disorder; BD-II, bipolar II disorder; and RMD, recurrent major depression.

## STATISTICAL ANALYSIS

The statistical analysis was performed using R, version 2.13.0 software (R Project). Univariate comparisons were performed using analysis of variance for normally distributed variables, the Kruskal-Wallis test for those that were not normally distributed, and  $\chi^2$  statistics for categorical variables.

The lifetime prevalence of PNEs underestimates the lifetime morbid risk, since some women have additional pregnancies and episodes of PNE. Morbidity risk is the probability that a woman will develop a PNE if she has children through the entire period at risk. To calculate morbid risk, the Stromgren method was used.<sup>15</sup> We assumed that the conditional distribution of age at the onset of the first PNE was normally distributed (mean [SD] age, 26.3 [5.29] years; Shapiro-Francia normality test,  $W=0.99$ ;  $P=.66$ ).

Multiple deliveries for 1 individual could not be considered independent observations. The general association Cochran-Mantel-Haenszel test statistic<sup>16</sup> was used to compare the differences in rates of deliveries affected across diagnostic groups.

Kaplan-Meier estimates and survival curves displayed the onset across diagnostic groups. The log-rank test was used to determine whether the survival curves were identical. Order of pregnancy and multiple episodes may influence the latency between childbirth and the onset of a postpartum episode, so the analyses were conducted only on first-time mothers.

## RESULTS

### SAMPLE

Inclusion criteria were met by 1212 women with BD (980 with BD-I and 232 with BD-II) and 573 women with RMD (**Figure 1**). Women with BD-I were overrepresented because of our ascertainment strategy and the duration of each study from which the samples were drawn. The focus of our BD recruitment was in mental health services, where we are more likely to identify individuals with BD-I than BD-II. Our studies recruiting BD probands were also 9 years longer than the study recruiting RMD probands. Demographic and clinical characteristics of the sample are reported in **Table 1**. Women with

**Table 1. Clinical and Demographic Information at the Time of Interview by Lifetime Diagnosis**

Characteristic	Lifetime Diagnosis		
	BD-I (n = 980)	BD-II (n = 232)	RMD (n = 573)
Age, mean (SD), y			
At interview	48.5 (11.36)	47.9 (11.74)	48.2 (11.74)
At impairment <sup>a</sup>	24.4 (8.61)	22.2 (9.27)	24.7 (8.33)
At first pregnancy	24.6 (5.00)	24.6 (5.70)	24.1 (5.25)
At first PNE	26.4 (4.88)	26.3 (5.42)	26.3 (5.45)
No. of pregnancies, median (range) <sup>b</sup>	2 (1-10)	3 (0-9)	3 (1-9)
No. of deliveries, median (range) <sup>c</sup>	2 (1-10)	3 (1-9)	3 (1-9)

Abbreviations: BD-I, bipolar I disorder; BD-II, bipolar II disorder; PNE, perinatal episode; RMD, recurrent major depression.

<sup>a</sup>Analysis of variance:  $F_2 = 7.02$ ,  $P < .001$ .

<sup>b</sup>Kruskal-Wallis  $\chi^2 = 13.36$ ,  $P < .001$ .

<sup>c</sup>Kruskal-Wallis  $\chi^2 = 30.54$ ,  $P < .001$ .

BD-I, BD-II, and RMD had similar age at interview and age at first pregnancy. The proportion of women with RMD who had at least 1 child was significantly higher than that of women with BD-I and BD-II ( $P < .001$ ). Age at onset of mood disorder (defined as the first episode of a mood disorder resulting in significant impairment), number of pregnancies, and number of deliveries significantly differed across lifetime diagnostic groups. Women with BD-II reported a significantly earlier age at onset than did women with either BD-I or RMD ( $P=.02$  and  $P=.001$ , respectively). The BD-I group had significantly fewer pregnancies and deliveries compared with the RMD group ( $W=157\,578.5$ ,  $P < .001$  for pregnancies and  $W=162\,277.5$ ,  $P < .001$  for deliveries).

