Psychiatric Disorders With Postpartum Onset

Possible Early Manifestations of Bipolar Affective Disorders

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Context: Childbirth has an important influence on the onset and course of bipolar affective disorder, and it is well established that there may be a delay of many years before receiving a diagnosis of bipolar disorder following an initial episode of psychiatric illness.

Objective: To study to what extent psychiatric disorders with postpartum onset are early manifestations of an underlying bipolar affective disorder.

Design: Survival analyses were performed in a register-based cohort study linking information from the Danish Civil Registration System and the Danish Psychiatric Central Register.

Setting: Denmark.

Participants: A total of 120,378 women with a first-time psychiatric inpatient or outpatient contact with any type of mental disorder excluding bipolar affective disorder.

Main Outcome Measures: Each woman was followed up individually from the day of discharge, with the outcome of interest being an inpatient or outpatient contact during the follow-up period with a first-time diagnosis of bipolar affective disorder.

Results: A total of 3062 women were readmitted or had an outpatient contact with bipolar affective disorder diagnoses. A postpartum onset of symptoms within 0 to 14 days after delivery predicted subsequent conversion to bipolar disorder (relative risk = 4.26; 95% CI = 3.11-5.85). Approximately 14% of women with first-time psychiatric contacts during the first postpartum month converted to a bipolar diagnosis within the 15-year follow-up period compared with 4% of women with a first psychiatric contact not related to childbirth. Postpartum inpatient admissions were also associated with higher conversion rates to bipolar disorder than outpatient contacts (relative risk = 2.16; 95% CI = 1.27-3.66).

Conclusions: A psychiatric episode in the immediate postpartum period significantly predicted conversion to bipolar affective disorder during the follow-up period. Results indicate that the presentation of mental illness in the early postpartum period is a marker of possible underlying bipolarity.

chiatric diagnoses. It is also possible, however, that a significant proportion of postpartum episodes that receive another diagnosis do in fact occur in women with underlying bipolar illness. This may result from misdiagnosis if, eg, features of high mood in a mixed episode are missed.

It is well known that there are difficulties in diagnosing bipolar disorder, with often a considerable delay in an accurate diagnosis being made. In the Bipolar Comprehensive Outcomes Study, individuals with bipolar disorder showed an average of 9 years between the first episode of major depression and diagnosis. Similarly, this study revealed an average 5-year delay in receiving a bipolar diagnosis following the first symptoms of a manic episode. Depressive episodes occur in patients with both unipolar and bipolar disorder. For all individuals presenting with depression, there is therefore a risk of subsequent episodes of high mood and a diagnostic conversion from unipolar disorder to bipolar disorder. A study by Angst et al has quantified this risk and found a diagnostic change from unipolar major depression to bipolar disorder in 1% of patients per year and to bipolar II disorder in about 0.5% of patients per year.

Although a diagnostic shift to bipolar disorder is more unusual than for other initial diagnoses, it can occur. For example, there are issues in the diagnostic stability of a first psychotic episode, with the later emergence of affective features resulting in a revision from a nonaffective psychosis to bipolar or schizoaffective disorder in a proportion of patients.

Given these diagnostic challenges and the very strong relationship between childbirth and bipolar disorder, we hypothesized that a postpartum onset of psychiatric illness could help in the difficult task of diagnosis with the triggering of illness by childbirth being a marker of underlying bipolarity. We aimed to study to what extent non-bipolar postpartum episodes convert to bipolar affective disorders over time using registry data in a longitudinal study based on data derived from the entire Danish population.

METHODS

STUDY POPULATION

We established a population-based cohort using information from the Danish Civil Registration System. The register was established in 1968 and holds information on sex, date of birth, and parents’ Civil Registration System numbers and is updated daily on vital status and migration. All citizens in Denmark are assigned a personal identification number (Civil Registration System number), which is used in all registers and makes linkage between and within registers possible. We included all women with records of 1 psychiatric contact who were born in Denmark from January 1, 1950, until December 31, 1991, who were alive on their 15th birthday (N = 120,378) who were born in Denmark from January 1, 1950, until December 31, 1991, who were alive on their 15th birthday (N = 120,378).

