The Use of Lithium and Management of Women With Bipolar Disorder During Pregnancy and Lactation

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The introduction of lithium salts almost a century ago and the subsequent approval of lithium carbonate for the treatment of patients with bipolar disorder represent one of the cornerstones of modern psychopharmacology. The onset of bipolar disorder in women often occurs during the childbearing years, which complicates the treatment decisions secondary to the possibility of conception while taking medication. The establishment of the lithium registry for fetal teratogenesis in the late 1960s ushered in a heightened level of concern for the use of lithium during the reproductive years; although, in the years to come, it has become apparent that alternative pharmacologic treatments for bipolar disorder may exceed the teratogenic risk of lithium monotherapy. In this paper, the available data on the use of antimanic medications during pregnancy and lactation are reviewed with an emphasis on providing a realistic risk/benefit assessment for medication selection and management of these patients. Treatment strategies are discussed for (1) women who are contemplating pregnancy (2) women who inadvertently conceive while taking medications (3) women who choose to become pregnant while taking medication, and (4) women who intend to breastfeed while taking medications.

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The reproductive years represent a time of enhanced vulnerability for the onset of both bipolar disorder and major depression in women. There are limited data to support the idea that pregnancy confers any protection from either onset or relapse of affective disorders, and several studies have demonstrated a profound increase in affective instability during the postpartum period.[1–5] Although the use of psychotropic medications during pregnancy and lactation has been extensively reviewed by several groups, the use of lithium carbonate or sustained-release lithium compounds in women of reproductive potential remains controversial and empirically discouraged.[6–15] With the exception of electroconvulsive therapy (ECT), lithium may be the safest first-line alternative for the treatment of bipolar disorder during pregnancy and may have distinct advantages in the postpartum period. The supporting evidence for this assertion is derived from reviewing (1) the lithium data, (2) the teratogenic risk of other treatment options, (3) the treatment data and impact of treatment interruption, and (4) suggested treatment guidelines. These data provide the basis for the risk/benefit assessment of lithium use during pregnancy and lactation.

RELAPSE OF BIPOLAR DISORDER

Although the ideal pregnancy and postpartum course would involve no fetal or infant exposure to any medications, the likelihood of such an ideal experience is small.[16] In the case of a woman with bipolar disorder, the likelihood of having this ideal of no drug exposure is even less. The treatment goal during pregnancy is to limit pharmacologic exposure by using the minimum effective dosage of medications and to limit the total number of medications while maintaining mental health. Education and an individualized risk/benefit assessment are helpful in reducing overall patient and/or clinician anxiety. The greater the number of prior affective episodes a patient has had, the greater the risk of a subsequent relapse of a bipolar episode.[7] Withdrawal of bipolar patients from stable lithium maintenance puts them at an increased risk of relapse, particularly mania, in the first 6 to 12 months after discontinuation.[3,4,17] Studies have found that a 50% recurrence rate occurs within 2 to 10 weeks after lithium discontinuation in bipolar patients who were treated for an average of 30 months.[17] Patients with bipolar I disorder have a 1.5 time

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greater and faster chance of relapse than patients with bipolar II disorder over a 5-year period.[5,17] Rapid discontinuation of lithium (< 2 weeks), and possibly other antimanic medications, greatly increases the risk and speed of illness recurrence.[4,17] Tapering medications over 2 to 4 weeks or maintaining the lowest effective dose of medications must be considered viable options to decrease the risk of relapse during the 9-month period of pregnancy and/or the postpartum nursing period in high-risk populations.[4] The high rate of relapse in bipolar women who discontinue medications must weigh heavily in the treatment decisions for pregnancy, as relapse may mean higher overall doses of medication or the use of multiple medications to achieve symptom control in the long run.

It is equally important to remember that physiologic changes in women during pregnancy may increase the urinary excretion of many medications. During pregnancy, a woman's glomerular filtration rate (GFR) increases and the creatinine clearance typically doubles. This causes many medications to be excreted more rapidly, and if medication dosage is not increased, serum levels may fall and the mother may again be at increased risk for symptom recurrence.

