Episodes of Mood Disorders in 2,252 Pregnancies and Postpartum Periods

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Objective: The risks of major affective episodes during pregnancy and during the postpartum period have rarely been compared in large samples across diagnoses. The authors hypothesized that perinatal episodes would mainly be depressive, would occur more in the postpartum than the prenatal period, and would be more prevalent with bipolar than unipolar depressive disorders.

Method: The authors pooled clinical information on 2,252 pregnancies of 1,162 women with clinically treated DSM-IV bipolar I disorder (479 pregnancies/283 women), bipolar II disorder (641/338), or recurrent major depressive disorder (1,132/541) to compare rates of affective episode types by diagnosis during pregnancy and the postpartum period and to identify risk factors.

Results: Among women with bipolar disorder, 23% had illness episodes during pregnancy and 52% during the postpartum period. Among women with unipolar depression, 4.6% had illness episodes during pregnancy and 30% during the postpartum period. Based on exposure-adjusted risk per pregnancy, episodes were 3.5 times more prevalent during the postpartum period than during pregnancy, and the risk was consistently higher with bipolar disorder. Depression was the most frequent morbidity during and following pregnancy. In multivariate modeling, factors associated with affective episodes in pregnancy, in descending order, were younger age at onset, previous postpartum episodes, fewer years of illness, bipolar disorder, fewer children, and not being married. Postpartum episodes were associated with younger age at onset, illness during pregnancy, bipolar disorder, fewer children, and more education. Moreover, pregnancy was less likely and perinatal episodes more likely if diagnosis preceded a first pregnancy. First lifetime episodes occurred in the perinatal period in 7.6% of cases.

Conclusions: Among women with major affective disorders, illness risk was much greater during the postpartum period than during pregnancy. Illness mainly involved depression and was strongly associated with younger age at illness onset, bipolar disorder, and high lifetime occurrence rates. The relative risk during pregnancy compared with nonpregnant periods remains uncertain.

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Knowledge of morbidity risks and optimal treatment of women with major psychiatric illnesses during pregnancy, at childbirth, and during the postpartum period is strikingly limited, particularly with major affective disorders (1–8). Such knowledge is clinically important given the considerable complexities of clinical management of affectively ill women during perinatal periods (9, 10). These complexities include the need to balance potential teratogenic and other adverse effects of medication on the offspring against the consequences of acute and potentially life-threatening untreated maternal illness, the impact of the illness on families, and the potential adverse effects of acute maternal illness on fetal and neonatal development (9–12). Despite their potential clinical impact, many cases of perinatal mood disorder go undiagnosed and untreated (5, 13).

A link between childbirth and psychiatric illnesses has been recognized clinically for centuries, including many observations of a strong association of major affective and psychotic episodes in the puerperal period (1, 14–17). Several epidemiologic studies suggest that pregnancy itself may not be associated with major elevations in risk of affective illness compared to periods unrelated to pregnancy, or even suggest a lower risk during pregnancy both in the general population and among women with a unipolar major depressive disorder (1, 2, 4, 5, 13). There is also uncertainty regarding the relative risks of illness episodes in women diagnosed with a bipolar disorder during pregnancy compared with during nonpregnant periods, but the early postpartum period is strongly associated with an elevated risk of major affective or psychotic episodes in association with bipolar disorders (1, 3, 5, 8, 18–26).

Most but not all studies involving clinical samples of women with identified mood disorders suggest that pregnancy and the postpartum period may be destabilizing, although rates of illness range widely, from 5% to 100%, usually with average risks somewhat higher soon after childbirth than during pregnancy (2, 3, 7, 18–26). As expected, reported risks of affective, especially depressive,

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symptoms or "blues" during pregnancy or the postpartum period are several times greater than those for major depressive episodes (2, 4, 5). Illness during pregnancy appears to be mainly depressive or dysphoric (including mixed states) in bipolar disorder and depressive in unipolar disorders. Risk is not only probably greater during the postpartum period than during pregnancy, but also much greater after discontinuing antidepressant or mood-stabilizing treatment (3, 6, 7). The timing of occurrences of mood disorders during pregnancy has, somewhat inconsistently, been associated with the early months of pregnancy, and discontinuation of maintenance treatment has been associated with greater risk in the first than in later trimesters (3, 6–8). Clinical features of postpartum affective illness appear to differ little from illness episodes unrelated to pregnancy (25–28), although an association of bipolar disorder with postpartum psychotic disorders as well as mania, mixed states, or depression has been emphasized (1, 3, 9, 17, 25). It is also becoming clearer that affective symptoms during pregnancy among women with either bipolar or unipolar disorders are strongly associated with continued or new postpartum morbidity, by perhaps as much as 10 times more than without affective illness during pregnancy (2, 3, 14, 23, 25, 29).

