Pregnancy and Bipolar Disorder: A Systematic Review

Verinder Sharma, MBBS, FRCPC, and Carley J. Pope, BA(hons), CCRP

ABSTRACT

Objective: The postpartum period is generally considered a time of heightened vulnerability to bipolar disorder; however, there is controversy about the effect of pregnancy on the course of bipolar disorder. This article reviews the literature on the relationship between pregnancy and bipolar disorder and suggests areas for future research.

Data Sources and Study Selection: Three electronic databases, MEDLINE (1966–2010), PsycINFO (1840–2010), and EMBASE, were searched on April 30, 2010, using the following keywords: *pregnancy, bipolar disorder, manic depressive disorder, suicide, hospitalization, pharmacotherapy,* and *psychotherapy*. The reference lists of articles identified were also searched. All relevant papers published in English were included.

Results: A total of 70 articles were identified and included in the review. Evidence from studies using nonclinical samples, some retrospective studies, and studies on psychiatric hospitalization rates is suggestive of a positive effect of pregnancy on bipolar disorder; however, recent studies conducted at tertiary care facilities have reported high rates of recurrence following discontinuation of mood stabilizers.

Conclusions: Understanding the relationship between pregnancy and bipolar disorder has implications for perinatal treatment and etiologic understanding of the disorder. Research is urgently needed to estimate the prevalence of bipolar disorder during pregnancy, using both clinical and nonclinical samples.

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Corresponding author: *Verinder Sharma, MBBS, FRCPC, Regional Mental Health Care London, 850 Highbury Ave North, PO Box 5532, Station B, London ON N6A 4H1, Canada (vsharma@uwo.ca).*

Bipolar disorder is a common, lifelong disorder characterized by recurrent episodes of depression, hypomania, or mania. The National Comorbidity Survey Replication reported lifetime (and 12-month) prevalence estimates for bipolar I disorder, bipolar II disorder, and bipolar disorder not otherwise specified (NOS) as 1.0% (0.6%), 1.1% (0.8%), and 2.4% (1.4%), respectively.[1] Comorbidity with other lifetime Axis I disorders is quite common, particularly anxiety disorders and substance use disorders. Patients living with bipolar disorder suffer substantial role impairment,[2] and, in fact, in a ranking of all psychiatric and medical conditions, the World Health Organization reported that bipolar disorder is the sixth leading cause of disability worldwide in those aged 15–44 years.[3] In addition, bipolar disorder has been associated with markedly increased morbidity and mortality from cardiovascular disease, other medical conditions, and suicide.[4] The recurrent nature of the disorder often leads to high direct and indirect health care costs,[5] making it a major public health problem.

There are gender differences in the prevalence, illness course, symptom profile, and comorbidity of bipolar disorder. While the prevalence of bipolar I disorder is equal between genders, bipolar II disorder is more common among women.[6] Women are more likely to have depressive episodes,[6,7] mixed mania,[7,8] more severe mania,[8] recurrence of mood episodes,[9] and a rapid-cycling illness course.[10,11] Women spend proportionately more time in the depressed phase of the illness.[12] Women also have higher rates of comorbid eating disorders,[9,13] as well as physical comorbidities including thyroid disorders and migraine headaches.[14–16]

As bipolar disorder usually begins in adolescence or early adulthood, women are at risk of having mood episodes throughout the reproductive years. In addition, the triggering role of reproductive events, particularly childbirth, causes a clustering of mood episodes during the reproductive lives of women. The postpartum period is widely considered a high-risk period for the onset or exacerbation of severe and potentially life-threatening mood or psychotic episodes of bipolar disorder.[10,17–21] There is an exponential rise in the rates of hospitalization immediately following delivery among women with bipolar disorder.[20,22–24] Hypomanic symptoms are also common after delivery and occur in 9.6%–20.4% of women in the early puerperium.[25–30]

There are conflicting data concerning the effect of pregnancy on bipolar disorder. Pregnancy has generally been considered to have an ameliorating effect on mental illness, but recent studies have reported high recurrence rates.[21,31,32] Kraepelin noted improvement in a subgroup of women: "There remains a small group of slight depressive states taking a favourable course which start in the beginning of pregnancy: these states are probably true forms of melancholia which correspond to those of the climacterium."[33(p46)] Marcé[34] reported on a total of 310 cases of childbearing-related mental illness. Of these, 27 (9%) had illness onset during pregnancy, 180 (58%) developed symptoms during the first 6 weeks after childbirth, and 103 (33%) developed symptoms after 6 weeks following childbirth. He observed that some women during pregnancy are "unduly anxious and some are unusually serene."

