Article

Risk of Recurrence in Women With Bipolar Disorder During Pregnancy: Prospective Study of Mood Stabilizer Discontinuation

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Objective: This study estimated the risk of recurrence of mood episodes among women with a history of bipolar disorder who continued or discontinued treatment with mood stabilizers during pregnancy.

Method: In a prospective observational clinical cohort study, the authors determined recurrence risk and survival-analysis-based time to recurrence of a new episode in 89 pregnant women with DSM-IV bipolar disorder. Eligible subjects were euthymic at conception and continued mood stabilizer treatment or discontinued treatment proximate to conception.

Results: The overall risk of at least one recurrence in pregnancy was 71%. Among women who discontinued versus continued mood stabilizer treatment, recurrence risk was twofold greater, median time to first recurrence was more than fourfold shorter, and the proportion of weeks ill during pregnancy was five times greater. Median recurrence latency was 11 times shorter after abrupt/rapid versus gradual discontinuation of mood stabilizer. Most recurrences were depressive or mixed (74%), and 47% occurred during the first trimester. Predictors of recurrence included bipolar II disorder diagnosis, earlier onset, more recurrences/year, recent illness, use of antidepressants, and use of anticonvulsants versus lithium.

Conclusions: Discontinuation of mood stabilizer, particularly abruptly, during pregnancy carries a high risk for new morbidity in women with bipolar disorder, especially for early depressive and dysphoric states. However, this risk is reduced markedly by continued mood stabilizer treatment. Treatment planning for pregnant women with bipolar disorder should consider not only the relative risks of fetal exposure to mood stabilizers but also the high risk of recurrence and morbidity associated with stopping maintenance mood stabilizer treatment.

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Bipolar disorder is a major public health problem with a high lifetime prevalence (≥1%) and substantial risk of long-term morbidity, comorbidity, and disability (1–7). Bipolar disorder also carries high rates of premature mortality due largely to suicide but including also the effects of accidents, substance abuse, and general medical disorders (8). Women with bipolar disorder encounter several obstacles to care with respect to pregnancy, including extraordinary knowledge gaps about the illness course during pregnancy, predictors of risk or protective factors for recurrence as well as reproductive safety data for various mood stabilizers (9, 10, 11). Currently, a common clinical practice is to stop ongoing mood stabilizing treatment during pregnancy in order to avoid potential adverse fetal developmental effects and purported associated liability risk (12–15). However, some progress has been made lately in applying the limited information available to develop treatment guidelines for the clinical management of women with bipolar disorder during pregnancy (16–18).

Whether pregnancy affects morbid risk favorably or unfavorably still remains uncertain (17–20). Most of the few available studies of pregnant women with bipolar disorder involve small case reports or retrospective analyses (15, 21–28). A few observations suggest that some bipolar disorder patients may remain euthymic during pregnancy after discontinuing mood stabilizing medication (21–24). For example, Grof and his colleagues (24) suggested that pregnancy may exert a favorable effect on the course of bipolar disorder, at least among a highly selected group of lithium monotherapy responders. However, the majority of recent studies, which include heterogeneous samples of women with bipolar disorder, suggest that pregnancy is, indeed, a period of substantial risk for recurrence, with estimates of recurrence as high as 50% based on retrospective assessments (15, 25–28).

To our knowledge, no controlled, prospective longitudinal studies of the course of bipolar disorder during pregnancy have been reported. Studies that specifically consider the effects of diagnostic subtypes, illness history, and

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current treatment are required to quantify risks of bipolar disorder morbidity during pregnancy. Accordingly, we now report on a prospective study of recurrence risk among pregnant women diagnosed with bipolar disorder, comparing risk rates and time to recurrence among those who continued or discontinued mood stabilizer treatment.

Method

Subject Selection

Pregnant women (N=89) diagnosed with DSM-IV type I (N=61) or II (N=28) bipolar disorder were enrolled in this prospective, observational study of pregnancy between March 1, 1999, and Aug. 31, 2004, at the Perinatal and Reproductive Psychiatry Clinical Research Program at Massachusetts General Hospital, Boston. The subjects were recruited among women planning pregnancy and seeking specialized psychiatric consultation, as recommended by their obstetricians or by self-referral.

Study subjects were eligible if they 1) had a history of bipolar disorder before pregnancy, 2) were euthymic for at least 4 weeks before their last menstrual period, 3) were receiving mood stabilizer therapy or 4) discontinued pharmacotherapy within 6 months before conception or 12 weeks after conception, and 5) were enrolled before 24 weeks of gestation. Patients were excluded if they 1) were actively suicidal, 2) had discontinued all mood stabilizer therapy >6 months before conception, or 3) met DSM-IV criteria for a primary psychotic, schizoaffective, or organic mental disorder or mental retardation. All subjects provided written informed consent to participate after approval of the study protocol by the Massachusetts General Hospital Institutional Review Board.