### LIFETIME OCCURRENCE OF PERINATAL ILLNESS

We examined the lifetime occurrence of our 3 definitions of PNE (**Table 2** and **Figure 2**). Although, as expected, our narrow definition of postpartum episode was predominantly found in the women with BD, under our broad definition, more than two-thirds of women in all 3 diagnostic groups reported at least 1 episode of illness during pregnancy or the postpartum period. For the broad definition of perinatal mood episode, there were no significant differences across the mood disorder spectrum ( $\chi^2 = 0.77$ ,  $P = .68$ ). Using the Stromgren method, the morbidity risk for broadly defined PNEs did not differ significantly across lifetime diagnoses (BD-I, 70.8%; BD-II, 70.9%; and RMD, 73.7%;  $\chi^2 = 1.6868$ ;  $P = .43$ ).

### INDIVIDUAL PERINATAL PERIODS

Information was available for 3017 pregnancies from 1410 women (**Table 3**). Women with BD-I reported approximately 1 pregnancy of 2 affected by a mood episode in pregnancy or the postpartum period (manic/mixed episode, hypomania, psychotic depression, and nonpsychotic depression); the proportion was lower in women with RMD or BD-II, with both approximately 40%. When

**Table 2. History of PNEs of Illness in Parous Women With Affective Disorders**

Definition of PNE, No. (%)	Lifetime Diagnosis		
	BD-I (n = 980)	BD-II (n = 232)	RMD (n = 573)
Narrow <sup>a</sup>	326 (33.3)	21 (9.1)	2 (0.3)
Intermediate <sup>b</sup>	544 (55.5)	93 (40.1)	270 (47.1)
Broad <sup>c</sup>	681 (69.5)	160 (69.0)	386 (67.4)

Abbreviations: BD-I, bipolar I disorder; BD-II, bipolar II disorder; PNE, perinatal episode; RMD, recurrent major depression.

<sup>a</sup>Defined as an episode of mania with or without psychotic features, hypomania, a mixed episode, or psychotic depression, all onset within 6 weeks of delivery.

<sup>b</sup>Defined as women meeting the narrow criteria plus those with an episode of major depression with onset within 6 weeks of delivery.

<sup>c</sup>Defined as women meeting either the narrow or intermediate criteria plus those with a history of an episode of any major mood disorder with onset in pregnancy or within 6 months of delivery.

data were compared accounting for multiple pregnancies, women with BD-I had a statistically significant higher incidence of any perinatal mood episode compared with women with RMD or BD-II ( $M_2^2 = 12.54$ ,  $P = .002$ ). For women with BD-I, more than 20% of pregnancies or postpartum periods were affected by a mania or psychotic depression and nearly 25% were affected by an episode of nonpsychotic depression.

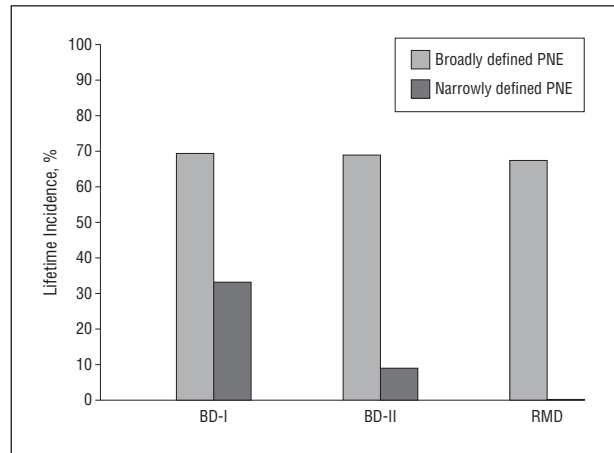
#### ONSET IN PREGNANCY OR THE POSTPARTUM PERIOD

The proportions of perinatal episodes with onset in pregnancy and the postpartum period are reported in Table 3. In all diagnostic groups, most PNEs had a postpartum onset; however, the proportion of episodes that occurred in pregnancy in women with BD-II (18.4%) was approximately twice as high as the proportion in those with BD-I (8.6%) and RMD (11.0%). Episodes in pregnancy were equally represented across trimesters ( $\chi_2^2 = 1.7$ ,  $P = .42$ ).