PREGNANCY

Embryology/Exposure

Inadvertent conception is not rare for women who have a diagnosis of bipolar disorder.[7,18,19] To evaluate the data on medications and ECT in order to treat bipolar disorder in pregnancy, it is necessary to review fetal development and placental passage of medications. In the United States, there is a 2% to 4% malformation rate documented at birth that typically increases in the first year of life as defects are identified that were indiscernible at birth.[10] The ideal pregnancy, as described by the Centers for Disease Control and Prevention, includes taking prenatal vitamins for 4 to 6 weeks prior to conception, keeping maternal body weight within 15% of the ideal body weight, regular prenatal care, no medication exposure, and no exposure to tobacco, alcohol, or drugs of abuse. To maximize the chance for an uncomplicated obstetrical course and minimize the risk of malformation, all women of reproductive potential should be educated about the ideal standards of a pregnancy and the rarity with which they are probably met, particularly with respect to medication exposure. Moreover, they should also be taught that inadvertent conception accounts for more than 50% of all pregnancies. Most women learn of their pregnancy after a missed menstrual period and are already at 3 to 7 weeks gestation.[16] They have seldom taken prenatal vitamins and are often exposed to potential environmental and over-the-counter toxins during this time. Any toxic exposure during Day 1 to Day 17 after conception will usually result in death of the embryo and miscarriage.

The development of the central nervous system begins by Day 16 to Day 18 of gestation with formation of the neural plate. The neural tube closes by the end of the fourth week of gestation. Defects of neural tube closure are termed spina bifida and include a wide range of defects with varying degrees of functional impairment and survival.[20] Maternal obesity, folic acid deficiency, and hypervitaminosis A increase the risk of a neural tube defect. Brain and neuronal development continues throughout pregnancy.

The cardiovascular system develops from mesenchymal cell clusters that form the cardiogenic area and later develop into a single heart tube by Day 22 of gestation. The heart develops over the following weeks with the major speta forming between Days 27 to 37, valvular development starting at Day 35, and complete development by Day 56 to Day 60 of gestation.[20] Organogenesis is typically complete by Day 56 of gestation.

Use of Lithium During Pregnancy

The use of lithium during pregnancy has undergone considerable scrutiny. For years, it was taught that first trimester exposure caused Ebstein's anomaly. While there is reasonable agreement that lithium exposure during the first trimester is associated with an increased number of cardiovascular anomalies in infants compared with the general population, its association with Ebstein's anomaly is suspect. Ebstein's anomaly is a rare condition, which occurs in 1 infant per 20,000 live births[21–23]; it is characterized by right ventricular hypoplasia and congenital downward displacement of the tricuspid valve into the right ventricle.[24] The bulk of lithium data is derived from physician reports to The International Register of Lithium Babies, started in 1968 in Scandinavia, Canada, and the United States. A lithium baby is defined as one with first trimester exposure to lithium. The registry acknowledges its limitations in that overreporting of adverse effects is common, underreporting of nonadverse deliveries is expected, women exposed to multiple medications in pregnancy may be included, and control groups for well women or women with untreated mental illness may not be used.[25,26] The original registry report on 118 babies identified 6 (5.1%) with significant congenital cardiovascular problems, including ventricular septal defect, mitral atresia, tricuspid atresia, coarctation of the aorta, and two cases of Ebstein's anomaly.[25] This report was later extended with two additional cases of infants born with Ebstein's anomaly.[21] The final report from the registry on 225 lithium babies identified 25 cases of congenital anomalies (11.1%), of which 18 babies (8.0%) had cardiovascular defects and 6 (2.7%) had Ebstein's anomaly.[27]

A cohort study conducted from the Swedish birth registry identified 59 infants exposed to lithium early in pregnancy; 4 (6.8%) had congenital heart disease and none had Ebstein's anomaly.[28] This study included 228 infants of

women with bipolar disorder who were not treated with lithium during pregnancy, and only 2 infants (0.9%) had cardiac malformation. A prospective study[29] of 148 women, who consulted a teratogen information center about taking lithium during the first trimester of their pregnancy, was compared with a control group of 148 women who also consulted a center about exposure to medications without known teratogenic effects. Four (2.7%) of the lithium-exposed infants had congenital anomalies; one infant had Ebstein's anomaly and 3 of the control infants had congenital anomalies. Four case-control studies have tested the relationship between lithium and Ebstein's anomaly.[23] A total of 208 children with Ebstein's anomaly were found through various defect registries, and none of these children had been exposed to lithium during pregnancy.[23] A control group of 398 children was taken from the same sources—two of these children had been exposed to lithium during pregnancy and no anomalies existed. Thus, the study concluded that the risk of Ebstein's anomaly was not as high as previous studies indicated. Kallen, in 1991, conducted a nested, case-control cohort study investigating the rate of birth defects in the children of women who had a manic depressive illness.[30] Eleven children had possible or proven congenital heart disease; 3 (27%) of these children were exposed to lithium in utero while 4 (20%) of 20 mothers of the control infants were treated with lithium during pregnancy. The study found only 1 child with Ebstein's anomaly, and this child was not exposed to lithium. In this study, no statistical association between lithium in pregnancy and congenital heart defects was found.[23,30]