The subjects were followed through the end of pregnancy and for 12 months postpartum, regardless of their decisions concerning continued use of psychotropic medication. All subjects initially received individual evaluations by the first author (A.C.V.), including an extensive clinical assessment that included the Structured Clinical Interview for DSM-IV (SCID) (29), and comprehensive review of potential risks and benefits of continuing or stopping treatment, as detailed elsewhere (17). This review covered current knowledge of the potential teratogenicity of mood stabilizing, antipsychotic, sedative-hypnotic, and antidepressant drugs, their potential adverse effects on neonates, and maternal and potential fetal risks associated with discontinuing treatment.

Assessments

Initial SCID assessment confirmed a DSM-IV lifetime diagnosis of bipolar disorder and evaluated the presence of comorbid psychiatric illnesses. Demographic and clinical characteristics of interest were recorded at baseline, including family history, estimated age at onset of bipolar disorder, approximate number of prior episodes and hospitalizations, and occurrence of suicide attempts, as well as the type, severity, and time since the approximate onset and end of the last major affective episode and treatment history (medicines, doses, and estimated exposure times). The subjects were followed up prospectively by A.C.V. at a study visit each trimester and at 6, 12, 24, and 52 weeks postpartum to ascertain the presence of major symptoms and their clinical severity (mild, moderate, or severe) and current treatments (drugs, doses, apparent benefits, and adverse effects), noting any changes. In addition, the primary outcome variable of recurrence of a new DSM-IV illness episode was determined by an independent rater (trained and experienced research assistant) who was blind to treatment status with the SCID mood module, as reported previously in a prospective, longitudinal study of risk recurrence among pregnant women with recurrent major depressive disorder (30). The blinded assessment covered the interval from the last to the current study visit, with a best estimate of the gestational week of illness onset, all verified with A.C.V. when a recurrence was detected. All subjects were managed clinically by their treating psychiatrist without blinding to treatment status.

Analytic Plan

The primary outcome variables were recurrence and weeks to the start of an illness recurrence fulfilling DSM-IV criteria based on the SCID mood modules for mania, hypomania (lasting ≥1 week), major depression, or a mixed state. Neonatal and postpartum outcomes will be reported separately. Given the complexity and multiple changes in pharmacologic regimens among patients with bipolar disorder, we stratified the study group into two treatment groups based on mood stabilizer treatment status only: 1) use of at least one mood stabilizer at conception and continued at least through the first 12 weeks of pregnancy or 2) discontinuation of all mood stabilizer treatment during the period ranging from 6 months before conception to 12 weeks of gestation.

We first compared the distribution of demographic and clinical characteristics between the treatment groups to identify potential confounding factors. Associations of treatment status with risk and latency of recurrence were then assessed. Kaplan-Meier survival analyses determined median weeks to start of a first recurrence with 95% confidence intervals (CIs), with unadjusted univariate Mantel-Cox log-rank tests (χ^2) to compare survival times between treatment groups, and censoring at birth or miscarriage (31). Cox multivariate proportional hazards modeling estimated the hazard ratio and 95% CI for median time to recurrence between treatment groups, with adjustment for predictors of recurrence suggested by preliminary univariate analyses. This modeling employed forward variable selection to adjust for the effects of potential confounders and to identify potential risk factors for illness recurrence. We also used survival analysis to compare weeks to recurrence dated from the point of discontinuation of mood stabilizer treatment to compare subgroups that discontinued abruptly or rapidly (1–14 days) versus gradually (≥15 days of dose reduction). Finally, we used logistic regression modeling to evaluate risk factors for significant and independent association with recurrence.

Summary data are reported as means with standard deviations for continuous variables, survival-computed median weeks to events and hazard ratios with 95% CIs, and proportions (percentages) for categorical data, which were compared with contingency tables (χ^2) or Fisher's exact test (p). Statistical tests of hypotheses were two-sided, at $\alpha=p\leq0.05$. Analyses used commercial statistical programs (STATA version 8.2, College Station, Tex.).

Results

Subject Characteristics

Among 89 women with bipolar disorder (69% bipolar I disorder, 31% bipolar II disorder) in the study group, 85 had a live birth, two subjects had stillbirths at term, one woman miscarried after a recurrence, and one subject dropped out of the study after a recurrence. Table 1 illustrates demographic, clinical, and treatment characteristics of all participants as well as those who discontinued or maintained treatment with a mood stabilizer. Overall, the mean age of the subjects was 32.7 years (SD=5.4). The majority of subjects were Caucasian (96.6%), had ≥12 years of education (98.9%), and were married (82%), employed outside the home (76.0%), and multiparous (64%). Most subjects (>70%) were taking more than one psychotropic,

TABLE 1. Demographic and Clinical Characteristics Associated With Mood Stabilizer Treatment Status Among Pregnant Women With Bipolar Disorder