Approximately 80% of PNEs in women with BD-I and 72% in women with RMD met the 4-weeks' postpartum onset criteria of *DSM-IV*, while only 53% of PNEs in mothers with BD-II had an onset within the first 4 weeks following childbirth. Mood episodes were significantly more common in the first month post partum than in pregnancy across all lifetime diagnoses ( $P < .001$  for BD-I: odds ratio [OR], 44.5; 95% CI, 26.9-76.0; BD-II: OR, 4.7; 95% CI, 2.4-9.8; and RMD: OR, 22.1; 95% CI, 13.0-39.1). Only 3.7% of episodes occurred between 6 and 12 months, with no significant differences between the diagnostic groups ( $\chi_1^2 = 2.86$ ,  $P = .09$ ).

#### TIME OF ONSET OF POSTPARTUM EPISODES

Given the common use of a 6-month threshold to define postpartum episodes, we focused our survival analyses on this period. **Figure 3A** shows a significant difference in the onset of postpartum episodes for each lifetime diagnosis ( $\chi_2^2 = 23.9$ ,  $P < .001$ ). Women with BD-I reported a significantly earlier onset of a postpartum epi-



**Figure 2.** Lifetime perinatal episodes (PNEs) of illness in parous women with affective disorders. Narrowly defined PNE: an episode of mania/hypomania or affective psychosis with onset within 6 weeks of delivery. Broadly defined PNE: any major mood disorder with onset in pregnancy or within 6 months of delivery. For simplicity we have not presented the intermediate definition. BD-I indicates bipolar I disorder; BD-II, bipolar II disorder; and RMD, recurrent major depression.

sode than did women with RMD ( $\chi_1^2 = 7.3$ ,  $P = .007$ ), and women with RMD reported a significantly earlier onset of a postpartum episode than did women with BD-II ( $\chi_1^2 = 7.4$ ,  $P = .007$ ).

Given that, by definition, women with RMD do not experience manic episodes, analysis was conducted for depressive episodes alone (Figure 3B). Women with RMD and BD-I had overlapping survival curves ( $\chi_1^2 = 0$ ,  $P = .93$ ), but women with BD-II displayed a delayed onset of depressive episodes (post hoc comparison vs BD-I:  $\chi_1^2 = 8.4$ ,  $P = .004$ ).

We then looked at the onset of different episode types in women with BD-I, namely, postpartum (nonpsychotic) depression, mania/mixed episode, and psychotic depression (Figure 3C). Interestingly, the survival curves for mania and psychotic depression overlapped ( $\chi_1^2 = 0$ ,  $P = .92$ ), and nonpsychotic depression had a significantly later onset in the postpartum period ( $\chi_1^2 = 13.7$ ,  $P = .002$ ).

#### NUMBER OF POSTPARTUM EPISODES VS THOSE NOT RELATED TO CHILDBIRTH

High rates of PNEs may be the result of merely the highly recurrent course of mood disorders. The Wilcoxon signed rank test was used to compare the rates of PNEs with the rates of lifetime episodes. A conservative approach was used, with women who showed a rapid cycling course (defined as  $\geq 4$  episodes/y) excluded from this analysis. Episodes occurring within 4 weeks post partum were significantly overrepresented in women with BD-I ( $V = 25\,738.5$ ,  $P < .001$ ) and RMD ( $V = 14\,878$ ,  $P < .001$ ), but not in women with BD-II ( $V = 3157$ ,  $P = .74$ ). In women with BD-I, episodes of mania or psychotic depression ( $V = 48\,657.5$ ,  $P < .001$ ) were overrepresented in the first postpartum month, but this was not the case for episodes of nonpsychotic depression. With a broader definition of postpartum onset (within 6 months), postpartum episodes were no more common