Understanding the effect that pregnancy has on the course of bipolar disorder has important implications for perinatal management of bipolar disorder. This article reviews the published literature on the effect of pregnancy on bipolar disorder, including the illness course, symptom profile, and suicide risk, and makes suggestions for future research.

Clinical Points

- Understanding the effect of pregnancy on bipolar disorder has implications for perinatal treatment of the disorder.
- There appears to be a discrepancy in findings of clinical studies of bipolar disorder versus studies using nonclinical samples.
- Evidence from studies using nonclinical samples reveals that pregnancy may have a positive effect on bipolar disorder.

METHOD

On April 30, 2010, 3 electronic databases, MEDLINE (1966–2010), PsycINFO (1840–2010), and EMBASE, were searched in order to systematically examine the effect of pregnancy on bipolar disorder. Combinations of the following keywords were used: *pregnancy, bipolar disorder, manic depressive disorder, suicide, hospitalization, pharmacotherapy,* and *psychotherapy*. The reference lists of articles identified were also searched to select other relevant publications. All relevant papers published in English were included. Although all individual case reports and case series have been referred to, only studies with at least 10 participants are described in detail.

RESULTS

A total of 70 articles were identified and included in the review.

Prevalence in Nonclinical Samples

Four studies have assessed the prevalence of bipolar disorder during pregnancy.[27,35–37] An Italian study[35] of 1,066 women attending an obstetric clinic at the third month of pregnancy for the first ultrasound examination reported a lifetime prevalence of 0.3% for bipolar I disorder, 1.1% for bipolar II disorder, and 0.6% for bipolar disorder NOS. Using the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[38] criteria, the corresponding rates for the current prevalence were 0%, 0.3%, and 0.2%, respectively. All of the women with bipolar II disorder were in partial remission during pregnancy. Notably, the overall lifetime and current prevalence rates of any current Axis I diagnosis in the study were 50.4% and 26.3%, respectively, which are in line with estimates from similar studies. For 66% of the study participants, it was their first pregnancy. The details of treatment including pharmacotherapy or psychotherapy were not provided.

Bipolar disorder was similarly uncommon during the second trimester in a Swedish study[36] of 1,795 pregnant women attending second-trimester routine ultrasound screening. Using the *DSM-IV*–based Primary Care Evaluation of Mental Disorders, the researchers identified only 1 individual with bipolar disorder. Very few of the women had psychiatric treatment; only 5.0% had received some form of psychotherapy, and 1 patient had been prescribed antidepressant treatment.

Results of the National Epidemiologic Survey on Alcohol and Related Conditions,[37] the largest nationally representative survey to date to provide data on psychiatric disorders in pregnant women, found that currently pregnant women had a lower risk of having any mood disorder, including bipolar disorder, than nonpregnant women. Face-to-face interviews were conducted, and women were diagnosed using *DSM-IV* criteria.

Results of a longitudinal study from the United Kingdom[27] that assessed the prevalence of hypomania during and after pregnancy in a total of 446 women showed that only 1.4% of women met the criteria for hypomania at 12 weeks of pregnancy. The number of cases of hypomania as assessed by the Highs scale[26] increased to 11.7% in the immediate postpartum period. The Highs questionnaire is a self-rating scale that is based on the Schedule for Affective Disorders and Schizophrenia-Lifetime Version[39] and is designed specifically to assess hypomanic symptoms after childbirth. The scale has 7 items including feeling elated, more active than usual, more talkative than usual, racing thoughts, feelings of being an especially important person, decreased need for sleep, and trouble concentrating due to attention jumping to unimportant things. A score of ≥ 8 is indicative of the "highs" (hypomania). The correlation between the Highs score and the blind observer-rated diagnosis by the Comprehensive Psychopathological Rating Scale was 0.62 ($P < .01$).[27] The cases of probable depression, as defined by a score of 13 or higher on the Edinburgh Postnatal Depression Scale,[40] did not significantly increase from pregnancy to postpartum, indicating that childbirth is a unique and potent trigger of hypomania.