Characteristic	All Subjects (N=89)		Subjects Who Discontinued Treatment (N=62)		Subjects Who Maintained Treatment (N=27)		p[a]
	N	%	N	%	N	%	
Demographic							
Age ≥30 years	63/89	70.8	45/62	72.6	18/27	66.7	0.62
Caucasian	86/89	96.6	59/62	95.2	27/27	100.0	0.55
Single	16/89	18.0	13/62	21.0	3/27	11.1	0.37
Education ≥12 years	88/89	98.9	61/62	98.4	27/27	100.0	1.00
Not employed outside the home	21/87	24.1	17/60	28.3	4/27	14.8	0.28
Previous pregnancy	57/89	64.0	41/62	66.1	16/27	59.3	0.63
Unplanned current pregnancy	30/89	33.7	24/62	38.7	6/27	22.2	0.15
Clinical							
Bipolar type I	61/89	68.5	36/62	58.1	25/27	92.6	0.001
Early onset at age <15 years	43/89	48.3	36/62	58.1	7/27	25.9	0.006
Lifetime illness ≥5 years	41/89	46.1	34/62	54.8	7/27	25.9	0.02
Average episodes/year ≥1	26/89	29.2	21/62	33.9	5/27	18.5	0.21
Current psychiatric comorbidity[b]	35/89	39.3	26/62	41.9	9/27	33.3	0.49
Prior rapid cycling	36/89	40.5	30/62	48.4	6/27	22.2	0.03
Prior psychiatric hospitalization	63/89	70.8	41/62	66.1	22/27	81.5	0.21
Prior psychotic features	58/89	65.2	36/62	58.1	22/27	81.5	0.05
Prior suicide attempt	31/88	35.2	25/61	41.0	6/27	22.2	0.10
≥12 months since last episode	53/88	60.2	33/61	54.1	20/27	74.1	0.10
Prior episodes in pregnancy or postpartum	42/47	89.4	31/34	91.2	11/13	84.6	0.61
Treatment							
Lithium as primary mood stabilizer	55/89	61.8	32/62	51.6	23/27	85.2	0.004
Anticonvulsant as primary mood stabilizer	32/89	36.0	29/62	46.8	3/27	11.1	0.001
Current adjunctive antidepressant use[c]	46/89	51.7	41/62	66.1	5/27	18.5	<0.001
Current adjunctive antipsychotic use[c]	24/89	27.0	13/62	21.0	11/27	40.7	0.07
≥Two psychotropics	63/89	70.8	50/62	80.7	13/27	48.2	0.004

[a] p values are from bivariate Fisher's exact tests comparing women who continued versus discontinued mood stabilizer treatment in pregnancy. Other factors not different between treatment groups included the following: family history of mood disorders, age at diagnosis and at first mood stabilizer treatment, prior mixed episodes, and recent sedative use (not shown).
[b] Anxiety disorder, obsessive-compulsive disorder, eating disorder, or substance use disorders.
[c] Within 6 months of conception.

which included a mood stabilizer in combination with an antidepressant and/or antipsychotic (Table 1). Across the study group, primary mood stabilizer type ranked as follows: lithium (55 of 89=61.8%) > anticonvulsants (32 of 89=36.0%; valproic acid, N=15; lamotrigine, N=8; carbamazepine, N=6; gabapentin, N=3) > atypical antipsychotics (two of 89=2.3%; olanzapine, N=1; and quetiapine, N=1). Over half the study group were exposed to an antidepressant (51.7%, 46 of 89; bupropion, N=15; sertraline, N=7; fluoxetine, N=8; fluvoxamine, N=1; paroxetine, N=5; venlafaxine, N=2; citalopram, N=4; selegiline, N=1; tricyclic, N=1; tranylcypromine, N=2) in addition to a mood stabilizer. Among subjects who continued taking a mood stabilizer, 18.5% used adjunctive antidepressants versus 66.1% (41 of 62) of those who discontinued mood stabilizer. In addition, 27% (24 of 89) of the cohort was exposed to an antipsychotic (olanzapine, N=6; quetiapine, N=2; perphenazine, N=4; risperidone, N=4; thiothixine, N=2; haloperidol, N=3; or ziprasidone, N=3), and the proportion of adjunctive antipsychotic use was higher among subjects who maintained versus discontinued a mood stabilizer (Table 1).

At study entry, the two treatment groups did not differ significantly with respect to demographic features (i.e., age, race, marital status, years of education, employment, and previous pregnancy) and several characteristics, including unplanned pregnancy, average episodes/year, current comorbidity, prior hospitalizations, prior suicide attempts, time since last episode, and prior perinatal and postpartum episodes (Table 1), as well as family history of mood disorders, age at diagnosis and at first mood stabilizer treatment, prior mixed episodes, and recent sedative use (not shown). However, the two groups did differ along several important measures of illness severity (Table 1). Those who *continued* maintenance mood stabilizers during pregnancy were more likely to 1) have bipolar I disorder, 2) be maintained with lithium as the primary mood stabilizer, 3) have a history of psychotic features, and 4) be treated with adjunctive antipsychotics. The women who *discontinued* mood stabilizer treatment were more likely to 1) have a bipolar II disorder diagnosis, 2) have discontinued an anticonvulsant, 3) have experienced onset of bipolar disorder at a younger age and with a depressive first episode, 4) be treated with ≥two psychotropics, 5) be ill more total years, 6) experience a history of rapid cycling (≥4 episodes in any year), and 7) be treated with an antidepressant (Table 1).