**Table 3. PNEs in Women With Mood Disorders**

Characteristic	Lifetime Diagnosis		
	BD-I (n = 671)	BD-II (n = 193)	RMD (n = 546)
No. of deliveries	1404	424	1189
Pregnancies or postpartum periods affected by any <i>DSM-IV</i> affective episode, No. (%) <sup>a</sup>	700 (49.8)	179 (42.2)	508 (42.7)
Episodes occurring in pregnancy	60 (8.6)	33 (18.4)	56 (11.0)
Episodes occurring in the postpartum period <sup>b,c</sup>	640 (91.4)	146 (81.6)	452 (89.0)
Individual PNE diagnosis			
Perinatal manic/mixed episode, No. (%)	277 (19.7)		
Proportion with onset in the postpartum period, %	94.9		
Perinatal hypomanic episode, No. (%)	37 (2.6)	17 (4.0)	
Proportion with onset in the postpartum period, %	87.5	80.0	
Perinatal psychotic depression episode, No. (%)	38 (2.7)	12 (2.8)	18 (1.5)
Proportion with onset in the postpartum period, %	81.8	78.0	93.3
Perinatal nonpsychotic depression episode, No. (%)	348 (24.8)	150 (35.4)	490 (41.2)
Proportion with onset in the postpartum period, %	90.0	82.2	89.1

Abbreviations: BD-I, bipolar I disorder; BD-II, bipolar II disorder; PNE, perinatal episode; RMD, recurrent major depression.

<sup>a</sup>Cochran-Mantel-Haenszel  $M_2^2 = 12.54$ ,  $P = .002$ , after correction for multiple pregnancies.

<sup>b</sup>Defined as within 12 months of childbirth.

<sup>c</sup>Cochran-Mantel-Haenszel  $M_2^2 = 10.92$ ,  $P = .004$ , after correction for multiple pregnancies.

than expected in all diagnostic groups. Episodes occurring in pregnancy were significantly overrepresented in women with RMD ( $V = 25\ 737.5$ ,  $P < .001$ ) but not in those with BD-I or BD-II.

#### COMMENT

We investigated the burden of PNEs in a large, well-characterized clinical sample of women with mood disorders, including BD-I, BD-II, and RMD. The lifetime prevalence of PNEs was high across all disorders, affecting more than 2 of 3 women in all diagnostic groups.

Women with BD-I reported fewer pregnancies and deliveries than those with RMD but reported more PNEs than women with RMD or BD-II. Most PNEs in women with BD-I and RMD occurred within 4 weeks after childbirth. In women with BD-I, there was a significantly shorter latency for manic or psychotic episodes than for episodes of nonpsychotic depression. For BD-II, onsets of psychiatric episodes had a wider distribution across the perinatal period, with more onsets in pregnancy and later in the postpartum period. Moreover, mood episodes were significantly more common in the postpartum period than at other times in women with BD-I and RMD, but not in those with BD-II.

#### BURDEN OF PNEs

Despite differences in inclusion criteria, assessment, and phenotypic definitions making direct comparisons of studies difficult, our findings corroborate and extend previous research that has reported high rates of perinatal mood disturbances in relation to childbirth (eTable).

Consistent with previous research,<sup>17-19</sup> we found that women with BD-I reported fewer pregnancies and deliveries than did those with RMD. Robust evidence of an association between BD and severe postpartum episodes has been reported. In the Danish population-based cohort study,<sup>6</sup> the cumulative incidence of admis-

sion from 0 to 3 months post partum was 22% for first-time mothers with BD. Similar rates were reported in an analysis of smaller numbers of women with BD from our sample, with 26% of deliveries followed by a severe episode.<sup>20</sup> Consistent with previous research, we found that, in women with BD-I, more than 1 in 5 pregnancies are complicated by mania or psychotic depression with onset in the first postpartum weeks—episodes corresponding to the concept of postpartum psychosis.