Surprisingly, direct comparisons of risks of specific types of episodes across the range of major affective disorders are rare (14, 15). The need for quantitative estimates of risks of particular types of affective episodes during and following pregnancy in women with known or later diagnosed major affective disorders was a primary impetus for the present study. Our aims were 1) to compare rates of specific forms of affective episodes between pregnancy and the postpartum period and among women diagnosed with types I or II bipolar disorder or with unipolar depression, and 2) to identify potential risk factors among selected clinical and demographic measures for illness episodes during pregnancy and in the postpartum period. Based on previous studies (1–9, 14, 15, 20–26), we hypothesized that 1) perinatal risks of episode occurrence would be mainly depressive with bipolar as well as unipolar disorders, 2) risks would be greater soon after childbirth than during pregnancy, and 3) patients diagnosed with bipolar I and II disorders would have similar perinatal risks, both greater than with unipolar depression.

Method

Methods of diagnostic and clinical assessment and computerized record-keeping followed at the study sites have been reported previously (3, 7). Data were collected systematically at the perinatal psychiatry programs at Massachusetts General Hospital (Boston) and the Lucio Bini Mood Disorders Centers (Cagliari [Sardinia, Italy] and Rome) from 1980 to 2010, after referrals by clinicians for specialized clinical assessment and care. All participants were followed and treated clinically. They typically received single treatments or varying combinations of antidepressants, mood stabilizers, other drugs, and psychotherapy as indicated by changing clinical requirements. Study protocols were reviewed and approved by appropriate ethical review boards at the collaborating study institutions, and all participants provided written informed consent for anonymous and aggregate reporting of their clinical findings, with explicit assurance that their treatment would not be affected by study participation or protocols.

Potential study subjects were women at least 18 years of age for whom data were available for at least one completed pregnancy and who were diagnosed with DSM-IV bipolar I, bipolar II, or unipolar major depressive disorder, based on multiple expert clinical assessments and semistructured examinations at the study centers. Primary diagnoses were updated to DSM-IV criteria between 2008 and 2010. Categorization of perinatal episode types was based on DSM-III or DSM-III-R criteria in assessments made in the 1980–1994 period, and on DSM-IV criteria thereafter. Information concerning episodes of affective illness during and after pregnancy was gathered retrospectively and then recorded in life charts, which were converted to digital databases after 2000. Illness occurrence was defined as a clinically identified episode of major depressive, manic/hypomanic, or mixed manic-depressive states or of an anxiety disorder including panic—all meeting DSM-III or DSM-IV diagnostic criteria. Periods considered in the same women included pregnancy and the postpartum period, defined as 6 months following live births to include potential effects of lactation and other stressors commonly encountered during the initial months after delivery.

Analytic Plan

Diagnostic groups were compared for frequency and types of illness episodes during pregnancy and the initial 6 months after childbirth for all pregnancies in each patient. Demographic and clinical factors, including long-term morbidity measures and number and years of pregnancies, were compared between women with and without illness occurrences during pregnancy or the postpartum period. Preliminary bivariate comparisons employed analysis of variance for continuous measures and contingency tables for categorical measures. We also compared presence and absence of selected clinical and demographic factors in association with illness episodes during pregnancy and the postpartum period, based on computed odds ratios. Incidence rates were calculated with a nominal exposure time of 0.75 years for pregnancy and a defined exposure time of 0.5 years for the postpartum period. We also used random-effects Poisson regression models to compare illness rates during pregnancy and during the postpartum period, including covariates of interest or found suggestively (with p values ≤0.10) related to illness occurrence in preliminary bivariate analyses. The threshold for statistical significance was a two-tailed alpha of 0.05, except when the Bonferroni correction was used for multiple comparisons. For statistical computations, we used Statview, version 5 (SAS Institute, Inc., Cary, N.C.) and Stata, version 8 (StataCorp, College Station, Tex.).

Results

Study Subjects

Data were pooled from the sites in Cagliari (47%), Rome (43%), and Boston (10%) for analyses based on a total of 2,252 pregnancies in 1,162 women diagnosed with DSM-IV mood disorders. Single-pregnancy observations involved 48.4% of the patients, two pregnancies 32.2%, three pregnancies 11.7%, and ≥4 pregnancies 7.72%. Other patient characteristics are summarized by diagnosis in Table 1.

