

Managing Bipolar Disorder During Pregnancy: Weighing the Risks and Benefits

Adele C Viguera, MD¹, Lee S Cohen, MD², Ross J Baldessarini, MD³, Ruta Nonacs, MD, PhD⁴

Background: Challenges for the clinical management of bipolar disorder (BD) during pregnancy are multiple and complex and include competing risks to mother and offspring.

Method: We reviewed recent research findings on the course of BD during pregnancy and postpartum, as well as reproductive safety data on the major mood stabilizers.

Results: Pregnancy, and especially the postpartum period, are associated with a high risk for recurrence of BD. This risk appears to be limited by mood-stabilizing treatments and markedly increased by the abrupt discontinuation of such treatments. However, drugs used to treat or protect against recurrences of BD vary markedly in teratogenic potential: there are low risks with typical neuroleptics, moderate risks with lithium, higher risks with older anticonvulsants such as valproic acid and carbamazepine, and virtually unknown risks with other newer-generation anticonvulsants and atypical antipsychotics (ATPs).

Conclusions: Clinical management of BD through pregnancy and postpartum calls for balanced assessments of maternal and fetal risks and benefits.

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Clinical Implications

- Clinical management of bipolar disorder (BD) through pregnancy and the postpartum period calls for balanced assessments of maternal and fetal risks and benefits.

Limitations

- Information about the course of BD during pregnancy remains limited, and risk of recurrence is not well quantified.
- Information about the reproductive safety of psychotropic drugs used to treat BD also remains limited, especially for newer drugs commonly employed to treat the disorder.

Key Words: bipolar disorder, women, lithium, anticonvulsants, pregnancy, postpartum, psychosis, teratogenic risk

Bipolar, or manic-depressive, disorder (BD) is a serious, recurrent psychiatric illness with a lifetime prevalence well above 1% (1,2). The disorder typically begins in adolescence or early adulthood and tends to be a lifelong condition characterized by high relapse rates, comorbid anxiety and substance use disorders, persistent subsyndromal morbidity and dysfunction, and premature mortality, mainly due to extraordinarily high suicide rates (3–8). Owing to its relatively high prevalence, BD is perhaps the most common idiopathic psychotic disorder, but only recently has it been recognized as a major public health problem (2,3,9).

BD represents a significant source of distress, disability, and family burden. Its prevention and treatment are particularly important and complicated for women of reproductive age. Yet, despite its undoubtedly great clinical importance, remarkably little is known about the impact of the female reproductive life cycle—the menstrual cycle, pregnancy, postpartum, nursing, and menopause—on the course and treatment of BD (10). Typically, women diagnosed with the disorder encounter significant obstacles from the professional community with respect to pregnancy. They are often counselled to avoid or terminate pregnancy to prevent fetal

exposure to potentially teratogenic medications and to avoid the risk for recurrence of manic or depressive illness (11). Women with BD seeking prepregnancy consultation at a major medical centre were recently surveyed (12). These women wanted advice regarding management of their mood disorder during pregnancy. Of those surveyed, 45% reported that a psychiatrist or other mental health professional had advised them to avoid pregnancy altogether. Following their prepregnancy consultation, 37% decided to avoid pregnancy. The most frequently stated reasons for this decision were fear of adverse effects on fetal development from the medicines and fear that, if treatment were discontinued, the illness would recur.

Physicians caring for pregnant women with BD face a complex clinical challenge: they must minimize risk to the fetus while limiting the impact of maternal morbidity on the mother, her unborn offspring, and her family that might result from potentially severe untreated psychiatric illness. Patients and their clinicians also face the difficult reality that decisions either to use or not to use psychotropic medications can be associated with complications. Deciding what constitutes reasonable risk during pregnancy requires shared responsibility but ultimately rests with the informed patient. Such informed choices, coupled with close psychiatric follow-up and coordinated care with the obstetrician, are components of an emerging model of care aimed at optimizing the clinical management of women with BD during pregnancy.

This overview considers information about the course of BD in pregnancy and about the reproductive safety of established and proposed mood stabilizers. A major aim of this report is to stimulate further discussion and research on this important, complex, and insufficiently considered public health problem for women of childbearing age with BD. We also present tentative guidelines for improved clinical care of such women.

Pregnancy and Recurrence Risk in BD

There is wide agreement that the early postpartum period presents unusually high risk for recurrence of BD and other psychiatric illnesses (13,14). In the mid-19th century, Marcé provided compelling early reports of severe psychotic and affective disorders arising in women during the postpartum period (15). Later, in his classic descriptions of manic-depressive syndrome, Kraepelin observed that attacks of mania and melancholia were common in pregnancy, but even more so following childbirth (16). Modern studies have sustained this general impression that the postpartum period brings high risks of acute psychiatric illness in women with manic-depressive illness. However, the risks associated with pregnancy itself remain less well characterized, and evidence is conflicting as to whether pregnancy alters the risk that major affective illness will recur. Some clinical observations

suggest that pregnancy may reduce the risks of acute psychiatric illness and specifically protect against recurrences of BD, major depression, psychotic disorders, and suicide (17–20). Other studies have found rates of psychiatric hospitalization to be either somewhat lower or unchanged during pregnancy, but these studies did not evaluate morbidity in nonhospitalized pregnant women with BD (13,14,21–23).