Risk and Timing of Recurrences During Pregnancy

During pregnancy, a total of 70.8% (63 of 89) of the subjects experienced at least one episode of illness meeting

TABLE 2. Morbidity During Pregnancy Versus Treatment Status

Variable	All Subjects (N=89)		Subjects Who Maintained Treatment (N=27)		Subjects Who Discontinued Treatment (N=62)	
	N	%	N	%	N	%
Risk of at least one recurrence[a]	63/89	70.8	10/27	37.0	53/62	85.5
First recurrence risk by trimester						
First	42/89	47.2	6/27	22.2	36/62	58.1
Second	15/47	31.9	3/21	14.3	12/26	46.2
Third	6/32	18.8	1/18	5.6	5/14	35.7
Recurrence polarity (all recurrences)[b]						
Depression	34/89	38.2	5/27	18.5	29/62	46.8
Mixed state	26/89	29.2	0/27	0.0	26/62	41.9
Hypomania	15/89	16.8	7/27	25.9	8/62	12.9
Mania	6/89	6.7	2/27	7.4	4/62	6.5
Percent of pregnancy weeks ill						
	Mean	SD	Mean	SD	Mean	SD
All cases[c]	32.8	31.5	8.8	21.3	43.3	29.6
	N	%	N	%	N	%
Stable subjects (%)[d]	26/89	29.2	17/27	63.0	9/62	14.5

[a] Risk ratio for any recurrence, comparing subjects who discontinued versus maintained mood stabilizing treatment (2.3, 95% CI=1.4–3.8, p<0.001).
[b] Sixty-three subjects experienced a total of 81 episodes of varying polarity during pregnancy (1.43 versus 0.32 episodes/subject with mood stabilizer treatment discontinued versus continued).
[c] Absolute difference between the mean percentages of weeks ill, comparing subjects who discontinued versus maintained mood stabilizing treatment (34.5%, 95% CI=22.1%–46.9%, p<0.001).
[d] For the percent of subjects remaining stable throughout pregnancy, comparing subjects who maintained versus discontinued mood stabilizing treatment (rate ratio=4.3, 95% CI=2.2–8.5, p<0.001).

DSM-IV SCID criteria. Overall, there were a total of 81 episodes, including shifts in polarity without intervening recovery, yielding an average of 1.3 episodes per affected subject (81 in 63) during the study period (Table 2). Recurrence risk was 2.3 times greater after discontinuation of mood stabilizer treatment (53 of 62, 85.5%) than with continued treatment (10 of 27, 37.0%; Table 2). In addition, the proportion of time spent ill (i.e., with a mood episode) during pregnancy was nearly a third (33%) of the pregnancy across the entire cohort. The subjects who discontinued the mood stabilizer spent over 40% of pregnancy in an illness episode, versus only 8.8% of pregnancy among subjects who maintained the mood stabilizer (Table 2).

Based on Kaplan-Meier survival analyses, the median time to first recurrence was 9.0 (95% CI=8.0–13.0) weeks after discontinuing treatment and >40 weeks (95% CI indeterminate) with continued treatment (Figure 1). With respect to the timing of recurrences, the majority of new episodes emerged early in pregnancy: 47.2% risk in the first trimester, 31.9% in the second, and 18.8% in the third (Table 2).

Rate of Discontinuation of Mood Stabilizer

Women who discontinued abruptly or rapidly (1–14 days; N=35) experienced a 50% risk of recurrence within 2.0 (95% CI=1.0–6.0) weeks, and those who discontinued gradually (≥15 days, N=27) required 22.0 (95% CI=16.0–38.0) weeks to reach the same level of recurrence risk (χ^2= 25.9, df=1, p<0.0001; not shown). It is noteworthy, and perhaps not surprising, that unplanned pregnancy covaried with greater likelihood of rapid discontinuation of mood stabilizer treatment (23 of 24, 95.8%, versus 12 of 59, 20.3%, in planned pregnancies; p<0.0001, Fisher's exact test).

Polarity of Recurrences

The distribution of polarities across all first recurrences ranked as follows: major depression (41.3%, 26 of 63) > mixed states (38.1%, 24 of 63) > hypomania (11.1%, seven of 63) > mania (9.5%, six of 63), indicating a 3.8-fold excess of depressive or dysphoric (mixed) versus manic or hypomanic recurrences (79.4%, 50 of 63, versus 20.6%, 13 of 63). The excess of depressive-dysphoric versus manic-hypomanic episodes was even greater after discontinuation of mood stabilizer treatment (55 of 62 recurrences, 88.7%, versus 12 of 62, 19.3%, or 4.6-fold) compared to continued treatment (five of 27, 18.5%, versus nine of 27, 33.3%, or only a 1.8-fold difference). The excess of new depressive-dysphoric versus manic-hypomanic illness was found among both bipolar I disorder cases (25 of 61, 40.9%, versus 12 of 61, 19.6%, or 2.1-fold) and bipolar II disorder subjects who demonstrated a 24-fold excess of depression over hypomania (25 of 28, 89.3%, versus one of 28, 3.7%).