The cohort and case-control studies after the initial registry reports have found no significant association between first trimester lithium exposure and Ebstein's anomaly. These recent studies[18,31] suggest a more modest cardiovascular teratogenic risk for first trimester lithium exposure. A recent reevaluation of lithium exposure during pregnancy combined the two cohort studies and the four case-control studies. The findings supported an association between first trimester exposure to lithium and cardiovascular anomalies and found the risk is 10 to 20 times (between 0.05%–0.1%) more likely than in the general population.[23,31]

The potential adverse effects of lithium in utero are not limited to cardiovascular malformation. A case of cardiac arrhythmia before and after delivery occurred in an infant exposed to lithium throughout pregnancy; the condition completely resolved on the 12th postpartum day. The authors pointed out that bradycardia and irregularity of the fetal heart do not necessarily mean fetal distress if the mother is taking lithium.[32] Several groups have reported nontoxic goiters in the infants of mothers treated with lithium during pregnancy; mothers of these children also had nontoxic goiters.[27,33,34] Limited to case reports, a definitive relationship between lithium exposure during pregnancy and thyroid goiter has not been established.[23,35,36] A second group reports both nephrogenic diabetes insipidus and hypothyroidism in an infant exposed to lithium in utero.[23,37] A floppy baby syndrome characterized by cyanosis and hypertonicity has also been reported.[33,38,39]

Schou[27] and colleagues conducted a subjective, parental report, follow-up study on 60 children from the original lithium registry. They found that 83% of the children had normal development compared with a control group of 57 siblings of the group who had 89% normal development; this is not a statistically significant difference. Despite the evidence supporting lithium as a teratogen, it is important to note that these reports predated the introduction of extended-release lithium compounds, and it is unknown if the serum concentration peaks and troughs are more or less hazardous in pregnancy. The lithium data support a careful risk/benefit assessment and individualized treatment plan (design and rationale of these plans will be discussed later). It is also important to remember that the alternative pharmacologic treatments to lithium have significant teratogenic potential.

Use of Other Treatments During Pregnancy

Other than lithium and lithium compounds, the primary pharmacologic treatment options for women with bipolar disorder include valproic acid, carbamazepine, and newer anticonvulsant agents such as gabapentin and lamotrigine. The follow-up data on infant development after exposure to anticonvulsants, while more extensive than lithium, have conflicting reports. However, a recent study[40] failed to demonstrate alterations in the IQ of carbamazepine-exposed infants at 5-year follow-up.

Electroconvulsive therapy (ECT) should also be considered as an alternative treatment to medication exposure. The data on ECT exposure in pregnant women have been reviewed and, to date, the literature contains over 300 reports of ECT use during pregnancy with no clear evidence of teratogenic effects.[41] Miller, in 1994, suggested guidelines for minimizing potential adverse effects of ECT, including (1) positioning the patient in the left lateral decubitus position, (2) monitoring the fetus and uterus, and (3) limiting exposure to anticholinergic medications.[41] Finally, there are also reports of successful treatment for bipolar disorder by using thyroid hormone and calcium channel blockers.[41] The role of atypical antipsychotics as monotherapy in this population remains understudied. Teratogenic data on the use of anticonvulsants are primarily derived from their use in women who have epilepsy and are therefore subject to the potential confounds of a primary seizure disorder. Specifically, the risk of spina bifida associated with prenatal exposure to anticonvulsants is 15-fold higher than in the general population. Carbamazepine exposure during the first trimester is associated with a 0.5% to 1.0% risk of spina bifida, and valproic acid exposure is associated with a 1% to 5% risk.[42–45] Prospective

investigations have indicated that multiple anticonvulsants and higher plasma concentrations of anticonvulsants may enhance the teratogenic risk.[46] The teratogenic effects of anticonvulsants are not limited to neural tube defects, and numerous reports of both major and minor malformations have been documented.[47,48] The role of supplemental folic acid taken prior to conception and maternal body weight in the rates cited above are unclear.[49]

Pregnancy Summary

All medications that have documented monotherapy efficacy for patients with bipolar disorder are potentially teratogenic. The organ systems most likely to be affected by antimanic medications have started to develop prior to the patient's knowledge of the pregnancy. In contrast to anticonvulsants, lithium affords a narrow window of opportunity to taper medications, if appropriate, when pregnancy is detected, prior to the development of the affected major organ system.

LACTATION

The benefits of breastfeeding are well documented, and breast milk is supported as the ideal form of nutrition for infants by most professional organizations. Depending on geographic location, approximately 55% of postpartum women in the United States leave the hospital planning to breast-feed their baby. It is beyond the scope of this review to debate the merits of breastfeeding for women with bipolar disorder, but some women may insist on breastfeeding.