Grof and colleagues recently suggested that pregnancy has an apparent protective effect on the course of lithium-responsive BD I (with mania) (24). They describe a benign course and even improvement during pregnancy, based on comparisons before and after pregnancy in women whose illness could be managed without mood-stabilizing medication for prolonged periods. They propose that these findings support the view that pregnancy may protect against and prevent recurrences of BD, but the study sample may not represent broader groups of women with BD (25). Moreover, other recent research and growing clinical experience suggest that pregnancy probably does not consistently protect against recurrences of mania or major depression in women with BD. Instead, pregnancy has been found to be a time of substantial risk for relapse, particularly following discontinuation of ongoing mood-stabilizing treatment (25–28). In a large, well-characterized clinical sample, Blehar found that about 45% of women with BD experienced an exacerbation of their illness during pregnancy (29). More recently, Freeman and colleagues also found that at least 50% of a sample of women with BD became symptomatic during pregnancy (30).

We recently studied the course of BD I and BD II (recurrent major depression with hypomania) in a sample of 101 age-matched, pregnant ($n = 42$) and nonpregnant ($n = 59$) women who discontinued lithium maintenance treatment. Survival analysis demonstrated that BD recurred in 52% of the pregnant women and 58% of the nonpregnant women, with indistinguishable relapse time-courses (25,26). In contrast, within the preceding year only 21% of the entire sample had experienced a recurrence during ongoing treatment with lithium. Risks were similar with both BD I and II subtypes, but significantly higher for women with a history of 4 or more prior episodes and for women who abruptly or rapidly (< 2 weeks) discontinued lithium treatment proximate to conception. These findings are consistent with the view that either pregnancy may have little effect on recurrence risk in BD or discontinuation of maintenance treatment itself represents a major, and perhaps dominant, stressor (25–36).

These studies seem to suggest that any protective effects of pregnancy on risk for recurrences of mania or depression in women with BD are limited. Moreover, these effects are probably insufficient to protect most patients from recurrence if ongoing maintenance mood-stabilizing treatment is discontinued. To some extent, the risks for recurrence may be

predicted by the history of illness or severity, as well as by a history of prolonged wellness or proven ability to tolerate long periods without mood-stabilizing treatment. Clearly, more studies that control specifically for past illness, DSM-IV diagnostic subtypes (I, II, and rapid-cycling), and treatment status are required to clarify the course of BD during pregnancy.

Postpartum Recurrence Risk in BD

Whereas data on the course of BD during pregnancy are sparse, the postpartum period has received more systematic study. This period of the female reproductive cycle has been recognized consistently for more than a century as a time of heightened vulnerability to relapse of mood disorders and acute psychosis, although quantitative specification of that risk has been inconsistent. Recurrence rates within the first 3 to 6 postpartum months among women with BD have ranged from 20% to 80% (15,16,26,28,30,37–42). These rates have been well above 60% (range, 67% to 82%) in more recent studies, perhaps reflecting more reliable diagnosis and greater interest in the problem (26,29,30,42).

BD is also closely associated with postpartum psychosis (13,15,37–48). Several studies have demonstrated that many women presenting with postpartum psychosis later develop BD (13,15, 37–48). Postpartum psychosis is a rare condition in the general population, with an estimated prevalence in postpartum women of 0.1% to 0.2%. However, for women with BD, the risk is perhaps 100 times higher, at 10% to 20% (13,39,42). Postpartum psychosis is characterized by rapid onset of symptoms—often within the first 48 to 72 hours after delivery. The disorder may present with delirium, but it is often indistinguishable from a manic or mixed manic-depressive episode with psychotic features. Postpartum psychosis is a psychiatric emergency associated with high risk of infanticide and potential suicide; it requires immediate treatment with a mood stabilizer and antipsychotic agent or electroconvulsive treatment (ECT), usually in an inpatient setting (39,40,43–48). Following an episode of such illness, risk for a recurrent episode of postpartum psychosis with a subsequent pregnancy is estimated to be as high as 90% (43–45).