Perinatal Risks of Affective Illnesses

The proportion of women experiencing illness episodes was similar for patients with bipolar I and II disorders and

TABLE 1. Clinical and Demographic Characteristics of 1,162 Women With Perinatal Episodes of Major Affective Disorders

Measures	Bipolar I Disorder (N=283)		Bipolar II Disorder (N=338)		Unipolar Depression (N=541)		All Cases (N=1,162)	
	N	Ratio	N	Ratio	N	Ratio	N	Ratio
Pregnancies per person	479	1.69	641	1.90	1,132	2.09	2,252	1.94
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Onset age (years)	29.4	11.4	34.1	13.1	39.4	15.6	37.5	15.2
Age at first pregnancy (years)	26.0	5.63	26.6	4.47	25.8	4.78	26.0	4.86
Duration of illness (years)	18.7	14.0	19.6	14.0	14.0	13.7	16.0	14.0
Episodes per year	0.63	0.78	1.05	1.24	0.15	0.40	0.53	0.91
Episodes per person								
During pregnancy	0.23	0.41	0.18	0.37	0.03	0.15	0.11	0.26
During postpartum period	0.43	0.46	0.41	0.45	0.22	0.37	0.33	0.42
	N	%	N	%	N	%	N	%
Education beyond high school	119	42.0	121	35.8	60	11.1	258	22.2
Unemployed	20	7.10	19	5.62	14	0.26	31	2.67
Marital status								
Married	227	80.2	266	78.7	403	74.5	891	76.7
Separated or divorced	28	9.90	27	8.00	33	6.10	85	7.32
Widowed	16	5.70	40	11.8	103	19.0	168	14.5
Single	12	4.24	5	1.50	24	0.44	17	1.45

much lower for those with unipolar depression (Table 1). During pregnancy, this risk averaged 22.7% with bipolar disorder and 4.62% with unipolar depression (χ^2=47.8, df=1, p<0.001); during the postpartum period, the corresponding risks were 51.5% and 29.8%, respectively (χ^2=55.9, df=1, p<0.001).

The distribution of risks of occurrences of episodes of affective illness per pregnancy, by type, was determined for each diagnostic group and compared during pregnancy and the postpartum period for the same women (Table 2). Overall, the occurrence risks were ranked as follows: bipolar I ≥ bipolar II > unipolar depression during both pregnancy and the postpartum period. The most prevalent form of morbidity during both periods and in all three diagnostic groups was major depression. Women with bipolar disorder experienced substantial numbers of mixed manic-depressive states, whereas mania and psychosis were uncommon, including during the postpartum period.

The overall risks of episodes per pregnancy were consistently and significantly higher during the postpartum period than during pregnancy (Table 2), by a crude average of 1.97-fold (95% CI=1.69–2.30) overall. Although risks were greater in patients with bipolar than in those with unipolar disorder during both pregnancy and the postpartum period, the observed postpartum period-pregnancy risk ratio ranked as follows: unipolar depression (3.68-fold [95% CI=3.16–4.30]) > bipolar II disorder (1.68 [95% CI=1.20–2.01]) ≥ bipolar I disorder (1.52 [95% CI=1.15–2.03]). Based on observed episode occurrence risks (Table 2) adjusted for exposure time (0.75 years for pregnancy and 0.5 years for the postpartum period), rates of episodes per pregnancy per year during pregnancy and the postpartum period ranked as follows: bipolar I disorder (0.330 and 0.762, respectively), bipolar II disorder (0.271 and 0.700, respectively), and unipolar depression (0.062 and 0.344, respectively). That is, the risk with bipolar disorders (types I and II did not differ significantly) was greater than the risk with unipolar disorder during pregnancy (incidence rate ratio=4.85 [95% CI=3.32–7.23) and during the postpartum period (incidence rate ratio=2.10 [95% CI=1.77–2.50]). Postpartum rates were consistently greater than during pregnancy overall (incidence rate ratio=3.46 [95% CI=2.88–4.15]), as well as by diagnosis, which ranked as follows: unipolar depression (incidence rate ratio=5.58 [95% CI=3.91–8.16]), bipolar II disorder (incidence rate ratio=2.58 [95% CI=1.90–3.57]), and bipolar I disorder (incidence rate ratio=2.31 [95% CI=1.73–3.12]) (Figure 1).