To sum up, the few studies that have examined the prevalence of bipolar disorder in nonclinical samples have shown that bipolar disorder may have a low prevalence during pregnancy.

Illness Onset During Pregnancy

We found no published studies on the onset of hypomania or mania during pregnancy. Also, there were no data on how frequently bipolar disorder begins with a depressive episode during pregnancy. There were reports of prepartum onset of "postpartum psychosis."[41,42] Although there is some controversy about its diagnostic status, postpartum psychosis is generally considered a variant of bipolar disorder.

Paffenbarger and colleagues[43] applied a case finding method to identify patients in Cincinnati, Ohio, from 1940 to 1958 who had experienced their first psychotic episode during pregnancy or within 6 months after childbirth. There were a total of 147 patients with parapartum psychosis, including 21 cases with prepartum onset. The prepartum cases were evenly distributed during pregnancy: 6 in the

first trimester, 7 in the second trimester, and 5 in the third trimester. The authors speculated about the salutary effect of pregnancy and the sudden rise in postpartum cases due to the removal of the "protective barrier." They concluded that "the data suggest an etiology that is active during pregnancy but exerts its full effect only after loss of a hormone-producing organ, the placenta."[43(p171)]

Illness Course During Pregnancy

There is controversy regarding the effect of pregnancy on bipolar disorder. Two prospective[31,32] and 6 retrospective[16,18,21,44–46] studies have examined the course of bipolar disorder. Table 1 outlines the details of studies on bipolar disorder during pregnancy.

The prospective study by Viguera and colleagues[31] found that pregnant women who discontinued mood stabilizers had greater recurrence rates (85.5%) vs those who continued mood stabilizers (37.0%). Further, women had shorter times to recurrence and spent more time during the depressed phase of the illness after the discontinuation of maintenance treatment compared with those who remained on treatment with mood stabilizers. The overall risk of at least 1 recurrence in pregnancy was 71%. Recurrence risks were greater after rapid discontinuation than after gradual discontinuation. For women who discontinued the mood stabilizer, over 40% of pregnancy was spent in an illness episode, versus 8.8% of pregnancy for those who continued treatment with the mood stabilizer. Rate of antidepressant use was 66.1% among participants who discontinued mood stabilizer treatment versus 18.5% among those who continued mood stabilizer treatment. Since the median time to first recurrence was only 9 weeks, it is possible that the high recurrence rate was partly due to treatment discontinuation rather than a manifestation of the natural illness course.

Results of another prospective study[32] demonstrated that the risk of new episodes of illness was exceptionally high (100%) after the discontinuation of mood stabilizers. Continued treatment with lamotrigine appeared to be effective, as only 30% of women experienced a mood recurrence.

Viguera and colleagues[21] retrospectively compared the risk of recurrence in pregnant and nonpregnant women diagnosed with bipolar disorder following the discontinuation of lithium maintenance treatment. Rates of recurrence during the first 40 weeks after lithium discontinuation were similar for pregnant (52%) and nonpregnant women (58%) but were higher for both than in the year before lithium was discontinued (21%). It is not clear whether the patients were on any other psychotropic drugs. The researchers concluded that pregnancy has a neutral effect on bipolar disorder but acknowledged that for milder forms of the illness, pregnancy may not be destabilizing and might even have a beneficial effect.[47]

In another retrospective study, Viguera and colleagues[46] compared risks of mood episodes in 2,252 pregnancies of 1,162 women with mood disorders including bipolar I disorder (479 pregnancies/283 women), bipolar II disorder (641/338), and recurrent major depressive disorder (1,132/541). The overall risks in bipolar and major depressive disorders were 22.7% and 4.6%, respectively, during pregnancy, and 51.5% and 29.8%, respectively, after delivery, with an overall preponderance of depressive episodes.