PSYCHIATRIC DISORDERS

Data on psychiatric disorders came from the Danish Psychiatric Central Register, which holds information on all admissions to psychiatric hospitals in Denmark since 1969.

more, it contains records of psychiatric contacts at outpatient clinics since 1993. At present, the register holds information on more than 725,000 persons and 3.25 million contacts. From 1969 to 1993, the diagnostic system used in the registries was the Danish adaptation of the International Classification of Diseases, Eighth Revision (ICD-8) and ICD-10 from 1994 and onward. The study population and their parents were linked to the register to obtain information on mental illness to study psychiatric disorders in both the probands and presence or absence of psychiatric disorders in their families. Women and their parents were classified as having a psychiatric disorder if they had records of either inpatient or outpatient contacts at a psychiatric hospital with any type of mental illness (main diagnoses only). For the women in the study, diagnoses were grouped as follows: bipolar affective disorders (ICD-8 codes 296.19, 296.39, and 298.19; ICD-10 codes F30 and F31), unipolar affective disorders (ICD-8 codes 296.09, 296.29, 296.99, 298.09, 300.49, and 300.1x; ICD-10 codes F32, F33, F34.1, F38.8, and F39.0), schizophrenia-like disorders (ICD-8 codes 295.xx, 297.xx, 298.39, and 301.89; ICD-10 code F20.xx), adjustment disorders (ICD-8 codes 307.xx and 308.4x; ICD-10 code F43.xx), personality disorders (ICD-8 code 301.xx minus 301.83; ICD-10 codes F60 and F61), puerperal disorders not elsewhere classified (ICD-8 code 294.49; ICD-10 code F53.xx), and other disorders (remaining diagnoses). Parents of the children in the study were categorized by their history of psychiatric disorders in the following way: history of psychiatric contact with bipolar affective disorder (ICD-8 codes 296.19, 296.39, and 298.19; ICD-10 codes F30 and F31), history of psychiatric contact with any type of mental illness excluding bipolar disorder (remaining diagnoses), and no history of psychiatric contacts.

STUDY DESIGN

Based on information from these registries, we studied the largest possible homogenous population for which we had sufficient information. The study population consisted of women born in Denmark from 1930 to 1991 who were alive and had a history of a first-time psychiatric contact with any type of psychiatric disorder excluding bipolar affective disorder (N = 120,378) (Figure 1). Data derived from the registries were...
time-dependent variables, whereas the remaining variables were psychiatric disorders in parents of the women were treated as bipolar affective disorder diagnoses. Age, calendar period, and (1000 years), ie, incidence rates of first psychiatric contacts with first psychiatric contact (Figure 1).

Women diagnosed with bipolar affective disorder during a psychiatric contact immediately following the first contact (discharge and readmission within 24 hours) were also excluded psychiatric contact at either an inpatient or outpatient psychiatric facility). This method approximates a Cox regression. The person-years as an offset using SAS version 9.1 (SAS Institute Inc). This method approximates a Cox regression.15,16 The follow-up period using survival analysis techniques. Data during 1970 to 2006, 120 378 women had an initial psychiatric contact (admission or outpatient contact) with any type of psychiatric disorder excluding bipolar affective disorder. A total of 2870 of these women had their first psychiatric contact within the first year after delivery of their first child. During follow-up, 3062 of the 120 378 women received diagnoses of bipolar affective disorder at a subsequent psychiatric admission or outpatient contact, of which 132 had their initial psychiatric contact 0 to 12 months post partum (Figure 1).

Women having a first-ever psychiatric contact within the first month post partum demonstrated an increased probability of converting to bipolar affective disorder at a later stage: initial contact 0 to 14 days post partum, RR=4.26 (95% CI=3.11-5.85) and initial contact 15 to 30 days post partum, RR=2.65 (95% CI=1.72-4.07) (Table 1). This was compared with the reference category, which was women with initial psychiatric contacts at other points excluding the first year after delivery. A total of 47 women specifically received a diagnosis of mental and behavioral disorders associated with the puerperium, not elsewhere classified (ICD-8 code 294.49; ICD-10 code F53.XX). Since these disorders are restricted to an onset within the first 6 weeks post partum, women with these diagnoses will, by necessity, at subsequent nonpostpartum psychiatric contact receive an alternative diagnosis. We have therefore conducted additional analysis (Table 2) excluding the women with an initial diagnosis of puerperal disorders in which a similar pattern of results were observed.