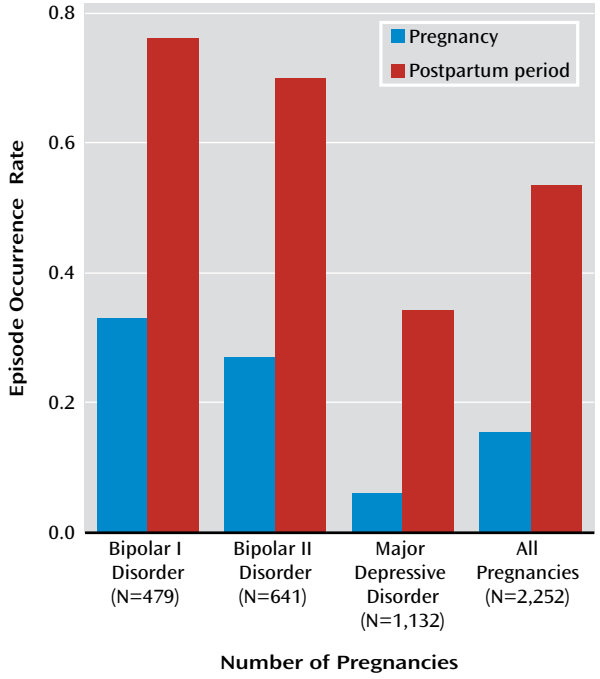
Risks With Pregnancy Before and After Illness Onset

We compared rates of affective illnesses among 1,093 pregnancies with data for women with affective illness that preceded (N=852) or followed first pregnancies (N=241). A mood disorder first presented during pregnancy or postpartum in 7.6% (N=83) of the women. We considered the distribution of pregnancies among women diagnosed with a mood disorder before or after a first conception. Pregnancy was nearly three times more likely to precede than to follow diagnosis and treatment, and more so with unipolar depression (82.2%/17.8%=4.62) than with bipolar disorders (64.7%/35.3%=1.83). In addition, the risk of illness occurrence during first pregnancies was greater if diagnosis preceded pregnancy, but only with bipolar disorders (33.3%/10.4%=3.20; χ^2=10.5, df=1, p=0.001), not with unipolar depression (15.4%/9.50%=1.62; χ^2=1.14, df=1, p=0.290). The associated postpartum risk also was greater if diagnosis preceded first pregnancies, in both bipolar (49.3%/25.3%=1.96; χ^2=11.5, df=1, p<0.001) and unipolar disorders (44.1%/16.3%=2.71; χ^2=25.1, df=1, p<0.001).

TABLE 2. Perinatal Major Affective Episodes During and Following 2,252 Pregnancies in 1,162 Women With Major Mood Disorders

Group and Clinical Type	Prevalence (%)	
	During Pregnancy	During Postpartum Period
All pregnancies (N=2,252)		
Major depression	5.44	20.28
Mania	0.46	1.11
Hypomania	1.07	1.69
Mixed states	2.30	2.09
Anxiety or panic	2.15	0.93
Psychosis	0.23	0.44
All episodes	11.65	26.54
Bipolar I disorder (N=479)		
Major depression	8.88	19.21
Mania	2.32	7.93
Hypomania	2.70	1.25
Mixed states	8.11	6.47
Anxiety or panic	1.54	1.25
Psychosis	1.16	1.88
All episodes	24.71	37.99
Bipolar II disorder (N=641)		
Major depression	10.36	28.71
Hypomania	2.79	2.34
Mixed states	3.59	2.50
Anxiety or panic	3.59	0.94
Psychosis	0.00	0.00
All episodes	20.37	34.49
Unipolar depression (N=1,132)		
Major depression	2.77	16.06
Anxiety or panic	1.89	1.15
Psychosis	0.00	0.00
All episodes	4.68	17.21

FIGURE 1. Episode Occurrence Rates of Major Affective Episodes During Pregnancy and During the Postpartum Period in 1,162 Women With Bipolar I, Bipolar II, or Major Depressive Disorder[a]



[a] Episode occurrence rates are reported as illness episodes per pregnancy per year.

Factors Associated With Illness During or Following Pregnancy

We made preliminary bivariate comparisons of potential risk factors among women who experienced new affective illnesses during pregnancy or the postpartum period (Table 3). During pregnancy, associated factors ranked by odds ratio were as follows: having an illness onset after 1992 (the median year); never married; unemployed and not a homemaker, student, or retiree; educated beyond high school; having an onset age below the median (33 years); having a bipolar (I or II) diagnosis; and having relatively few pregnancies (less than four versus four or more). During the postpartum period, associated factors ranked by odds ratio were as follows: never married; educated beyond high school; having an onset age below the median; having an episode during any pregnancy; being unemployed; having a bipolar diagnosis; having less than four pregnancies; and having a more recent onset.

Multivariate Modeling

Factors having suggestive associations (p values ≤0.10) with occurrence risks were then entered, forward and stepwise, into Poisson regression modeling for illness during pregnancy and the postpartum period, with clinical and demographic factors modeled separately (Table 4). Clinical factors associated with illness during pregnancy were as follows: younger onset age, any postpartum episodes, fewer years since illness onset, and bipolar > unipolar diagnosis. Demographic factors associated significantly and independently with illness during pregnancy were as follows: having fewer children and being unmarried.