A Turkish study by Akdeniz and colleagues[44] of the risk factors associated with childbearing-related episodes reported data on 72 women with bipolar disorder who had a combined total of 252 pregnancies. Women were diagnosed using the Structured Clinical Interview for *DSM-IV*.[81] Childbearing-related episodes were defined as onset of a mood episode during pregnancy or during the postpartum period (following the delivery of > 26 weeks of gestation). Non–childbearing-related episodes included every mood episode with no relationship to childbearing. During pregnancy, there were a total of 11 mood episodes (4.4%, 11 of 252 pregnancies), including 4 periods of depression and 7 of mania. Seven women had a mood episode during the first pregnancy; 2, during the second pregnancy; 1, during the fourth pregnancy; and 1, during the fifth pregnancy. The mood episodes had a mean duration of 5.5 weeks and occurred during the second and eighth months of pregnancy. Among 49 women with non–childbearing-related bipolar disorder, there were 10 women in whom the illness began before the childbearing events; however, none of these women had any mood episodes during pregnancy or in the postpartum period.

Another retrospective study[18] of 50 women (36 with bipolar I disorder, 13 with bipolar II disorder, and 1 with bipolar disorder NOS) reported that 50% of women with children had no change or experienced fewer mood symptoms while the other half had more symptoms of bipolar disorder during pregnancy. Notably, the majority (90%) of women were not on treatment with any psychotropic medication before, during, or immediately after delivery even though all but 1 woman reported onset of mood episodes prior to having children. A lack of change in condition or an improved illness course during pregnancy was protective against the development of postpartum mood episodes.

As part of the International Group for the Study of Lithium-Treated Patients, Grof and colleagues[45] retrospectively compared the clinical course of the illness in 28 mothers with typical bipolar I disorder and a control group of 33 childless women with bipolar disorder. The recurrence risk during pregnancy was markedly lower, and, moreover, women with bipolar I disorder had significantly fewer and shorter recurrences compared to before and after pregnancy. These women were not on treatment with any psychotropic medication but were later considered responsive to lithium therapy. Unlike other studies that reported high recurrence rates during early pregnancy, the few recurrences observed during pregnancy occurred in the last 5 weeks.

Blehar and colleagues[16] reported data on 186 women with bipolar I disorder. Subjects, who were ascertained as part of the NIMH Genetics Initiative, were interviewed using the Diagnostic Interview for Genetic Studies, which included a medical history and questions concerning psychiatric

Table 1. Summary of Studies of Bipolar Disorder During Pregnancy

Author	Study Design and Description	Sample Size, Illness Type	Diagnostic Instruments Used	Recurrence Rates		Before Pregnancy Rates	Medications
				Study Group	Controls		
Viguera et al, 2011[46]	Retrospective study comparing the risk and type of mood episodes in women with bipolar disorder (type I or II) and major depressive disorder during pregnancy and the postpartum period	1,162 (283 bipolar I, 338 bipolar II, 541 MDD)	*DSM-IV*	51.5% bipolar disorder (types I and II), 29.8% MDD	NA	22.7% bipolar disorder (types I and II), 4.6% MDD	Not specified
Viguera et al, 2007[31]	Prospective observational study of recurrence risk for women with bipolar disorder who continued or discontinued mood stabilizers during pregnancy	89 (61 bipolar I, 28 bipolar II)	SCID	85.5%	37.0%	NA	51.7% of women were on antidepressants, and 71% were on psychotropic medications
Newport et al, 2008[32]	Prospective observational study that compared recurrence risk for women with bipolar disorder who discontinued mood stabilizers (16) or continued lamotrigine (10)	26 (19 bipolar I, 6 bipolar II, 1 bipolar NOS)	SCID	100%	30%	NA	Antidepressants, antipsychotics, and sedatives
Freeman et al, 2002[18]	Retrospective observational study to determine the impact of female reproductive hormones on the course of bipolar disorder	50 (36 bipolar I, 13 bipolar II, 1 bipolar NOS)	*DSM-IV*	50% had fewer symptoms or no change; half had more symptoms	NA	NA	10% of women were on medication
Viguera et al, 2000[21]	Retrospectively compared the course of bipolar disorder during pregnancy and postpartum or during equivalent periods for age-matched nonpregnant subjects who discontinued lithium during pregnancy	101 (68 bipolar I, 33 bipolar II)	*DSM-IV*	52%	58%	21%	Not specified
Akdeniz et al, 2003[44]	Retrospectively evaluated the impact of psychosocial and clinical factors on the course of bipolar disorder during pregnancy and the postpartum period	72 bipolar disorder	SCID	Mood episode occurred in 4.4% of pregnancies; none occurred in women with non–childbearing-related bipolar disorder	NA	NA	Not specified
Grof et al, 2000[45]	Retrospective study of pregnant women prior to receiving successful lithium prophylaxis	28 bipolar I	RDC	14% 0.14[a] episodes	NA	0.43[b] episodes	No medications
Blehar et al, 1998[16]	Retrospective study of temporal relation of mood disturbance to reproductive transitions	139 bipolar I	DIGS	45.3%[c]	NA	NA	Most were not on medications