As discussed earlier, the rates of subsequent conversion to bipolar disorder are likely to differ depending on the initial diagnosis and it is well established that a family history of bipolar disorder predicts higher rates of bipolar affective disorders in offspring. Therefore, we conducted multivariate analyses to adjust for these and other potential confounders. After taking first diagnoses and family history of psychiatric illness into account, conversion rates to bipolar disorder were still significantly predicted by the timing of initial contact. Although reduced compared with the results presented in Table 1, there was a significantly higher conversion rate to bipolar affective disorder in women having their initial psychiatric contact within the first postpartum month: initial contact 0 to 14 days post partum, RR=2.53 (95% CI=1.57-4.07) and initial contact 15 to 30 days post partum, RR=1.82 (95% CI=1.07-3.10) (Table 3). Additionally, there is evidence that the severity of the initial postpartum episode may be important because inpatient admissions were associated with a higher conver-
sion rate than outpatient contacts (RR = 2.16; 95% CI = 1.27–3.66). Specific diagnosis at the initial postpartum psychiatric contact also predicted increased conversion rates to bipolar disorder: unipolar affective disorder, RR = 2.88 (95% CI = 1.53–5.43); schizophrenia-like disorders, RR = 2.57 (95% CI = 1.19–5.57); and puerperal disorders, RR = 2.99 (95% CI = 1.51–5.92). An initial diagnosis of a personality disorder did not predict an increased conversion rate. Additionally, if the father of the woman had a history of bipolar affective disorder, conversion rates were significantly higher (RR = 3.49; 95% CI = 1.22–10.01) compared with both women with a family history of other psychiatric disorders (RR = 0.98; 95% CI = 0.53–1.82) and women with psychiatrically healthy parents (reference category) (Table 3).

Kaplan-Meier curves were made to illustrate the conversion rates to bipolar disorder among the women in the cohort. Fifteen years after initial contact, 13.87% (95% CI = 10.00–17.58) of women with onset in the immediate postpartum period (0–30 days after delivery) had converted to bipolar affective disorder. In comparison, after 15 years, 4.69% (95% CI = 1.37–5.90) of women with later postpartum onset (31–365 days after delivery) and 4.04% (95% CI = 1.51–5.92) with onset at other points had converted to bipolar disorder (Figure 2), with the later numbers not being significantly different. We extended the Kaplan-Meier curves to include up to 22 years after first admission. Because there were few cases in the final years of the follow-up period, results should be interpreted cautiously; however, 18.98% (95% CI = 13.86–23.80) of the women with immediate postpartum onset had converted to bipolar disorders within 22 years after the initial postpartum psychiatric contact. In comparison, only 6.51% (95% CI = 4.81–8.18) with later postpartum onset and 5.43% (95% CI = 5.19–5.66) with onset outside the first postpartum year converted to bipolar disorder within the same follow-up period.

**COMMENT**

**MAIN FINDINGS**

The results of this study clearly demonstrate that a postpartum onset raises the possibility of underlying bipolarity. Almost 14% of women with a first-time psychiatric contact during the first month after delivery converted to bipolar affective disorder within 15 years after their initial postpartum episode, which was 3 times more often than women with initial psychiatric contact at other points. Our results show additional factors that are important determinants of the risk of conversion to bipolar affective disorder.

**Onset Following Delivery**

Timing of initial psychiatric contact was a major predictor for conversion to bipolar disorder. Contact with psychiatric services during the first 30 days post partum predicted conversion to a subsequent diagnosis of bipolar disorders.
affective disorder, whereas psychiatric contacts later in the first postpartum year did not show an increased risk of conversion.

Severity of Episode

Inpatient admissions in the postpartum period were associated with a higher conversion rate to bipolar disorder than outpatient contacts.

CLINICAL IMPLICATIONS

Despite improvements in reliability over recent decades, the diagnosis of psychiatric disorders, particularly of first episodes, is often unclear and needs to be revised as the illness develops. Although conversion from bipolar disorder to another diagnosis may be rare, a conversion to bipolar disorder is more common. The findings of this study present further evidence that the onset of psychiatric illness in the early postpartum period is of potential diagnostic importance. Postpartum onset should be added to the list of features in the presentation of depression that raise the likelihood of latent bipolarity. These include early age at onset, the presence of psychosis, atypical features, and an abrupt onset. In addition, our work demonstrates that an early postpartum onset of illness has prognostic implications and raises the chance of subsequent conversion to a diagnosis of bipolar disorder. This does not apply merely to women with postpartum unipolar depression (RR=2.88; 95% CI=1.53-5.43) but also to women with nonaffective psychosis/schizophrenia-like disorders (RR=2.57; 95% CI=1.19-5.57) (Table 3).