Predictors of Recurrence During Pregnancy-Unadjusted Analysis

We examined whether certain demographic or clinical variables, other than discontinuation of mood stabilizer, were associated with recurrence during pregnancy. No statistically significant association was noted between recurrence risk and race, educational status, or marital status. However, several other clinical factors, including illness history, pregnancy, and treatment-related factors were associated with illness recurrence during pregnancy. Significant illness-history-related predictors included the following in rank order by risk ratio: 1) ≥5 years of illness (risk ratio=1.7, p<0.001), 2) younger age at onset (risk ratio=1.6, p<0.001), 3) bipolar II disorder diagnosis (risk ra-

tio=1.5, p<0.002), 4) history of rapid cycling (risk ratio=1.5, p<0.002), 5) shorter clinical stability since the last episode before conception (risk ratio=1.5, p<0.004), 6) one or more prior episodes per year (risk ratio=1.5, p=0.004), 7) previous mixed-state episodes (risk ratio=1.5, p=0.004), 8) prior suicide attempts (risk ratio=1.4, p=0.01), and 9) current psychiatric comorbidity (risk ratio=1.4, p=0.02). Pregnancy-related risk factors associated with recurrence only included 10) unplanned index pregnancy (risk ratio=1.5, p=0.006), but not previous live birth or prior history of a mood episode during pregnancy or the postpartum period. Treatment-related risk factors, besides discontinuation of mood stabilizer, included 11) polytherapy with two or more psychotropic agents (risk ratio=2.3, p<0.001), 12) use of antidepressants (risk ratio=2.0, p<0.001), 13) primary mood stabilizer other than lithium (risk ratio=1.6, p<0.001), 14) previous switch from depression to mania-hypomania during treatment with an antidepressant (risk ratio=1.5, p<0.009), and 15) abrupt discontinuation of mood stabilizer (risk ratio=1.4, p=0.008). Factors *not* associated with recurrence included race, age, education, marital status, employment, previous pregnancy, prior illness in pregnancy or during the postpartum period, first episode depressive, any family history of mood disorder, and current use of more than one mood stabilizer, among others (not shown).

Multivariate Modeling of Risk-Factors-Adjusted Analysis

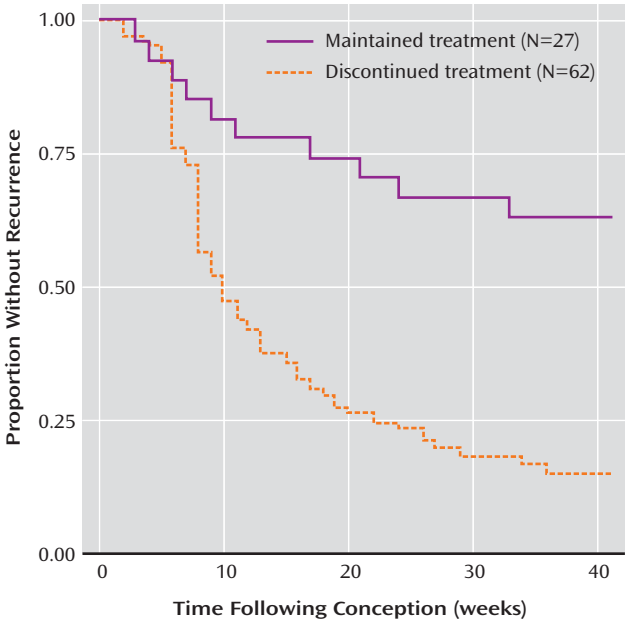
The preceding factors preliminarily associated with recurrence of bipolar disorder illness during pregnancy were subjected to multivariate analysis with Cox proportional hazards modeling to test for factors remaining independently associated with recurrence latency (not shown). Without adjustment for covariates, time to recurrence was much shorter after treatment discontinuation (hazard ratio=3.80, 95% CI=1.90–7.60) and remained so (hazard ratio=2.50, 95% CI=1.20–5.20) even after adjustment for indices of illness severity (lifetime years ill and number of prior episodes), bipolar disorder diagnostic subtype (I or II), and antidepressant use. Furthermore, in this multivariate model, indices of illness severity and bipolar type were no longer associated with increased hazard, but antidepressant use remained a robust predictor of recurrence risk along with treatment discontinuation (hazard ratio=2.2, 95% CI=1.2–4.2, p=0.02).