Postpartum illness was associated with the following clinical factors: younger at illness onset, illness in pregnancy, and bipolar > unipolar diagnosis. Demographic factors associated with postpartum illness were as follows: having fewer children and having relatively more education.

Discussion

Our findings support the impression arising from clinical experience and from previous reports (13–25) that the perinatal periods carry substantial risks of illness episodes in women diagnosed with a major affective disorder. Overall incidence rates of illness occurrences (episodes per patient-year) were greater in patients with bipolar illness than in those with unipolar illness, although the postpartum period-pregnancy risk ratio was greater with unipolar depression (Figure 1). These findings are congruent with reports over the past 150 years (17) that especially high risks for episodes of major mood disorders occur in the postpartum period among women diagnosed with either unipolar

TABLE 3. Factors Associated With Affective Episodes During Pregnancy or the Postpartum Period in 1,162 Women With 2,252 Pregnancies[a]

Factor	Percentage		Odds Ratio	95% CI
	Present	Absent		
During pregnancy				
Onset after 1992	86.0	14.0	6.14	4.25–8.92
Never married	36.4	6.2	5.83	1.32–20.2
Unemployed	55.9	10.5	5.33	2.78–9.91
Educated > high school	31.8	6.3	5.03	3.44–7.14
Onset age < median	21.0	4.3	4.92	3.24–7.67
Bipolar diagnosis	22.6	4.6	4.84	3.25–7.34
Fewer than 4 pregnancies	13.7	5.8	2.85	2.12–3.85
During the postpartum				
Never married	64.5	24.3	5.65	4.71–6.80
Educated > high school	20.9	4.5	4.55	3.57–5.88
Onset age < median	42.2	10.5	4.01	3.21–5.04
Ill duing pregnancy	67.8	20.6	3.28	2.44–4.41
Unemployed	61.8	25.3	2.44	1.33–4.40
Bipolar diagnosis	36.4	17.4	2.08	1.72–2.53
Fewer than 4 pregnancies	28.7	19.2	1.49	1.16–1.92
Onset before 1992	77.0	23.0	1.39	1.14–1.67

[a] Data are percentage of pregnancies and odds ratios for risk with factor present or absent, in order of odds ratios. The Bonferroni-adjusted critical p value for comparisons during pregnancy is 0.007 (0.05/7) and during the postpartum period 0.006 (0.05/8), but all factors listed differed at $p<0.0001$ (all χ^2 values ≥16.7). Onset year is based on the median (1992).

TABLE 4. Poisson Regression Models for Clinical and Demographic Factors Associated With Major Affective Episodes During Pregnancy and the Postpartum Period in 1,162 Women With 2,252 Pregnancies

Factor[a]	Incidence Rate Ratio[b]	95% CI	z Score	p
Episode during pregnancy				
Clinical model				
Younger illness-onset age	1.05	1.03–1.06	7.15	<0.0001
Previous postpartum episodes	2.91	2.10–4.04	6.42	<0.0001
Fewer years of illness	1.04	1.02–1.06	5.97	<0.0001
Bipolar > unipolar diagnosis	1.42	1.18–1.70	3.73	<0.0001
Demographic model				
Fewer children	1.46	1.20–1.78	3.81	<0.0001
Unmarried	3.49	0.99–12.3	1.94	0.05
Episode during postpartum period				
Clinical model				
Younger illness-onset age	1.04	1.03–1.05	12.2	<0.0001
Episodes during any pregnancy	1.80	1.44–2.24	5.31	<0.0001
Bipolar > unipolar diagnosis	1.18	1.06–1.32	2.93	0.003
Demographic model				
Fewer children	1.14	1.04–1.24	2.84	<0.005
More education	1.34	1.01–1.72	2.00	0.05

[a] Factors are ranked by z score.
[b] Incidence rate ratio: episodes per pregnancy (0.75 years) or postpartum period (0.50 years).

or bipolar disorders (1–5, 13, 15, 16, 19). In the sample we studied, overall risks in bipolar and unipolar disorders were 23% and 4.6%, respectively, during pregnancy, and 52% and 30%, respectively, during the postpartum period. First-illness episodes occurred during pregnancy or the postpartum period in 7.6% of women. Although the postpartum period appears to carry major risks compared to pregnancy, it remains unclear whether pregnancy itself is stressful or protective with respect to affective illness occurrences. Resolution of this uncertainty will require well-matched—and, ideally, prospective—comparisons of episode occurrence rates and exposure times during pregnancy compared with periods unrelated to pregnancy (12, 13).