Several investigators have evaluated the ability of treatment to attenuate the high postpartum risk for recurrence of BD or acute psychosis (43–49). Most of this research has been limited to use of lithium prophylaxis. When lithium was given either several weeks prior to delivery or immediately postpartum, the risk for postpartum recurrences of BD was reduced on average by two- to fivefold, compared with untreated women (17,43–49). These reports leave important questions unanswered, including those of optimal dose and treatment timing and the comparative efficacy of lithium vs other mood stabilizers. A preliminary study of 11 women with BD found that introducing the anticonvulsant divalproex

shortly after delivery resulted in fewer recurrences than observed in otherwise similar, but untreated, women (49). In view of the very limited research on this important problem, further systematic study of perinatal and postpartum prophylaxis with anticonvulsants, atypical antipsychotics (ATPs), and nonpharmacologic interventions is urgently needed.

Potential Risks of Pharmacotherapy in Pregnancy

Clinicians face particularly urgent challenges when a woman with BD plans to conceive or becomes pregnant. Information accumulated in recent decades suggests that some psychotropic drugs may be safe for use during pregnancy (50–55). Nevertheless, knowledge regarding the risks of prenatal exposure to psychotropic medications remains far from complete.

All psychotropics diffuse readily across the placenta, and no psychotropic drug has been approved by the US Food and Drug Administration (FDA) for use during pregnancy. For obvious ethical reasons, it is not possible to conduct randomized placebo-controlled studies on medication safety in pregnant women. Accordingly, most information about the reproductive safety of drugs derives from case reports, case series, and retrospective studies. Very few reports involve prospective designs (56,57). To guide physicians seeking information about the reproductive safety of various prescription drugs, the FDA has established a system that classifies medications into 5 risk categories (A, B, C, D, and X), based on data derived from human and animal studies. Category A medications are designated as safe for use during pregnancy (no psychotropics have this rating), while Category X drugs are contraindicated by having demonstrated fetal risks that outweigh any benefit to the patient. Drugs in Categories B to D are considered to have intermediate risks, which are greatest in category D. Most psychotropic drugs are classified as Category C agents for which adequate human studies are lacking and risk cannot be ruled out. This classification system is often ambiguous, inaccurate, and misleading. In fact, the Teratology Society recommends that the FDA pregnancy categories be deleted from drug labelling and replaced with narrative statements summarizing and interpreting available data on teratogenic risk (58). At present, physicians must rely on other sources of information when recommending the use of psychotropic medications during pregnancy (50–55).

It is important to emphasize that random fetal anomalies are remarkably common and represent a high background rate against which to compare any teratogenic effects specific to psychotropic agents. The baseline incidence of major congenital malformations in newborns in the US is approximately 2% (59). Basic formation of major organ systems takes place early in pregnancy and is virtually complete within the first 12 weeks after conception. However, pregnancy is often not

Table 1 Fetal risks associated with drugs used to treat bipolar disorder

<p>Lithium</p> <ul style="list-style-type: none"> • Ebstein's cardiac malformation (approximately 0.05% risk vs 0.1% base rate) • Neonatal hypothyroidism, diabetes insipidus, polyhydramnios (rare) • Secreted in breast milk • FDA Pregnancy Category D <p>Valproic acid</p> <ul style="list-style-type: none"> • Spina bifida (approximately 1% to 5% risk) • Structural defects of heart, limbs, and dysmorphic facies • Secreted in breast milk • FDA Pregnancy Category D <p>Carbamazepine</p> <ul style="list-style-type: none"> • Spina bifida (approximately 1% risk) and dysmorphic facies • Secreted in breast milk • FDA Pregnancy Category C (as for oxcarbazepine) <p>Other anticonvulsants</p> <ul style="list-style-type: none"> • Unknown risks with gabapentin, lamotrigine, oxcarbazepine, and topiramate • Possible cleft lip and palate risk with some benzodiazepines (estimated risk based on metaanalysis: 0.7%) • All are secreted in breast milk • FDA Pregnancy Category C <p>Antipsychotics</p> <ul style="list-style-type: none"> • Teratogenic risks probably low • Unknown risks with atypical neuroleptics: clozapine, olanzapine, risperidone, quetiapine, and ziprasidone. • All are secreted in breast milk • FDA Pregnancy Category C (except clozapine: Category B Phenothiazines and thioxanthenes are not categorized)

diagnosed for 6 to 8 weeks, during which time critical steps in major organ development have already occurred. Teratogens are agents, including drugs, that interfere with this process to produce malformations of varying severity. Each organ system appears to be vulnerable to teratogenic effects during relatively specific and limited time periods during the first trimester (60).

It is important to point out that dating the age of the embryo differs from gestational dating by 2 weeks, in that gestation is dated by clinical convention from the last menstrual period [LMP = first day of menses], whereas embryonic age is dated from conception. Since the date of conception can be difficult to determine, gestational dating is preferred clinically. For example, formation of the heart and great vessels takes place from 5 to 10 weeks from last menstrual period, equivalent to embryonic ages 3 to 8 weeks, and formation of the lips and palate is typically complete by gestational weeks 8 to 14 (embryonic ages 6 to 12 weeks). Folding and closure of the neural-tube to form the brain and spinal cord occur within the first 5 to 6 weeks of gestation, or as early as 3 to 4 weeks of embryonic age—often well before pregnancy has been diagnosed. Exposure to a toxic agent before 2 weeks of gestation, or within the first week after conception usually results in a nonviable, blighted conceptus (60).