The rates of hypomania were surprisingly low. It may be associated with difficulties in recollecting minor episodes and in differentiating hypomania from the extreme happiness following motherhood. In addition, mixed states may be common in the postpartum period, and it is possible that women focused on depressive symptoms when asked about postpartum episodes. Another possible explanation is that childbirth is more likely to trigger a full-blown mood episode in women with a history of mood disorder, whereas in the general population without an underlying diathesis for major psychiatric illness, more minor mood symptoms are triggered.

#### TIMING OF PNEs

Consistent with several reports,<sup>6,21</sup> we found the incidence of mood episodes to be considerably lower in pregnancy than during the postpartum period. Other studies, however, have found high rates of recurrence during pregnancy in women with BD. Viguera and colleagues,<sup>22</sup> for example, found a recurrence rate of 52% in pregnancy in women discontinuing prophylactic mood-stabilizing medication, and a later study from the same group<sup>20</sup> found an even higher pregnancy recurrence rate (71%). It is possible that the women participating in these studies, identified through a tertiary academic center specializing in reproductive psychiatry, had a more severe form of illness compared with the women in our study. It is also possible that the high recurrence rates during pregnancy in these studies were a result of stopping medi-

cation, and the lower rate in our study is because women either continued medication through pregnancy or were receiving no medication before the pregnancy. In the later study, Viguera et al<sup>20</sup> found considerably lower rates of recurrence (37%) in pregnancy in women who continued medication through the perinatal period. Finally, another important difference between our study and the previous ones is that we rated only the most severe episode for each pregnancy/delivery. It is possible that several less severe episodes with onset in pregnancy were not recorded if there was a later severe postpartum episode related to that pregnancy.

Our findings also corroborate evidence of a strong link between severe manic episodes and the first postpartum weeks.<sup>6,19</sup> For episodes of postpartum depression, however, it is interesting that we did not find significant differences in onset between the BD-I and RMD groups. In the Danish population-based cohort study,<sup>4</sup> the risk of hospital admission for unipolar depression was distributed throughout 5 months, but mothers with BD had the highest risk of readmission within the first 3 weeks post partum. However, the Danish study used hospital admissions data and did not discriminate between bipolar depression and mania. Our results showed that in women with BD-I the onset of depressive episodes is more widely distributed in the postpartum period compared with manic episodes. This finding suggests that, rather than differences between unipolar and bipolar disorder lifetime diagnoses, the latency of onset after childbirth is associated with the polarity of the puerperal episode itself.

In our sample, BD-II showed a pattern of onset that was different from that of BD-I and RMD, both when all PNEs or when episodes of depression alone were considered. Moreover, mood episodes were significantly over-represented in the postpartum period in BD-I and RMD, but not in BD-II. Further work is clearly needed in prospective studies to clarify the relationship of BD-II to childbirth.