Discussion

To our knowledge, this is the first prospective and systematic assessment of risk and predictors of recurrence among pregnant women with bipolar disorder. The main findings of this study are a twofold greater recurrence risk and the more than fourfold shorter latency to new illness among women who discontinued maintenance mood stabilizing treatment proximate to conception, compared to those who continued treatment (Table 2, Figure 1). Moreover, recurrence risk was even greater and earlier after rapid discontinuation of mood stabilizing treatment. These findings replicate and extend our previously published retrospective findings of high recurrence rates during pregnancy among women with bipolar disorder who discontinued lithium, especially abruptly (15, 32–34). In the present study, recurrence risk in pregnancy (85%) was approximately 33% higher compared to our previous estimate of 52%, perhaps reflecting the current study's prospective design, with greater sensitivity to detecting new illness episodes, and a more heterogenous study group that included women who discontinued mood stabilizers other than lithium.

We also observed a striking excess of depressive or dysphoric mixed illness, especially early in pregnancy, in the present cohort (74.1% of all episodes), whereas mania and hypomania were relatively infrequent. Some of this excess of depression may be accounted for by including bipolar II disorder cases (31.5% of subjects), but a similar excess of depression-dysphoria over mania or hypomania was found among bipolar I disorder cases (40.9% versus 19.6%). It may be that pregnancy predisposes vulnerable patients to depressive-dysphoric recurrences, as observed nearly 150 years ago by Louis-Victor Marcé of Paris (35, 36). Modern reports also indicate an excess of depressive morbidity during pregnancy among women with bipolar

FIGURE 1. Kaplan-Meier Survival Functions for Pregnant Patients With Bipolar Disorder Who Maintained or Discontinued Treatment[a]



[a] Median time to first recurrence from the estimated date of conception was >41 weeks (95% CI=indeterminate) when mood stabilizer treatment was *maintained* (N=27) and only 9.0 weeks (95% CI=8.0–13.0) when treatment was *discontinued* (N=62; $\chi^2 \geq 17.9$, df=1, p<0.0001), a 4.6-fold difference.

disorder (15, 24, 26, 27), but also among treated, nonpregnant samples of bipolar disorder patients (4–6).

Predictors of illness recurrence during pregnancy, besides the most robust risk factor of discontinuing mood stabilizer treatment, included characteristics associated with illness severity. Such factors were younger onset, more years of illness and more recurrences, a history of rapid cycling, suicide attempts, presence of comorbid disorders, and antidepressant use. Cox multivariate analyses indicated that antidepressant use and treatment discontinuation each operated independently as risk factors even after adjustment for other indices of illness severity.

Several of these risk factors for mainly depressive recurrences during pregnancy also are associated with general risk of depressive morbidity in bipolar disorder patients, including a bipolar II disorder diagnosis and use of an antidepressant during pregnancy (4, 6). Use of antidepressants during pregnancy, especially after discontinuing mood stabilizers, may have exerted mood-destabilizing effects (36–39). Alternatively, antidepressant use during pregnancy may reflect the presence of bipolar II disorder patients, who are often treated with antidepressants, or may simply be an indicator for more severe illness (40–42). Moreover, their use may also be further encouraged by current impressions that antidepressants might have less risk of teratogenic or other adverse developmental effects than some mood stabilizers (17, 18, 43, 44).

It is also noteworthy that nearly 70% of the present study subjects and their physicians elected to discontinue mood stabilizing treatment at the start of pregnancy, particularly among women with severe illness histories. Not surprisingly, patients with a diagnosis of bipolar I disorder with a history of previous psychotic features or current antipsychotic treatment were more likely to continue maintenance medications (Table 1). However, many other subjects with similar morbid histories, including early onset and relatively high number of prior illness recurrences, chose to discontinue mood stabilizer. Similarly, we have found that among women with recurrent major depressive disorder, decisions to maintain or discontinue antidepressant treatment during pregnancy appeared to be largely independent of severity of past illness or clinical recommendations (30). Other observations suggest that decisions about continuing or discontinuing pharmacological treatment for mood disorders during pregnancy often are ill-informed, based primarily on fear of psychotropic use during pregnancy (12–15).

This study has notable limitations. Although prospective and systematic, it is a naturalistic, observational study. Treatment was determined clinically, without experimental control or random assignment, and in some cases was complex and variable over time. Moreover, the subjects in each treatment subgroup were limited in number and, in the absence of random assignment, not necessarily matched on all potentially relevant clinical variables (Table 1). Nevertheless, there was little evidence of differences in illness history or major demographic variables between treatment groups (Table 1). We also attempted to control for potentially relevant differences with Cox multivariate modeling of survival functions to test for the independent contribution of treatment discontinuation as well as other relevant risk factors identified in preliminary bivariate analyses.

An additional limitation of the study is that the patients included may not be representative of broader samples of bipolar disorder patients, including less well-educated women, members of minority groups, and others who may be less likely to seek highly specialized care during pregnancy. Nevertheless, it is sobering to find that, even among women who seemed highly motivated to seek out expert care, the morbid risks of bipolar disorder during pregnancy and especially with discontinued treatment were very high.