Fetal Risks Associated With Drugs Used to Treat BD (Table 1)

Lithium

Since the early 1970s, there has been concern about an association between prenatal exposure to lithium and risk for major congenital anomalies. Reports from an early International Register of Lithium Babies, based on a voluntary physician-reporting system, describe an excess of cardiovascular malformations, and particularly Ebstein's anomaly, in lithium-exposed newborns (61,63,64). Ebstein's anomaly is characterized by right ventricular hypoplasia and downward displacement of the tricuspid valve, often with varying septal defects. The risk for this malformation in infants with first-trimester lithium exposure was initially proposed to be 400 times higher than the background baseline rate of about 1/20 000 live births found in the general population (11,61,63,64). However, despite the fact that the reliability of this initial estimate was highly suspect in view of almost certain selective reporting of adverse outcomes to such registries, this risk estimate influenced clinical practice for the next 2 decades.

More recent, controlled epidemiologic studies suggest a real, but more modest, teratogenic risk of Ebstein's anomaly following first-trimester lithium exposure (11,62,65–70). Based on a pooled analysis of the data, Cohen and others estimated the risk for Ebstein's anomaly following first-trimester

exposure to be between 1/1000 (0.1%) and 1/2000 (0.05%) births (11). Based on relatively well-designed studies, rates of other congenital cardiovascular defects among lithium-exposed infants have varied from 0.9% to 12% (11,67,69). Although the estimated risk of Ebstein's anomaly in lithium-exposed infants is 10 to 20 times higher than in the general population, the absolute risk is small (0.05% to 0.1%), and lithium arguably remains the safest mood stabilizer for use during pregnancy. Nevertheless, the FDA fetal risk rating for lithium is D. Prenatal screening with a high-resolution ultrasound and fetal echocardiography is recommended at or about weeks 16 to 18 of gestation to screen for cardiac anomalies (11,62,65,70).

While reintroduction of lithium after the first trimester is not associated with increased risk for major malformations, additional risks from exposure later in pregnancy include reports of neonatal toxicity in offspring exposed to lithium during labour and delivery. These include several cases of muscular hypotonia with impaired breathing and cyanosis, often referred to as "floppy baby" syndrome (62,65,70–72). Isolated cases of neonatal hypothyroidism, nephrogenic diabetes insipidus, and polyhydramnios have also been described (70,72).

Based on these case reports of toxicity in infants born to lithium-treated mothers, some authors have recommended discontinuing lithium several days or weeks prior to delivery to minimize the risk of neonatal toxicity (11,65,70,73,74). However, there is a low incidence of neonatal toxicity with lithium exposure, and this practice carries significant risk, since it withdraws treatment from patients precisely as they are about to enter the postpartum period. A recent naturalistic survey found no direct evidence of neonatal toxicity in newborns whose mothers received lithium either during pregnancy or during labour and delivery (46).

Limited information is available regarding behavioural outcomes of children exposed to lithium in utero, but a 5-year follow-up of 60 children exposed to lithium during the second and third trimesters of pregnancy found no evidence of significant behavioural problems (74). A preliminary report of 13 children (average age 3.5 years) of women with BD who had been exposed to lithium in utero and 11 children (average age 3.3 years) of women with BD not exposed to medication in utero found no significant differences in neurobehavioural outcome, using blinded and well-validated neurocognitive assessments (75). The small sample, however, precludes conclusions about lithium exposure and long-term neurobehavioural sequelae.

Anticonvulsants

Compared with lithium, anticonvulsants may pose a much more serious teratogenic risk. All commonly used older

anticonvulsants have been associated with teratogenicity, and the risk for major birth defects in infants born to women receiving anticonvulsants is 2 times greater than that in the general population (76). Although most information about the reproductive safety of anticonvulsants derives from patients with epilepsy rather than BD, recent findings suggest that exposure to certain anticonvulsants, rather than the presence of a seizure disorder, is the relevant variable (77). Fetal exposure to anticonvulsants has been associated not only with relatively high rates of neural tube defects (NTDs), such as spina bifida, but also with multiple anomalies, including craniofacial abnormalities (also known as the "anticonvulsant face"), congenital heart disease, cleft lip or palate, growth retardation, and microcephaly (76–79). Factors that may increase the risk for teratogenesis include high maternal serum anticonvulsant levels and exposure to more than a single anticonvulsant (77,82–84). The lowest effective dosage should be used, and given in frequent divided doses over the course of the day (85). Anticonvulsant levels should be monitored closely, with the dosage adjusted appropriately (82). Prenatal screening for congenital malformations (including NTDs and cardiac anomalies), using fetal ultrasound at 18 to 22 weeks of gestation, is recommended (79,84,85). The possibility of fetal NTDs should be evaluated with maternal serum alpha-fetalprotein (MSAFP) and ultrasonography. In addition, 4 mg daily of folic acid is recommended before conception and in the first trimester for women receiving anticonvulsants, even though it is unknown whether supplemental folic acid can attenuate the risk of NTDs in the setting of anticonvulsant exposure (79,84,85).