[a]Mean number of episodes per 9 months during pregnancy.
[b]Mean number of episodes per 9 months before pregnancy.
[c]Mood disturbance during pregnancy or within 1 month after childbirth.
Abbreviations: DIGS = Diagnostic Interview for Genetic Studies, MDD = major depressive disorder, NA = not available, NOS = not otherwise specified, RDC = Research Diagnostic Criteria, SCID = Structured Clinical Interview for *DSM* Disorders.

disorders in relation to childbearing. Almost half of women (63) who had been pregnant (139) reported a history of severe emotional disturbances in relation to childbearing, with over one-third (19/51) reporting episode onset including mania during pregnancy and 13.7% (7/51) reporting episodes both during and after pregnancy. No information was provided on the treatment status of these women. Five women were hospitalized during the perinatal period, 3 of whom were hospitalized during pregnancy.

In a hospital-based epidemiologic study from Pittsburgh, Pennsylvania, Wisner and colleagues[48] compared the demographic variables and psychiatric diagnoses of women with childbearing-related illness onset (n = 168) and those with non–childbearing-related illness onset (n = 1,004). These women had presented for inpatient or outpatient evaluation at a university hospital from January 1, 1984, to June 30, 1986. Childbearing-related illness onset was defined as onset of an episode during pregnancy or within 3 months of birth. Surprisingly, none of the women with childbearing-related illness onset was given a diagnosis of bipolar disorder.

To sum, clinical studies of bipolar disorder during pregnancy have shown mixed results. The results of the mood stabilizer discontinuation studies[21,31,32] may have been confounded by the lack of treatment randomization and the specialized nature of treatment settings. These studies were conducted at academic centers specializing in the treatment of perinatal mood disorders, and hence there is an increased likelihood of preselection of individuals with refractory mood disorders requiring complex medication regimens. Moreover, the possible protective effect of pregnancy could have been offset by the destabilizing effect of antidepressant use or by the abrupt withdrawal of mood stabilizers during pregnancy.

Predictors of Recurrence

Predictors of recurrence of mood episodes following the discontinuation of mood stabilizers have included a diagnosis of bipolar II disorder, earlier onset and unplanned pregnancy, more recurrences per year, recent illness, use of antidepressants, and use of anticonvulsants versus lithium.[31] However, the multivariate modeling of risk-factors-adjusted indicated that only antidepressant use and treatment discontinuation remained robust predictors of recurrence risk after adjusting for other indices of illness severity.[31] In addition, Akdeniz and colleagues[44] concluded that biological factors including a younger age, illness onset at an early age, prenatal mood episodes, and obstetric/somatic complications during pregnancy and not psychosocial factors were associated with childbearing-related episodes. Also, women with a childbirth-related onset of illness had a higher risk of peripartum episodes compared to those with non–childbirth-related illness onset. Paffenbarger and colleagues[43] found that compared to controls, women with prepartum illness were older, were more parous, were less likely to be primiparae, and had a longer interval since their last viable pregnancy.

Clinical Presentation During Pregnancy

Several studies have demonstrated that women with bipolar disorder are more likely to have depressive or mixed episodes than periods of hypomania or mania during pregnancy. Viguera and colleagues,[21,31] as well as Newport and colleagues,[32] concluded that pregnancy may predispose vulnerable patients to depressive episodes; however, this finding is not borne out by the findings of nonclinical samples showing low rates of depression during pregnancy. The mood episodes tend to cluster during the first trimester and are more frequent following an abrupt discontinuation rather than a gradual discontinuation of mood stabilizers. In contrast, all the recurrences in one study in which women were taking no medication occurred in the late third trimester.[45]

There were no studies of how pregnancy affects the symptom profile of bipolar disorder. Compared to major depressive disorder, bipolar disorder is more likely to be characterized by atypical symptoms including hypersomnia,[49] but no study has examined whether this atypical symptom profile is preserved during pregnancy. Similarly, there were no data on the extent and type of other Axis I comorbidity.