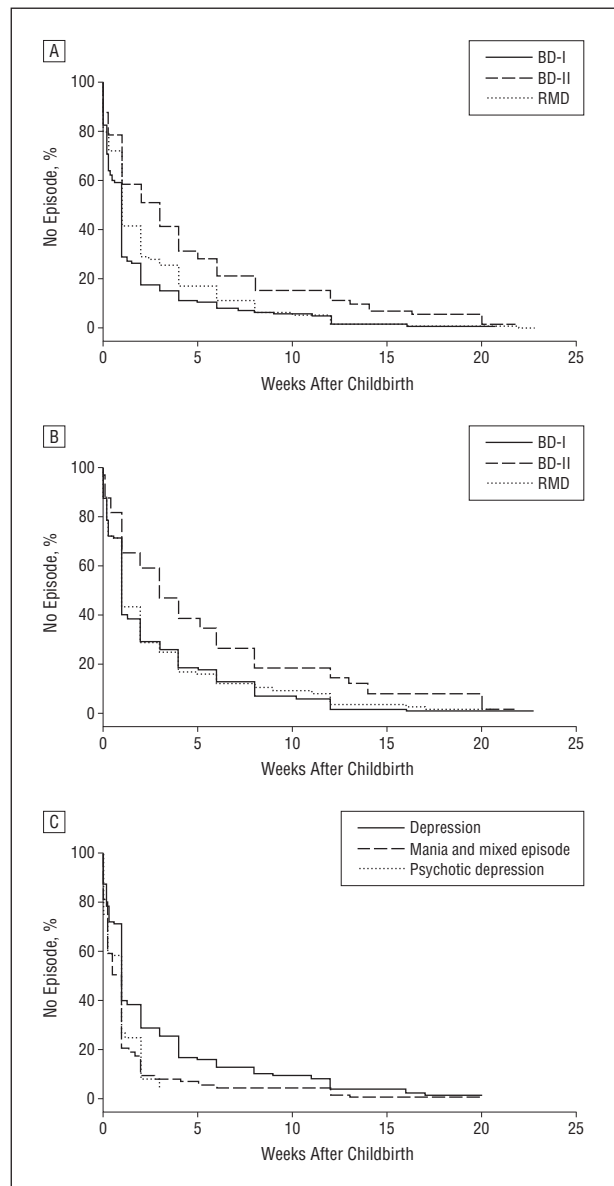
## STRENGTHS AND LIMITATIONS

Our study has many strengths:

1. A large sample size was included and a number of different perinatal mood episodes across the bipolar/unipolar spectrum were compared.
2. Participants were enrolled with no selection on the basis of having a postpartum episode. This represents an advantage over previous studies<sup>20,23</sup> in which participants were obtained from perinatal psychiatry programs and subject to selection bias, potentially raising the rates of postpartum episodes.
3. Diagnoses, both lifetime and of PNEs, were based on a validated semistructured interview and case-note review, explicitly defined according to *DSM-IV* criteria, and showed excellent interrater reliability.

There are also several limitations:

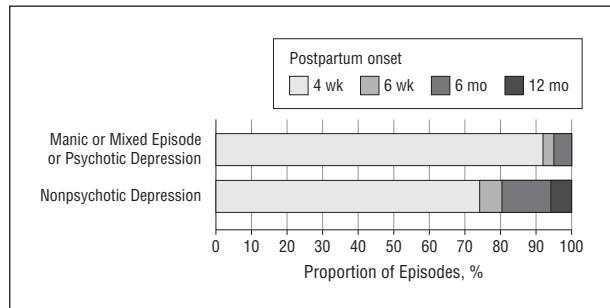
1. Information on PNEs was collected retrospectively; therefore, the rates may not equate with the risk for women with an existing mood disorder who become pregnant. There are 2 reasons for this limitation. First, a



**Figure 3.** Survival curves of time of onset of postnatal episodes in first-time mothers. A, Survival distributions of all postnatal episodes by *DSM-IV* lifetime diagnosis. B, Survival distributions of postnatal depression by *DSM-IV* lifetime diagnosis. C, Survival distributions of postnatal episodes in bipolar I disorder (BD-I). BD-II indicates bipolar II disorder; RMD, recurrent major depression.

small number of pregnant women with a previous diagnosis of BD-II or RMD may develop a postpartum episode of mania and therefore switch diagnosis to BD-I. It has recently been reported<sup>24</sup> that 14% of women having a first psychiatric admission soon after childbirth developed BD during a 15-year follow-up period. In our study these women would be included in the BD-I group. Second, some pregnancies may have been before the first episode of mood disorder. The risk of postpartum episodes may be higher if the pregnancy follows an episode of mood disorder than for women who are yet to experience an episode of illness.

2. A further issue is the reliability of the women's recollections of perinatal mood episodes. In the present study, however, the reporting of episodes at interview was in



**Figure 4.** Proportion of postpartum episodes identified as related to childbirth according to different definitions of postpartum onset.

agreement with the medical records, and the recollection of episodes of illness in relation to childbirth was, in our experience, excellent.<sup>19</sup>

3. Individuals in the RMD group were excluded from the study if they had ever experienced mood-incongruent psychosis or psychosis outside of mood episodes; thus, the rates of psychotic PNEs in women with RMD may be underestimated.