First-trimester exposure to carbamazepine is associated with risk of NTDs estimated to be about 1.0% (86). Infants exposed to carbamazepine prenatally are also at increased risk for craniofacial abnormalities, microcephaly, and growth retardation (77,86). It is not known whether the new derivative, ox-carbamazepine, is associated with similar fetal risks (88). However, among the anticonvulsants used to treat BD, valproic acid and its various derivatives and preparations, including divalproex, may be even more serious teratogens, with rates of NTDs in the range of 1.0% to 5.0%, or about a two- to tenfold increase in risk above the general-population base rates of about 0.5% (89,90). These risks are of particular concern because formation of the neural tube occurs within the first month of gestation, often before the pregnancy has been diagnosed. Prenatal exposure to valproate has also been associated with characteristic craniofacial abnormalities, cardiovascular malformations, limb defects, and genital anomalies, as well as other central nervous system (CNS) structural abnormalities, including hydrocephalus (76–78,89,90).

Information about possible untoward neurobehavioural effects of anticonvulsant exposure is very limited. There is no

evidence to suggest increased risk for mental retardation following antenatal exposure to anticonvulsants, but subtle cognitive effects have been suggested, including after second-, or even late third-trimester, drug exposure (91–94). These subtle deficits may be correlated with the presence of midface hypoplasia (93).

Information about the reproductive safety of newer anticonvulsants sometimes used to treat BD—including lamotrigine, gabapentin, oxcarbazepine, and topiramate—remains very sparse (95). Most of the available information is limited to a few case reports pertaining to such drugs, given alone or often in combination with other anticonvulsants, and almost always to pregnant women with epilepsy. A pregnancy registry was established recently by the manufacturer of lamotrigine, with a preliminary suggestion that the risk of all malformations following prenatal exposure to lamotrigine monotherapy during the first trimester averaged 2.5% (96). Data from a UK registry suggest a similar risk with exposure to lamotrigine alone early in pregnancy (97). These registries have not shown a consistent excess of any specific form of birth defect, but the numbers of pregnancies accumulated so far remain small. Other efforts are under way to accumulate unbiased information regarding teratogenic risks across a broad range of anticonvulsants in pregnancies enrolled prospectively. For example, the North American Antiepileptic Drug Pregnancy Registry was recently established as a way of collecting such information rapidly and efficiently (its toll-free telephone number is 888-233-2334). The registry will release its findings only after information on neonatal outcome has been collected from at least 300 monotherapy exposures. It is estimated that this number will provide sufficient statistical power to detect at least a twofold excess of major birth defects. At this time, given the sparse data on the fetal safety of the newer anticonvulsants proposed for use in BD, it is difficult to justify their use as first-line agents during early pregnancy.

Antipsychotics

Switching from a prolactin-elevating antipsychotic agent, such as risperidone or an older neuroleptic, to a modern agent without such effects can increase the risk of becoming pregnant (98). Early case reports described limb malformations following first-trimester exposure to haloperidol (99,100), but several other studies have not demonstrated teratogenic risk associated with any of the older typical neuroleptics of either low or high potency (101,102). Nevertheless, a metaanalysis of available studies noted a suggestive elevation of overall risk for congenital malformations following first-trimester exposure to low-potency neuroleptics; however, no specific type of malformation was identified (50). In clinical practice, high-potency neuroleptic agents such fluphenazine, haloperidol, perphenazine, and trifluoperazine are recommended

because they have lesser autonomic, sedative, and cardiovascular side effects than do the low-potency agents. (50,52).

Information on the reproductive safety of newer ATPs remains very sparse. There are no adequate human studies to evaluate the risk for potential teratogenicity of clozapine, olanzapine, risperidone, quetiapine, or ziprasidone. There are perhaps 5 published case reports of women treated during pregnancy with the oldest ATP agent, clozapine; they yield no evidence of major congenital malformations (103–106). In addition, the original manufacturer of clozapine has collected information on at least 29 babies exposed to clozapine before birth (107). Of these, 25/28 were healthy, and 4/28 had problems, including neonatal convulsions, Turner's syndrome, collar-bone fracture, facial deformity, congenital hip dislocation, and blindness. However, the possible significance of these findings as evidence of teratogenic actions of clozapine is not clear. The manufacturer of olanzapine also established a registry that includes at least 96 reports of outcomes following prenatal exposure to this ATP (95,108). There was only 1 case of a major malformation (1/96) and 7 other instances of temporary perinatal complications. Experience to date with all these registries for atypical antipsychotic agents remains insufficient to provide for adequate assessment of fetal safety.