Suicidality During Pregnancy

There are no studies on the prevalence of suicidal behavior including suicide deaths, attempts, or thoughts of self-harm during pregnancy in women with bipolar disorder. Newport and colleagues' study[32] on suicidal ideation during pregnancy included women with bipolar disorder, but they did not separately report results on the association between bipolar disorder and suicidality. In general, suicide rates are lower during pregnancy relative to suicide rates in the general female population. A US study[50] found that the standardized mortality ratio for suicide during pregnancy was 0.33, while a British study[51] found that pregnant women were one-twentieth as likely to commit suicide as nonpregnant women of childbearing age. Two of a total of 139 women reported suicide attempts during pregnancy.[16]

Lower rates of suicidality cannot necessarily be explained on the basis of reduced levels of psychopathology during pregnancy. Various psychosocial factors including increased social support, concern for the unborn child, lower rates of mood disorders and substance use disorders, and more contact with caregivers may lower the suicide risk during pregnancy.

Rates of Hospitalization

There are no studies that have examined the rates of psychiatric hospitalization during pregnancy in patients with bipolar disorder. In general, studies have reported lower rates of psychiatric hospitalization during pregnancy. Results of a population-based register study from Denmark[50] that comprised all women who gave birth between 1973 and 1983 demonstrated that pregnancy was protective against admission to a psychiatric hospital. There were 271 women admitted during a 2-year period before childbirth and 510 during the same period after childbirth. The proportions of

admissions during the first, second, and third trimesters were 9.6%, 11.8%, and 10.3%, respectively. In comparison, 68.3% of the total admissions took place during the 15-month period prior to pregnancy. There was a preponderance of psychotic disorders among women admitted during the last trimester, while neurotic and personality problems were more prevalent among women admitted during the early part of pregnancy.

Using a linkage between obstetric and psychiatric case registers, Kendell and colleagues[20] studied the relationship between childbirth and psychiatric contact in 54,087 births over a 12-year period. For nonpsychotic illness, the average number of monthly admissions before pregnancy was 8, compared to a monthly rate of 5 during pregnancy. The corresponding rates for psychotic illness were 2.1 and 2.0. Women with a history of manic depressive illness had a much higher risk of psychiatric admission in the puerperium than those with a history of schizophrenia or depressive neuroses. Findings of this study and another study by Kendell and colleagues[52] demonstrated that pregnancy may have a protective effect for only nonpsychotic illness.

Pugh and colleagues[23] found a deficit of first admissions to Massachusetts psychiatric hospitals during 1950 at each trimester for psychoses and other disorders. McNeil and colleagues[53] compared rates of mental disturbance in 88 pregnant women with a history of hospitalization for nonorganic psychosis and 104 control women. Women with schizophrenia, cycloid psychosis, postpartum psychosis, and other psychoses were rated as being the most disturbed, while women with affective illness were the only diagnostic group that did not differ from the controls. Women's perception of the effect of pregnancy on their mental health also varied according to the diagnostic group. More improvement than worsening was reported by women with cycloid psychosis (40% better vs 20% worse) or affective illness (33% better vs 20% worse) as compared to women in other diagnostic groups.

It is possible that the threshold for admission to a psychiatric hospital is raised during pregnancy, as women may be more likely to be admitted to an obstetric ward.[54] There are factors including safety concerns, psychotic features, current substance use, and social support that affect rates of psychiatric hospitalization; nonetheless, hospitalization is a proxy measure of the severity of psychopathology.

Diagnosis of Bipolar Disorder

Despite an early age at illness onset, most women do not receive an accurate diagnosis of bipolar disorder or treatment with psychotropic drugs until after their pregnancies.[18,45] Women may be less likely to seek professional help during pregnancy than in the postpartum period because the symptoms may not be as severe as after childbirth. Owing to the lack of appreciation among the public or professionals of the potentially serious and life-threatening complications of untreated bipolar disorder, pregnant women are not routinely screened for bipolar disorder. This may be due in part to the lack of available validated screening instruments for use during pregnancy.[55,56] In recognition of the heightened risk of postpartum recurrence, the Canadian Network for Mood and Anxiety Treatments guidelines[57] have recommended universal screening of pregnant women for bipolar disorder.