Notably, major depression was the most prevalent form of perinatal morbidity—even among patients with bipolar disorder, who also had substantial risks of dysphoric-agitated mixed states (Table 2). These observations accord with reports that the prevalence of depression is high in pregnant women with either unipolar or bipolar disorders (3, 6, 7, 20, 21). In fact, the risk of affective episodes was found to be highest in the first trimester of pregnancy as early as the 1800s (15, 17) and to decline in later trimesters, for uncertain reasons (3, 6, 7). Moreover, a great many cases of mood disorder are overlooked and left untreated during pregnancy (5, 13, 14). Such episodes appear to be a major risk factor for subsequent postpartum affective illness (1, 2, 13, 20–22, 27).

The high risk of depression in bipolar patients may not be surprising in view of the difficulty of achieving successful long-term treatment and prophylaxis for bipolar depression (29). Although depression has been strongly associated with pregnancy in both bipolar and unipolar disorders, we expected (15, 16) and found more mania and psychosis among patients with bipolar disorders (Table 2). Moreover, the observed average perinatal illness risks, especially in patients with unipolar illness (Table 1), were lower than expected from observations in some studies but within the range of widely varied reported rates (4–6, 12, 13).

Since patients in the present study were treated clinically, it is possible that treatments aimed at depression, which have limited long-term effectiveness in unipolar and less in bipolar disorders (30–32), exerted clinically destabilizing effects in patients with bipolar disorders. In addition, the metabolic clearance of psychotropic drugs can shift during pregnancy and childbirth, further complicating assessment of their potential effects (32–34). However, treatment discontinuation just before or at the start of pregnancy is common and may contribute to the risk of illness episodes early in pregnancy (3, 6, 7). Understandably, potentially teratogenic treatments are most likely to be avoided early in pregnancy, making presumably protective psychiatric treatments least likely to be prescribed or accepted when most likely to be needed (9, 10), opening up the risk of major destabilizing effects (3, 6, 7, 35–37).

The observed lower risk of illness occurrence in women with four or more pregnancies may reflect self-selection against further pregnancies by women who experienced illness during or after pregnancy. This inverse relationship

might also reflect beneficial adjustments of treatment or better adherence to treatment over years of illness experience. In addition, younger age at illness onset was strongly associated with perinatal illnesses, especially during the postpartum period and with bipolar disorders (Table 3). Younger onset age may be an independent risk factor reflecting a more severe natural history of some mood disorders (38). The risk of an episode during a first pregnancy in women with bipolar disorders was greater for those whose illness onset was in 1992 or earlier, whereas postpartum episodes were more prevalent in women whose illness onset was after 1992 (Table 3). The secular increase in risk in more recent first pregnancies may reflect greater stressful effects of pregnancy, whereas the lower postpartum risk since 1992 may arise from advances in diagnosis and treatment. In addition, being unmarried and unemployed seemed to be stressful factors with a greater impact during pregnancy than during the postpartum period.

When a clinical diagnosis of mood disorder preceded pregnancy, the likelihood of becoming pregnant was lower than when pregnancy followed diagnosis, especially with bipolar disorder, and was probably a consequence of having a mood disorder (39). Moreover, risk of perinatal illness was greater when diagnosis preceded pregnancy. This risk was greater with bipolar disorders, evidently reflecting greater illness severity.

The bipolar I and II syndromes showed similar patterns of risk (Table 2). This similarity is consistent with other clinical evidence (including suicide rates) that bipolar II disorder is not a less severe form of bipolar disorder (30, 40).

Limitations to this study include the relative paucity of patients with multiple pregnancies, sampling from patients referred to specialty clinics, and the retrospective clinical ascertainment of illness episodes during most pregnancies. However, recall bias should be similar across diagnoses and for periods during and after pregnancy, even if it is greater with longer assessment delays. In addition, data on treatment status and on the severity and duration of each episode were not adequate to support analysis, and control data were not available on occurrence risks unrelated to pregnancy. Despite these possible limitations, our findings are based on a large, pooled international sample, which should limit potential effects of regional variance in case-finding and treatments. The findings provide quantitative comparisons of postpartum period and pregnancy risks for the three major affective disorders under similar conditions of assessment.

In conclusion, our findings indicate substantial risks of clinically ascertained major affective illness episodes during pregnancy and far greater risks during the postpartum period in bipolar I, bipolar II, and major depressive disorders, with a preponderance of depressive episodes overall. The highest risk of illness occurrence was found among women diagnosed with bipolar I disorder during both pregnancy and the postpartum period, and with all three diagnoses, the risk was much higher during the postpartum period than during pregnancy. Among prominent risk factors, younger age at illness onset and diagnosis before the first pregnancy were strongly associated with illness episodes in all diagnostic groups and both perinatal periods; moreover, illness during pregnancy strongly predicted illness during the postpartum period. In about one in 13 women, the first lifetime episode of major affective illness was perinatal. These findings may contribute to improved clinical management, support preventive efforts, and encourage critical assessment of the risks and benefits of particular treatments to mothers and their offspring during various phases of pregnancy and the postpartum period.