Several case reports have documented transient extrapyramidal symptoms (EPS), including motor restlessness, tremor, hypertonicity, dystonia, and parkinsonism in neonates exposed to neuroleptics during pregnancy (109,110). These problems have typically been of short duration and have been followed by apparently normal subsequent motor development (111). Risks for potential neurobehavioural or cognitive effects from prenatal exposure to older neuroleptics have also been considered, but the available data remain limited and inconclusive. A longitudinal study that evaluated general intelligence and behaviour of children exposed to low-potency neuroleptics in utero found no evidence of dysfunction or developmental delays up to age 5 years (111).

Treating Potentially Child-Bearing Women With BD

Current State of the Problem

Only recently has attention focused on treatment during pregnancy (11,26,62,65,73). Managing the illness of pregnant women with BD is very challenging, particularly since there are risks associated with the use of mood stabilizers as well as without such treatment, and these risks have not been fully examined or quantified in pregnancy. This limited information requires patients and their physicians to make treatment decisions based on risks that are only partly defined. Planning for pregnancy while the patient is euthymic and clinically stable for a prolonged period provides for thoughtful treatment

Table 2 General principles in managing bipolar disorder in pregnancy

- Planned pregnancy provides time for thoughtful treatment choices
- Streamline regimen
- Use minimum effective dose
- Consider patient a “high-risk” pregnancy and monitor closely
- Guidelines vary with severity of illness
- Consider pregnancy and the postpartum period as separate “risk periods” and individualize treatment plan accordingly
- Evaluate need for postpartum prophylaxis (strongly recommended)

choices and avoids the tendency to precipitously change treatment during an unplanned pregnancy. All decisions regarding the continuation or initiation of treatment during pregnancy must reflect an assessment of the following factors: 1) the highly variable but often poorly quantified risks of fetal exposure to drugs commonly used to treat BD; 2) the substantial risks to the patient, fetus, and family from untreated psychiatric illness in the mother; and 3) the typically high risk of relapse associated with discontinuation of maintenance treatment, particularly if it is abrupt. Each of these risks should be discussed frankly with the patient and her partner, ideally on more than 1 occasion, before and after conception. There should be ongoing communication with the patient’s obstetrician, and all these discussions should be documented in the patient’s medical record. Table 2 outlines general principles for managing BD during pregnancy

Close clinical monitoring during pregnancy is essential, and it may help to conceptualize care for pregnant women with BD as similar to “high-risk” pregnancies in general obstetrical care. Even if all psychotropic medicines have been safely discontinued, pregnancy in women with BD should be considered high-risk because risk of major psychiatric illness is increased without mood-stabilizing medication and particularly so postpartum. Unusually high vigilance is required for early detection of impending relapse of illness; rapid intervention can probably significantly reduce morbidity and improve overall prognosis.

Important factors to consider in the prepregnancy treatment-planning phase for women with BD are the illness history and the acceptability and estimated safety of specific clinical interventions, which may be pharmacologic or nonpharmacologic. Specific considerations include the previous frequency and severity of illness episodes, past and current levels of functioning or impairment, previous and recent duration of clinical stability with and without medication, the nature of prodromal symptoms that have been characteristic of impending relapse, and average time to recovery following reintroduction of treatment. In the assessment process, it is useful to inventory previous medication trials, responses, adverse effects, and reactions to treatment discontinuation. This process will guide selection of effective and safe treatment

options for the patient and minimize fetal exposure to potentially risky drugs. Newer drugs may seem to represent attractive alternatives to better-known treatments, but pregnancy is not an appropriate time to experiment with newer agents or complex drug combinations, especially when simpler and better-known options are available and have proved effective and tolerable for a particular patient.

Strategies for Treating BD During Pregnancy and Postpartum

Treating BD during pregnancy and postpartum is a dynamic process with decisions about treatment options evolving depending on the individual patient’s observed course of illness during pregnancy. In treatment planning, it also helps to conceptualize pregnancy and the postpartum period as 2 distinct risk periods; use of medications may have a specific set of treatment implications, depending on whether the patient is pregnant, postpartum, or nursing.

The most appropriate treatment algorithm depends on the severity of the individual patient’s illness (see Table 3). In the past, abrupt discontinuation of lithium or other ongoing psychotropic treatments was a common practice, probably largely driven by relatively unbalanced concern about avoiding liability associated with fetal exposure to a potential teratogen. However, a more appropriate approach is to consider risks more broadly, including the high risks of recurrent major psychiatric illness that can follow discontinuation of lithium or other mood stabilizers. A prepregnancy trial of gradual discontinuation of the mood-stabilizer can often be tried cautiously before the patient attempts to conceive. Such a trial can give useful information to the physician and the patient about how well the patient tolerates being medication-free. At any early indication of an impending relapse during this trial, the mood stabilizer can be rapidly reintroduced. If a patient fails such a trial, the feasibility of a pregnancy without mood-stabilizer treatment should be reevaluated.