Treatment of Bipolar Disorder

Exposure to untreated bipolar disorder during pregnancy can also have serious adverse consequences for the developing neonate such as premature birth, low birth weight,[58] and future behavioral disturbances. The majority of data on pharmacotherapy come from studies examining the effect of mood stabilizer discontinuation on the course of bipolar disorder. Remarkably little is known about the comparative efficacy of different medications to treat bipolar disorder during pregnancy.

The risk of teratogenicity associated with use of psychotropic drugs during the first trimester should be carefully weighed against the risks to the mother and the fetus of an untreated bipolar disorder. Lithium is associated with an increased relative risk of Ebstein's anomaly.[59,60] In women who require lithium treatment, serum lithium levels should be monitored closely, particularly during late gestation, when marked changes in glomerular filtration rate can alter lithium clearance. Higher lithium concentrations at delivery are associated with more perinatal complications including lower Apgar scores, longer hospital days, and higher rates of central nervous system and neuromuscular complications. Therefore, brief suspension of lithium therapy proximate to delivery may be necessary in some women.[61]

Early pregnancy exposure to anticonvulsants (eg, valproic acid, carbamazepine) increases the risk of fetal teratogenic effects.[62,63] Exposure to valproic acid in pregnancy is associated with reduced level of intelligence in children.[64] A recent controlled study[65] demonstrated that children of pregnant women taking valproic acid had an IQ 9 points lower than controls. Compared to older anticonvulsants, lamotrigine may pose less of a risk to the developing fetus.[32,66] For women taking lamotrigine, careful monitoring of symptoms is essential, since pregnancy may increase lamotrigine clearance and lower the lamotrigine levels.[67] Monitoring by blood level can be difficult because there is no established therapeutic blood level for lamotrigine.

Antipsychotic drugs have been used in combination with mood stabilizers but have not been systematically studied as monotherapy during pregnancy. Due to a paucity of reproductive safety data, it is difficult to draw any definitive conclusions on structural teratogenicity of antipsychotics.[68] Compared with first-generation antipsychotics, the use of several second-generation antipsychotics is more likely to be associated with maternal gestational diabetes,[69] as well as the risk of delivering large babies.[68] Whether there are any long-term effects on the glucose metabolism of children exposed to atypical neuroleptics prior to birth is currently unknown. The US Food and Drug Administration (FDA) issued a

safety alert[70] regarding the risks to newborns associated with prenatal exposure to typical or atypical antipsychotic drugs. The new drug labels now contain information about the potential risk for abnormal muscle movements and withdrawal symptoms including agitation, abnormal muscle tone, tremor, sleepiness, and breathing and feeding difficulties in newborns. The FDA warning must be interpreted in light of the fact that a majority of the cases were confounded by other factors, including the use of concomitant drugs known to be associated with withdrawal symptoms (antidepressants, benzodiazepines, nonbenzodiazepine hypnotics, and opioids), prematurity, congenital malformations, and obstetrical and perinatal complications. A recent study[71] found that prenatal exposure to antipsychotics compared with an antidepressant or no psychotropic exposure was associated with deficits in neuromotor performance. Despite the controversy surrounding their use, antidepressants are the most commonly prescribed initial treatment for bipolar disorder. Use of antidepressants increased from 2.0% in 1996 to 7.6% of deliveries in 2004 and 2005, and selective serotonin reuptake inhibitor use increased from 1.5% in 1996 to 6.4% in 2004 and 6.2% in 2005.[72] Even though antidepressants appear to be commonly used in pregnant women with bipolar disorder, there are no data on the prevalence of their use during pregnancy in the bipolar population. There are several concerns associated with the use of antidepressants in bipolar disorder, including induction of mania and mixed episodes, as well as acceleration of cycle frequency. Antidepressants are not as effective in bipolar disorder as in major depressive disorder[73] and have also been associated with treatment refractoriness[74] and increased suicidality.[75,76] Given the well-documented teratogenic risk of some drugs, it is surprising that the role of psychotherapy in the management of bipolar disorder during pregnancy has not been studied.