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References

1. Kendell RE, Chalmers JC, Platz C: Epidemiology of puerperal psychoses. Br J Psychiatry 1987; 150:662–673
2. O'Hara MW, Zekoski EM, Philipps LH, Wright EJ: Controlled prospective study of postpartum mood disorders: comparison of childbearing and non-childbearing women. J Abnorm Psychol 1990; 99:3–15
3. Viguera AC, Nonacs R, Cohen LS, Tondo L, Murray A, Baldessarini RJ: Risk of recurrence of bipolar disorder in pregnant and nonpregnant women after discontinuing lithium maintenance. Am J Psychiatry 2000; 157:179–184
4. Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Garlehner G, Swinson T: Perinatal depression: systematic review of prevalence and incidence. Obstet Gynecol 2005; 106:1071–1083
5. Jones I, Craddock N: Bipolar disorder and childbirth: the importance of recognizing risk. Br J Psychiatry 2005; 186:453–454
6. Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC, Suri R, Burt VK, Hendrick V, Reminick AM, Loughead A, Vitonis AF, Stowe ZN: Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA 2006; 295:499–507
7. Viguera AC, Whitfield T, Baldessarini RJ, Newport DJ, Stowe Z, Reminick A, Zurick A, Cohen LS: Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. Am J Psychiatry 2007; 164:1817–1824
8. Jones I, Cantwell R; Nosology Working Group, Royal College of Psychiatrists, Perinatal Section: Classification of perinatal mood disorders: suggestions for DSM-V and ICD-11. Arch Womens Ment Health 2010; 13:33–36
9. Yonkers KA, Wisner KL, Stowe Z, Leibenluft E, Cohen L, Miller L, Manber R, Viguera A, Suppes T, Altshuler L: Management of