Patients with histories of a single episode of mania and prompt, full recovery followed by sustained well-being may tolerate discontinuation of their mood stabilizer before an attempt to conceive (11,26). For women with BD who have a history of multiple and frequent recurrences of mania or

Table 3 Treatment options

Mild to moderate bipolar disorder

- Gradual taper and discontinuation of mood stabilizer before pregnancy (or at positive documentation of pregnancy)
- Maintain drug-free in first trimester if possible; maintain low threshold for reintroduction of mood stabilizer
- Preserving euthymia in pregnancy may predict better postpartum course

Severe bipolar illness

- Consider continuation of mood stabilizer in the first trimester and throughout pregnancy

bipolar depression, several options can be considered. Some patients may choose to discontinue a mood stabilizer prior to conception, as discussed above. An alternative strategy for this high-risk group is to continue treatment until pregnancy is verified, and then gradually remove the mood stabilizer. Since utero-placental circulation is not established until approximately 2 weeks postconception, the early risk of fetal exposure is minimal. Home pregnancy tests are reliable and can document pregnancy as early as 10 days postconception; with a home ovulation-predictor kit, a patient may be able to time her treatment discontinuation fairly accurately. The advantages of this strategy are that it minimizes fetal exposure to drugs and extends the protective treatment up to the time of conception, which may be particularly prudent for older patients, who may require more time to conceive. However, a potential problem with this strategy is that it may lead to relatively abrupt treatment discontinuation, thereby placing the patient at increased risk for relapse (11,26,52). With close clinical follow-up, however, patients can be monitored for early signs of relapse, and medication may be reintroduced as needed.

For women who tolerate discontinuation of maintenance treatment, the decision when to resume treatment is a matter for clinical judgement. Some patients and clinicians may prefer to await the initial appearance of symptoms before restarting medication; others may prefer to limit risk of a major recurrence by restarting treatment after the first trimester of pregnancy. Recent data suggest that pregnant women with BD who remain well throughout pregnancy may have a lower risk for postpartum relapse than those who become ill during pregnancy (30,112).

For women with particularly severe forms of BD—with, for example, multiple severe episodes and, especially, with psychosis and prominent suicidality—maintenance treatment with a mood stabilizer before and during pregnancy may be the safest option. If the patient decides to attempt a pregnancy, accepting the relatively small absolute increase in teratogenic risk with first-trimester exposure to lithium, for example, may be justified: such patients are at highest risk for clinical deterioration if pharmacologic treatment is withdrawn. Recurrence of mania or bipolar depression during pregnancy is

potentially dangerous to both mother and fetus. It may require hospitalization as well as exposure to multiple psychotropic agents at relatively high dosages. Thus, an informed decision to assume a limited risk associated with mood-stabilizer treatment may be preferable to the risk of relapse and more intense pharmacologic treatment.

For patients with severe depression, mania, or psychosis, hospitalization is often required, and electroconvulsive therapy (ECT) is frequently the treatment of choice. Two recent reviews of ECT use during pregnancy examined over 300 case reports and emphasize the efficacy and safety of this procedure (113,114). ECT may also be considered as an option, especially for women who fail to respond to standard mood-stabilizer therapy.

In certain cases of refractory illness, one may decide to use a medication for which information regarding reproductive safety is sparse. For instance, a woman with severe BD who has responded only to a newer anticonvulsant, or to an ATP for which reproductive safety data are unknown, may choose to continue this medication during pregnancy rather than risk relapse by discontinuing or switching to another agent. Patients with severe BD who present clinically late in the first trimester or early second trimester already stable on a newer anticonvulsant or atypical neuroleptic are another example. Continuing treatment, even with limited reproductive safety data, may be the most prudent course, given the high risk for destabilization with treatment withdrawal or the uncertain effect of switching to an alternative medication.

Treatment of BD Postpartum

Pregnant women with BD should be clearly informed of the unusually high risk for relapse as they enter the postpartum period. The high rate of postpartum recurrence of BD underscores the importance of prophylactic intervention at or before delivery (43–49). Lithium prophylaxis should be strongly recommended, especially for patients who have remained unmedicated during the pregnancy. An anticonvulsant or antipsychotic agent for postpartum prophylaxis can also be considered, particularly if lithium treatment has been unsuccessful or poorly tolerated in the past. Currently, no data exist on the use of atypical antipsychotics or anticonvulsants to

prevent postpartum illness in BD, but clinical experience suggests that such agents are also likely to be beneficial. Although research data demonstrate that introducing lithium prophylaxis within 48 hours postdelivery has been effective in reducing risk of postpartum relapse, earlier reintroduction of a mood stabilizer—2 to 4 weeks prior to the expected delivery date—may be a more prudent option that allows time to optimize medication dosage prior to entering a period of high relapse risk. While there are no research findings to support this recommendation directly, the disadvantages of intervention at 36 or 38 weeks of gestation are modest.