4. A single PNE was rated for each pregnancy. For women who experienced multiple episodes in relation to a single pregnancy, only information on the most severe episode was collected. Thus, we were not able to assess the likelihood of having multiple episodes during or after a single pregnancy.

5. Because of the retrospective design, we were not able to gather reliable information on the pharmacotherapy used through each perinatal period. Prospective studies are needed to assess the adherence and exposure to psychopharmacologic treatments in pregnancy and the postpartum period.

For these reasons, prospective longitudinal studies of women with the range of mood disorder diagnoses are needed. However, many of the limitations discussed indicate that the high rates of PNEs that we reported are likely to result in underestimation, to some extent, of the risk to women with existing mood disorders, particularly those with BD-II and RMD.

In addition, the retrospective design allowed us to put PNEs of illness into the context of lifetime diagnosis rather than focusing on a cross-sectional picture in the postpartum period. It has been recently reported,<sup>24</sup> for example, that a psychiatric episode of unipolar depression in the immediate postpartum period significantly predicts conversion to bipolar affective disorder in the longer term.

## CLINICAL IMPLICATIONS

### Burden of PNEs

The results of the present study emphasize the high rate of PNEs in women with mood disorders. More than 70% of parous women with mood disorders will experience at least 1 PNE in relationship to pregnancy and childbirth. The importance of pregnancy and childbirth for women with mood disorders should therefore not be underestimated.

For women with BD-I, approximately 20% of deliveries are associated with a postpartum episode of mania or psychotic depression; a further 25% of deliveries are associated with an episode of nonpsychotic major depression, and almost 50% of deliveries are associated with a PNE of a major mood disorder of some description. In discussing the risk of a PNE in women with BD-I, it is therefore important to consider the risk of postpartum depression in addition to the risk of postpartum mania/psychosis.

Moreover, it would be wrong to underestimate the importance of perinatal mood disorders to women with a lifetime diagnosis of BD-II or RMD. Although they experience perinatal mood disorders at lower rates than do women with BD-I, approximately 40% of deliveries in women with BD-II or RMD are associated with a PNE of major mood disorder.

Because more than 40% of pregnancies are unplanned,<sup>25</sup> the risk of PNEs should be discussed with all women of childbearing age with mood disorders, even those not planning a pregnancy. Given that women may not be in contact with psychiatric services, it is important that all professionals providing health care for pregnant women, including midwives, family physicians, and obstetricians, are aware of this increased risk.

### Timing of Postpartum Episodes

We found that, in BD-I and RMD, episodes of depression had a very similar pattern of onset following childbirth. When postpartum episodes in women with BD-I were analyzed according to episode type, postnatal depression with psychotic features and mania had an overlapping pattern of onset, while the onset of nonpsychotic depression was later in the postpartum period. Together, these findings suggest that if different postpartum-onset criteria are included in diagnostic criteria, this should be according to the polarity of the episode rather than the lifetime diagnosis. There is no justification here for separate onset criteria for bipolar and unipolar disorders.

Decisions about the postpartum-onset criteria are difficult. On one hand, a broader definition may be of benefit in clinical practice, where therapy for mothers who experience an onset within a few months of delivery should be informed by the postpartum context. On the other hand, a broad definition may be a problem for studies examining the mechanism of postpartum triggering. In our sample, 94% of episodes of mania or psychotic depression occurred within 4 weeks post partum, although this criterion included less than three-fourths (74.2%) of the episodes of nonpsychotic postpartum depression (**Figure 4**).

In conclusion, although women with BD-I reported higher rates of PNEs, the morbidity risk of an episode in relation to childbirth was high across all mood disorder diagnostic groups. Professionals involved in the care of women of childbearing age with a history of mood disorder should discuss with them the risk of illness in relation to childbirth. Pregnant women with a history of mood disorders should be monitored closely throughout pregnancy and especially in the postpartum period.

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