This study adds to evidence that discontinuation of ongoing maintenance mood stabilizing treatment in women with bipolar disorder carries a very high risk of illness recurrence during pregnancy. Pregnancy appears not to have a protective effect against new or worsening illness in bipolar disorder patients and may particularly increase the risk of new depressive morbidity, with uncertain effects on fetal development (45). Although a number of clinical risk factors were identified that may have clinical predictive value in identifying women at particularly high recurrence risk, mood stabilizer discontinuation itself appeared to be a very important predictor of recurrence. As we have proposed previously, any subtle positive or negative effects pregnancy may have on the illness course is likely dwarfed by the more dominant stressor of abrupt treatment discontinuation (15, 17, 32–34).

In conclusion, the present findings challenge the evidently common practice of abruptly stopping maintenance treatment for psychiatric disorders during pregnancy. Of importance, they underscore the significant benefits of continuing prophylactic mood stabilizing treatment during pregnancy with respect to overall reduction in recurrence risk and overall maternal morbidity (i.e., time spent ill during pregnancy). A major clinical implication of these findings is that for women with severe and frequent recurrences of bipolar disorder, maintenance treatment with a mood stabilizer during pregnancy may be the most prudent strategy, much as maintenance treatment is recommended for pregnant women with other serious and chronic medical conditions, such as epilepsy (46, 47). In short, given the high risk of maternal morbidity associated with discontinuation of mood stabilizing treatment and its uncertain impact on fetal development, we recommend a more balanced consideration of the entire spectrum of risks and benefits involved in the clinical management of pregnant women with bipolar disorder.