CONCLUSIONS AND FUTURE RESEARCH SUGGESTIONS

Given the significance of the subject, it is rather surprising that there is a paucity of systematic data on the effect of pregnancy on bipolar disorder. Only a total of 115 women, including 80 with bipolar I disorder, 34 with bipolar II disorder, and 1 with bipolar disorder NOS, have been studied prospectively.[31,32] Despite the prevalent nature of bipolarity beyond bipolar I disorder, particularly among women, the data on bipolar II disorder and bipolar disorder NOS are limited to only 35 study participants. Other methodological limitations of studies of bipolar disorder during pregnancy include

- Focus on women assessed at specialty clinic
- Inclusion of women who were all on treatment with psychotropic medications prior to conception
- Difficulties differentiating the effects of medications from the effects of pregnancy on the illness course
- High use of antidepressants
- Retrospective vs prospective methods
- Nonreporting of potential confounds such as parity status and psychiatric comorbidity

Despite limitations of the extant literature, the following conclusions can be drawn about the effect of pregnancy on bipolar disorder. There appears to be a discrepancy in findings of clinical studies versus studies using nonclinical samples. The latter studies have demonstrated uniformly low rates of bipolar disorder.[27,35–37] Some support for a protective effect of pregnancy also comes from clinical studies with either no use or low rates of use of psychotropic drugs during pregnancy.[44,45] Indirect evidence in support of the positive effect of pregnancy comes from large cohort studies reporting reduced rates of psychiatric hospitalization.[20,52] Even though there are no studies of suicidality in bipolar disorder, it is notable that there is a marked reduction in suicidal behavior during pregnancy.[50,51]

The patients in prospective studies were on treatment with psychotropic medications, including a large number treated with antidepressants[31,32]; thus, there are no contemporary prospective studies of women with unmedicated bipolar disorder to permit conclusions regarding the effect of pregnancy on the natural course of illness. Although frequently cited to support the contention that pregnancy does not have a positive effect on bipolar disorder, these studies[21,31,32] were designed primarily to assess the impact of mood stabilizer discontinuation rather than to ascertain the effect of pregnancy on bipolar disorder. For example, in Viguera and colleagues' study,[31] women who had discontinued all mood stabilizer therapy more than 6 months before conception were excluded. The disparity in recurrence rates in recent cohorts and other studies could partly be due to the increased use of antidepressants in more recent studies.

Large multicenter, prospective, controlled studies of women attending obstetric clinics or ultrasound clinics are needed to address the question of how pregnancy affects the course of bipolar disorder. Studies should compare the relapse rate in each trimester with the rate during the year before the pregnancy. Due to the different recurrence rates at different times during the pregnancy, women should be assessed during each trimester.[77] It is important to recruit pregnant women with different levels of illness severity, since polypharmacy is a common practice at specialty clinics. Participant recruitment from nonspecialty clinic settings will quite likely facilitate inclusion of women who may have undiagnosed or untreated bipolar disorder.

The paucity of research available on the topic of the effects of pregnancy on bipolar disorder limits the number of inferences that can be derived from this review. Therefore, it is hoped that this review will act to stimulate interest on this topic and encourage further research. Future studies should also consider the effect of gravid status because some women may experience worsening of illness course following childbirth. Whether or not the illness onset is childbirth-related is another important factor that may affect the risk

of peripartum recurrence. Researchers should also consider excluding pregnant women with current psychiatric comorbidity due to the differential effect of pregnancy on various psychiatric illnesses. Given the heterogeneity of the disorder, focusing on clinically homogeneous, well-characterized populations may be more helpful in elucidating the impact of pregnancy on bipolar disorder.

Research on the role of pregnancy as well as the postpartum period holds promise to a better understanding of the neurobiology of bipolar disorder in women. If pregnancy does indeed have a positive effect, some pregnant women with bipolar disorder may not require pharmacotherapy. The positive effect of pregnancy may not be unique to psychiatric disorders,[36] as certain physical illnesses such as multiple sclerosis[78,79] and rheumatoid arthritis[80] also improve during pregnancy. Better insights into how pregnancy affects bipolar disorder will also aid in the development of new and effective therapeutic strategies.

Drug names: carbamazepine (Carbatrol, Equetro, and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), valproic acid (Depakene, Stavzor, and others).

Author affiliations: Department of Psychiatry, University of Western Ontario (Dr Sharma); and Mood Disorders Program, Regional Mental Health Care (both authors), London, Ontario, Canada.

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