bipolar disorder during pregnancy and the postpartum period. Am J Psychiatry 2004; 161:608–620
10. Cohen LS, Wang B, Nonacs R, Viguera AC, Lemon EL, Freeman MP: Treatment of mood disorders during pregnancy and postpartum. Psychiatr Clin North Am 2010; 33:273–293
11. Weinstock M: Potential influence of maternal stress hormones on development and mental health of offspring. Brain Behav Immun 2005; 19:296–308
12. Lazinski MJ, Shea AK, Steiner M: Effects of maternal prenatal stress on offspring development: commentary. Arch Womens Ment Health 2008; 11:363–375
13. Dietz PM, Williams SB, Callaghan WM, Bachman DJ, Whitlock EP, Hornbrook MC: Clinically identified maternal depression before, during, and after pregnancies ending in live births. Am J Psychiatry 2007; 164:1515–1520
14. Vesga-López O, Blanco C, Keyes K, Olfson M, Grant BF, Hasin DS: Psychiatric disorders in pregnant and postpartum women in the United States. Arch Gen Psychiatry 2008; 65:805–815
15. Chaudron LH, Pies RW: The relationship between postpartum psychosis and bipolar disorder: a review. J Clin Psychiatry 2003; 64:1284–1292
16. Sit D, Rothschild AJ, Wisner KL: Review of postpartum psychosis. J Womens Health 2006; 15:352–368
17. Trede K, Baldessarini RJ, Viguera AC, Bottero A: Treatise on insanity in pregnant, postpartum, and lactating women (1858) by Louis-Victor Marcé: commentary. Harv Rev Psychiatry 2009; 17:157–165
18. Mota N, Cox BJ, Enns MW, Calhoun L, Sareen J: Relationship between mental disorders, quality of life, and pregnancy: findings from a nationally representative sample. J Affect Disord 2008; 109:300–304
19. Blehar MC, DePaulo JR Jr, Gershon ES, Reich T, Simpson SG, Nurnberger JI Jr: Women with bipolar disorder: findings from the NIMH Genetics Initiative sample. Psychopharmacol Bull 1998; 34:239–243
20. Terp IM, Mortensen PB: Postpartum psychoses: clinical diagnoses and relative risk of admission after parturition. Br J Psychiatry 1998; 172:521–526
21. Grof P, Robbins W, Alda M, Berghoefer A, Vojtechovsky M, Nilsson A, Robertson C: Protective effect of pregnancy in women with lithium-responsive bipolar disorder. J Affect Disord 2000; 61:31–39
22. Freeman MP, Smith KW, Freeman SA, McElroy SL, Kmetz GE, Wright R, Keck PE Jr: Impact of reproductive events on the course of bipolar disorder in women. J Clin Psychiatry 2002; 63:284–287
23. Akdeniz F, Vahip S, Pirildar S, Vahip I, Doganer I, Bulut I: Risk factors associated with childbearing-related episodes in women with bipolar disorder. Psychopathology 2003; 36:234–238
24. Munk-Olsen T, Laursen TM, Pedersen CB, Mors O, Mortensen PB: New parents and mental disorders: a population-based register study. JAMA 2006; 296:2582–2589
25. Harlow BL, Vitonis AF, Sparen P, Cnattingius S, Joffe H, Hultman CM: Incidence of hospitalization for postpartum psychotic and bipolar episodes in women with and without prior pre-pregnancy or prenatal psychiatric hospitalizations. Arch Gen Psychiatry 2007; 64:42–48
26. Munk-Olsen T, Laursen TM, Mendelson T, Pedersen CB, Mors O, Mortensen PB: Risks and predictors of readmission for a mental disorder during the postpartum period. Arch Gen Psychiatry 2009; 66:189–195
27. Manber R, Blasey C, Allen JJ: Depression symptoms during pregnancy. Arch Womens Ment Health 2008; 11:43–48
28. Colom F, Cruz N, Pacchiarotti I, Mazzarini L, Goikolea JM, Popova E, Torrent C, Vieta E: Postpartum bipolar episodes are not distinct from spontaneous episodes: implications for DSM-V. J Affect Disord 2010; 126:61–64
29. Milgrom J, Gemmill AW, Bilszta JL, Hayes B, Barnett B, Brooks J, Ericksen J, Ellwood D, Buist A: Antenatal risk factors for postnatal depression: a large prospective study. J Affect Disord 2008; 108:147–157
30. Baldessarini RJ, Vieta E, Calabrese JR, Tohen M, Bowden CL: Bipolar depression: overview and commentary. Harv Rev Psychiatry 2010; 18:143–157
31. Tondo L, Vázquez G, Baldessarini RJ: Mania associated with antidepressant treatment: comprehensive meta-analytic review. Acta Psychiatr Scand 2010; 121:404–414
32. Pacchiarotti I, Valentí M, Colom F, Rosa AR, Nivoli AM, Murru A, Moreno JS, Vieta E: Differential outcome of bipolar patients receiving antidepressant monotherapy versus combination with an antimanic drug. J Affect Disord 2011; 129:321–326
33. Sidor MM, MacQueen GM: Antidepressants for the acute treatment of bipolar depression: systematic review and meta-analysis. J Clin Psychiatry 2011; 72:156–167
34. O'Brien L, Baumer C, Thieme D, Sachs H, Koren G: Changes in antidepressant metabolism in pregnancy evidenced by metabolic ratios in hair: a novel approach. Forensic Sci Int 2010; 196:93–96
35. Pennell PB, Peng L, Newport DJ, Ritchie JC, Koganti A, Holley DK, Newman M, Stowe ZN: Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. Neurology 2008; 70:2130–2136
36. Faedda GL, Tondo L, Baldessarini RJ, Suppes T, Tohen M: Outcome after rapid vs gradual discontinuation of lithium treatment in bipolar mood disorders. Arch Gen Psychiatry 1993; 50:448–455
37. Baldessarini RJ, Tondo L, Ghiani C, Lepri B: Illness risk following rapid versus gradual discontinuation of antidepressants. Am J Psychiatry 2010; 167:934–941
38. Post RM, Leverich GS, Kupka RW, Keck PE Jr, McElroy SL, Altshuler LL, Frye MA, Luckenbaugh DA, Rowe M, Grunze H, Suppes T, Nolen WA: Early-onset bipolar disorder and treatment delay are risk factors for poor outcome in adulthood. J Clin Psychiatry 2010; 71:864–872
39. Tondo L, Lepri B, Baldessarini RJ: Reproduction among 1975 Sardinian women and men diagnosed with major mood disorders. Acta Psychiatr Scand 2011; 123:283–289
40. Weinstock LM, Strong D, Uebelacker LA, Miller W: DSM-IV depressive symptom expression among individuals with a history or without a history of mania. J Psychiatr Res 2010; 44:979–985

Clinical Guidance: Risk of Mood Disorder During and After Pregnancy

Mood disorder in over 2,200 pregnancies of over 1,100 women was examined by Viguera et al. to determine the risk for an episode. Among these women, 22.7% of those with bipolar disorder experienced an episode during pregnancy and 51.5% during the postpartum period. In comparison, 4.6% of those with unipolar disorder experienced an episode during pregnancy and 29.8% during the postpartum period. First lifetime episodes of mood disorder during the perinatal period occurred for 7.6% of women. Women who already had a mood disorder before their first pregnancy had the highest risk. These high risks are consistent with recommendations for close monitoring and continued treatment during and after pregnancy.