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References

1. Coryell W, Scheftner W, Keller M, Endicott J, Maser J, Klerman GL: Enduring psychosocial consequences of mania and depression. Am J Psychiatry 1993; 150:720–727
2. Gitlin MJ, Swendsen J, Heller TL, Hammen C: Relapse and impairment in bipolar disorder. Am J Psychiatry 1995; 152:1635–1640
3. Hirschfeld RM, Lewis L, Vornik LA: Perceptions and impact of bipolar disorder: how far have we really come? results of the National Depressive and Manic-Depressive Association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry 2003; 64:161–174
4. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB: The long term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002; 59:530–537
5. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, Solomon DA, Coryell W, Maser JD, Keller MB: Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. Arch Gen Psychiatry 2005; 62:1322–1330
6. Post RM, Denicoff KD, Leverich GS, Altshuler LL, Frye MA, Suppes TM, Rush AJ, Keck PE Jr, McElroy SL, Luckenbaugh DA, Pollio C, Kupka R, Nolen WA: Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. J Clin Psychiatry 2003; 64:680–690
7. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE: Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005; 62:617–627
8. Tondo L, Isacsson G, Baldessarini RJ: Suicidal behavior in bipolar disorder: risk and prevention. CNS Drugs 2003; 17:491–511
9. Viguera AC, Cohen LS, Bouffard S, Whitfield TH, Baldessarini RJ: Reproductive decisions by women with bipolar disorder after prepregnancy psychiatric consultation. Am J Psychiatry 2002; 159:2102–2104
10. Cohen LS, Friedman JM, Jefferson JW, Johnson EM, Weiner ML: Reevaluation of risk of in utero exposure to lithium. JAMA 1994; 271:146–150
11. Leibenluft E: Women with bipolar illness: clinical and research issues. Am J Psychiatry 1996; 153:163–173
12. Einarson A, Selbly P, Koren G: Abrupt discontinuation of psychotropic drugs during pregnancy: fear of teratogenic risk and impact of counseling. J Psychiatry Neurosci 2001; 26:44–48
13. Einarson A: Abrupt discontinuation of psychotropic drugs following confirmation of pregnancy: a risky practice. J Obstet Gynaecol Can 2005; 27:1019–1022
14. Bonari L, Koren G, Einarson TR, Jasper JD, Taddio A, Einarson A: Use of antidepressants by pregnant women: evaluation of perception of risk, efficacy of evidence based counseling and determinants of decision making. Arch Womens Ment Health 2005; 8:214–220
15. 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
16. Altshuler LL, Cohen L, Szuba MP, Burt VK, Gitlin M, Mintz J: Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. Am J Psychiatry 1996; 153: 592–606
17. Viguera AC, Cohen LS, Baldessarini RJ, Nonacs R: Managing bipolar disorder in pregnancy: weighing the risks and benefits. Can J Psychiatry 2002; 47:426–436
18. 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
19. Viguera AC, Cohen LS, Tondo L, Baldessarini RJ: Protective effect of pregnancy on the course of lithium-responsive bipolar I disorder. J Affect Disord 2002; 72:107–108
20. Viguera AC, Cohen LJ, Tondo L, Baldessarini RJ: Protective effect of pregnancy on the course of lithium-responsive bipolar I disorder. J Affect Disord 2002; 72:107–108
21. Sharma V, Persad E: Effects of pregnancy on three patients with bipolar disorder. Ann Clin Psychiatry 1995; 7:39–42
22. Lier L, Kastrup M, Rafaelsen O: Psychiatric illness in relation to pregnancy and childbirth: diagnostic profiles, psychosocial and perinatal aspects. Nord Psykiatr Tidsskr 1989; 43:535–542
23. Pugh TF, Jerath BK, Schmidt WM, Reed RB: Rates of mental disease related to childbearing. N Engl J Med 1963; 268:1224–1228
24. 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
25. Jones I, Craddock N: Bipolar disorder and childbirth: the importance of recognizing risk. Br J Psychiatry 2005; 186:453–454
26. Blehar MC, DePaulo JR, Gershon ES, Reich T, Simpson SG, Nurnberger JI: Women with bipolar disorder: findings from the NIMH Genetics Initiative Sample. Psychopharmacol Bull 1988; 34:239–243
27. Freeman M, Smith K, Freeman S, McElroy S, Kmetz G, Wright R, Keck P: The impact of reproductive events on the course of bipolar disorder in women. J Clin Psychiatry 2002; 63:284–287
28. Akdeniz F, Vahip S, Pirildar S, Vahip I, Dogner I, Bulut I: Risk factors associated with childbearing-related episodes in women with bipolar disorder. Psychopathology 2003; 36:234–238
29. First MB, Spitzer RL, Gibbon M, Williams JBW: Structured Clinical Interview for DSM-IV Axis I Disorders—Patient Edition (SCID-I/P, Version 2.0). New York, New York State Psychiatric Institute, Biometrics Research Department, 1995
30. 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
31. Cox DR: Regression models and life tables. J Roy Stat Soc B 1972; 34:187–220
32. Faedda GL, Tondo L, Baldessarini RJ, Suppes T, Tohen M: Outcome after rapid vs gradual discontinuation of lithium treatment in bipolar disorders. Arch Gen Psychiatry 1993; 50:448–455
33. Baldessarini R, Tondo L, Faedda G, Floris G, Suppes T, Rudas N: Effects of rate of discontinuing lithium maintenance treatment in bipolar disorders. J Clin Psychiatry 1996; 57:441–448
34. Baldessarini RJ, Tondo L, Floris G, Rudas N: Reduced morbidity after gradual discontinuation of lithium treatment for bipolar I and II disorders: a replication study. Am J Psychiatry 1997; 154: 551–553
35. Marcé LV: Traité de la Folie des Femmes Enceintes: Des Nouvelles Accouchés et des Nourrices. Paris, Baillière et Fils, 1858
36. Ghaemi SN, Hsu DJ, Soldani F, Goodwin FK: Antidepressants in bipolar disorder: the case for caution. Bipolar Disord 2003; 5: 421–433
37. Ghaemi SN, Ko JY, Goodwin FK: "Cade's disease" and beyond: misdiagnosis, antidepressant use, and a proposed definition of bipolar disorder. Can J Psychiatry 2002; 47:125–134
38. Visser HM, Van Der Mast RC: Bipolar disorder, antidepressants and induction of hypomania or mania: systematic review. World J Biol Psychiatry 2005; 6:231–241
39. Sharma V: A cautionary note on the use of antidepressants in postpartum depression. Bipolar Disord 2006; 8:411–414
40. Ghaemi SN, Rosenquist KJ, Ko JY, Baldassano CF, Kontos NJ, Baldessarini RJ: Antidepressant treatment in bipolar vs unipolar depression. Am J Psychiatry 2004; 161:163–165
41. Skeppar P, Adolfsson R: Bipolar II and the bipolar spectrum. Nord J Psychiatry 2006; 60:7–26
42. Altshuler LL, Suppes T, Black DO, Nolen WA, Leverich G, Keck PE Jr, Frye MA, Kupka R, McElroy SL, Grunze H, Kitchen CM, Post R: Lower switch rate in depressed patients with bipolar II than bipolar I disorder treated adjunctively with second-generation antidepressants. Am J Psychiatry 2006; 163:313–315
43. Einarson TR, Einarson A: Newer antidepressants in pregnancy and rates of major malformations: a meta-analysis of prospective comparative studies. Pharmacoepidemiol Drug Saf 2005; 14:823–827
44. Hallberg P, Sjoblom V: The use of selective serotonin reuptake inhibitors during pregnancy and breastfeeding: a review and clinical aspects. J Clin Psychopharmacology 2005; 25:59–73
45. Newport DJ, Wilcox MM, Stowe ZN: Maternal depression: a child's first adverse life event. Semin Clin Neuropsychiatry 2002; 7:113–119
46. Morrell MJ: The new antiepileptic drugs and women: efficacy, reproductive health, pregnancy, and fetal outcome. Epilepsia 1996; 37(suppl 6):S34–S44
47. Yerby MS, Kaplan P, Tran T: Risks and management of pregnancy in women with epilepsy. Cleve Clin J Med 2004; 71(suppl 2):S25–S37