Factors influencing the choice of mood stabilizer for acute postpartum prophylaxis may be further complicated by the fact that many women would like to breast feed. Two recent reviews have addressed the use of psychotropic medications, specifically mood stabilizers, during breast feeding (115,116). The American Academy of Pediatrics Committee on Drugs has generally considered carbamazepine and valproic acid (but not lithium) to be compatible with breast feeding. However, these recommendations are based on a paucity of data of varying quality, and these recommendations need to be reevaluated, because specific risks associated with each mood stabilizer have not been adequately examined (115,116). Decisions about medication use during breast feeding should be based on careful risk-benefit assessments for each individual. These assessments should take into consideration several clinical factors, including illness history, response to medications, impact of sleep deprivation on course of illness, and the potential long-term benefits of breast feeding to the mother and infant.

Conclusions and Clinical Implications

Safe treatment of BD during pregnancy is possible with prepregnancy treatment planning and close clinical monitoring. The goal of clinicians caring for women with BD who either are planning to conceive or are pregnant should be to provide the best information regarding the spectrum of risks associated with either pursuing or deferring treatment with psychiatric medications.

While the data strongly suggest that the postpartum period is a time of heightened risk for relapse, the extent to which pregnancy may have a protective effect on the course of BD in pregnancy is unknown. The data available thus far suggest that any protective effects of pregnancy are likely insufficient to protect most BD patients from recurrence, especially following discontinuation of ongoing maintenance mood-stabilizing treatment.

Among the mood stabilizers, lithium should be considered a first-line treatment option in pregnancy. Reproductive safety data on the newer mood-stabilizing agents remain limited, and these agents should be avoided. An algorithm of treatment

options should depend on the severity of illness and the individual patient's unique treatment needs. Treatment of BD during pregnancy and postpartum is a dynamic process, and decisions about treatment options may evolve over time, depending on the individual patient's illness course during pregnancy.

Conceptualizing the care of pregnant women with BD as a high-risk pregnancy emphasizes the importance of close clinical monitoring and the need for coordinated care among patient, partner, obstetrician, and psychiatrist. Pending controlled prospective data on both the risks for recurrence in pregnancy and the impact of medications on fetal development, clinicians will continue to have to care for pregnant women with BD while recognizing the limitations of our current knowledge base and weighing partly calculated risks.

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¹Associate Director, Perinatal and Reproductive Psychiatry Program, Massachusetts General Hospital; Instructor in Psychiatry, Harvard Medical School, Boston, Massachusetts.

²Director, Perinatal and Reproductive Psychiatry Program, Massachusetts General Hospital; Associate Professor of Psychiatry, Harvard Medical School, Boston, Massachusetts.

³Director, Bipolar and Psychotic Disorders and Psychopharmacology Programs, Laboratories for Psychiatric Research, and International Consortium for Bipolar Disorder Research, McLean Division of Massachusetts General Hospital; Professor of Psychiatry and, Neuroscience, Harvard Medical School, Boston, Massachusetts.

⁴Instructor in Psychiatry, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts.

Address for correspondence: Dr AC Viguera, Perinatal and Reproductive Psychiatry Program, Department of Psychiatry, WACC 812, Massachusetts General Hospital, Boston, MA 02114
e-mail: aviguera@partners.org

Résumé: Traitement du trouble bipolaire durant la grossesse : les risques et les avantages

Contexte : Les problèmes liés au traitement clinique du trouble bipolaire (TB) durant la grossesse sont profonds et peuvent entraîner des risques concurrents pour la mère et l'enfant.

Méthode : Nous avons examiné les résultats récents de la recherche sur le cours du TB durant la grossesse et le post-partum, de même que les données d'innocuité reproductrice des principaux régulateurs de l'humeur.

Résultats : La grossesse et surtout la période du post-partum comportent des risques élevés de récurrence du TB. Les risques semblent être limités par les traitements aux régulateurs de l'humeur et notablement accrus par la cessation abrupte de ces traitements. Toutefois, les médicaments utilisés pour traiter ou prévenir les récurrences du TB varient beaucoup en ce qui concerne les risques tératogènes : les risques sont faibles pour les neuroleptiques typiques, modérés pour le lithium, élevés pour les anciens anticonvulsivants comme l'acide valproïque et la carbamazépine, et presque inconnus pour les autres anticonvulsivants de la nouvelle génération et les antipsychotiques atypiques (APA).

Conclusions : Le traitement clinique des femmes souffrant du TB durant la grossesse et le post-partum demande des évaluations équilibrées des risques et des avantages pour la mère et le fœtus.