The results of this study provide further evidence linking childbirth-related episodes and bipolar disorder, building on our previous studies that have demonstrated a strong and specific link. Despite the strength of this association, the proportion of new postpartum episodes receiving a diagnosis of bipolar disorder was relatively low since many other disorders can have their onset after childbirth. Figure 1 illustrates that 38 women had their first-ever psychiatric contact with a bipolar diagnosis 0 to 30 days post partum, 27 had initial bipolar contact 31 to 365 days post partum, and 1662 had their initial contact with bipolar disorder at other points. All these women were excluded from the study, as their first psychiatric contact was specifically recorded as a diagnosis of bipolar affective disorder. Our results suggest, however, that at least some of the women receiving other diagnoses following childbirth have an underlying bipolar spectrum illness and, moreover, that this is considerably more common than for first episodes occurring at other times.

Because of the specific link between childbirth and bipolar affective disorder, it is critically important to conduct a comprehensive assessment of women presenting in the postpartum period. In particular, the clinician should pay careful attention to symptoms of hypomania.

Figure 2. Kaplan-Meier curves illustrating conversion rates to diagnoses of bipolar affective disorder during a 15-year follow-up period. CI indicates confidence interval; Other points, women having their initial psychiatric episode before giving birth to their first live-born child or later than 12 months after giving birth to their first live-born child; 1-30 d Post partum, women having their initial psychiatric episode within the first 30 days after giving birth to their first live-born child; and 31-365 d Post partum, women having their initial psychiatric episode from 31 to 365 days after giving birth to their first live-born child.
or a mixed episode because the misdiagnosis of a bipolar spectrum disorder can have serious consequences. For example, the prescription of antidepressants is exceedingly common in the treatment of unipolar major depression but can cause or exacerbate manic symptoms in bipolar spectrum disorders.21 The Mood Disorder Questionnaire was recently shown to be a useful screening instrument for bipolar disorder in the postpartum period,22 and there are other screening tools (both semistructured interviews and self-report measures) for bipolar disorder in general that can be used following childbirth.23

We speculated that severity of illness could predict conversion to bipolar disorder. For this reason, we studied differences in conversion rates between those women who received treatment at outpatient services vs those requiring inpatient hospitalizations at their first psychiatric contact. Interestingly, type of first contact did predict conversion to bipolar disorder since women having inpatient treatment were more likely to convert than women having outpatient treatment (RR = 2.16; 95% CI = 1.27-3.66). These results can most likely be explained by the severity of first-ever psychiatric contacts, with inpatient admissions being markers of more severe episodes vs milder episodes, which will be treated at outpatient clinics.

**IMPLICATIONS FOR CLASSIFICATION**

At a time when revisions to the DSM and ICD classification systems are being considered, our findings are very relevant to the debate about how postpartum disorders should be treated. Previous work has demonstrated that a postpartum onset has important prognostic implications; women with an episode in relation to childbirth are at considerably higher risk of a postpartum recurrence than women with an episode not in relation to childbirth. Recurrence is likely to have been before this date. In addition, some patients may have had a prepartum onset with exacerbation or symptoms after the delivery. Fourth, lifetime conversion rates to bipolar disorder could not be established since women in the cohort were aged up to 57 years. Furthermore, the classification of specific psychiatric diagnoses was based on clinical diagnoses in the registry rather than research diagnostic criteria. However, previous validation studies have found high agreement between clinical and research diagnoses.

Last and most importantly, from the available data it was not possible to study if women with subsequent bipolar diagnoses were misdiagnosed at initial contacts during the postpartum period or developed the disorder during the follow-up period. It is possible that the perinatal context has important influences on the presentation of mood and psychotic episodes and those features of severe postpartum psychiatric disorders. Perplexity and a rapidly changing clinical picture make it more difficult to make a correct diagnosis of the underlying clinical condition. Alternatively, it is possible that there are no differences in the accuracy of diagnosis in postpartum and nonpostpartum episodes and that the differences in subsequent conversion rates are real. We are unable to differentiate between these possibilities but whatever the balance between the two, the main implication for clinical practice—that a postpartum onset should raise the suspicion of an underlying bipolar disorder—would remain unchanged.

The present study confirms the well-established link between childbirth and bipolar affective disorder and specifically adds to this field of research by demonstrating that initial psychiatric contact within the first 30 days post partum significantly predicted conversion to bipolar af-
ffective disorder during the follow-up period. This was compared with both women with first psychiatric contact in the later part of the postpartum period and women with nonpostpartum initial contacts with psychiatric illnesses. The perinatal context of current or previous episodes is an important element to consider in psychiatric assessment, with both diagnostic and prognostic implications.

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