The use of lithium during lactation has been categorically discouraged in previous reports and is considered to be contraindicated by the American Academy of Pediatrics (1994).[50] Lithium, like all psychotropic medications, readily passes into breast milk and the nursing infant is exposed, yet there are remarkably few reports of lithium use during breastfeeding.[39,51–54] Nursing infants' serum lithium concentrations have been reported to be 10% to 50% of mothers' serum levels.[53,54] Goldfield and Weinstein, in 1973,[55] suggested that lithium not be used in breastfeeding women because lithium concentration in the breast milk approached that found in the maternal serum. Schou and Amdisen, in 1973,[52] studied the lithium concentration in the serum of infants who were exposed to lithium via breast milk. They found that the lithium concentration in breast milk was approximately half that found in the maternal serum. They also examined infant serum and found that during the first postpartum week the infant serum concentration was about 50% of the mother's serum concentration; after the first week, the infant concentration declined to about 33% of the maternal serum concentrations. In 1976, Sykes et al.[51] reported the case of a woman who had been taking 800 mg/day of lithium carbonate at conception. The dosage was reduced twice during pregnancy and the infant was mildly hypotonic for 2 days after birth. The mother chose to breast-feed. The infant's serum lithium level was similar to the mother's serum level at birth but fell to 0.03 mmol/L by the sixth postpartum day and increased only slightly once breastfeeding was established. The mother's serum and breast milk concentrations rose, but no appreciable rise in the infant's serum concentration was detected. The infant was assessed as having normal development after breastfeeding for 10 weeks. Linden and Rich in 1983,[56] stated that infants who are receiving lithium through breast milk should be monitored for hypotonia, lethargy, and cyanosis. While the data are limited, there is evidence that management of women who take lithium while breastfeeding warrants careful monitoring of the infant, especially the hydration status.

Valproic acid and carbamazepine are considered compatible with breastfeeding by the American Academy of Pediatrics (1994).[50] Alexander, in 1979,[57] reported the case of a woman who took sodium valproic acid in pregnancy and continued this treatment while breastfeeding. The serum concentration of valproic acid in the infant was of the same order as the mother's level at delivery, but fell to purportedly insignificant levels by the fifth day of life and was below the limits of detection at 29 days. Valproic acid was present in the breast milk on the fifth postpartum day at 50 mmol/L and fell to 21 mmol/L by postpartum Day 29. The authors suggested that sodium valproic acid would be found in the breast milk at a level between 5% to 10% of the maternal serum level, and no adverse sequelae were noted in the infant as a result of the breast milk exposure to valproic acid.

Transient cholestatic hepatitis in an infant, associated with carbamazepine use in pregnancy and lactation, was documented by Frey et al. in 1990.[58] The infant's mother took 600 mg/day of carbamazepine throughout the pregnancy and during the postpartum period. The child was admitted to the hospital at 3 weeks of age due to persistent jaundice that resolved after nursing discontinued. Carbamazepine-induced hepatitis has been noted previously in adults and children treated with the medication.[58] In lactating women, milk:plasma ratios of 0.24:0.69 have been reported along with infant serum concentrations of 1.7 μmol/L.[47] Merlob et al., in 1992,[59] reports the case of an infant exposed to carbamazepine in utero and through breast milk. The mother received 400 mg/day of carbamazepine throughout pregnancy and the postpartum period, and jaundice was noted in her infant on the first day of life.[59] The results of liver function tests were normal with the exception of a very high GGT (α-glutamyltransferase) that decreased slowly in the following postpartum days. The infant was fed only breast milk for 9 days, and then supplemental feeding was added. On postpartum Day 2, carbamazepine concentrations were 5.5 μg/mL in the maternal serum, 2.8 μg/mL in the breast milk, and 1.8 μg/mL in the infant serum. On postpartum

Day 63, concentrations were 6.5 μg/mL in the maternal serum, 2.2 μg/mL in the breast milk, and 1.1 μg/mL in the infant serum. The infant appeared to be developing normally at 2-, 4-, and 6-month follow-up visits.

Lactation Summary

The American Academy of Pediatrics Report (1994)[50] is of concern with respect to the available data on mood stabilizers during lactation. The sparse reports of lithium use, particularly when not also used in pregnancy, limits definitive conclusions. The ratios of breast milk concentration to maternal serum concentration observed for carbamazepine are similar to the ratios seen for lithium. The data on valproic acid demonstrate a decrease of excretion into breast milk and lower infant serum concentrations compared with maternal serum concentrations. For all mood stabilizers, the long-term follow-up data on breastfeeding exposure are limited.

Infant hydration is important in regard to lithium and lactation, but this issue does not make lithium an absolute contraindication. Advantages to lithium are that with hydration the serum concentration can be decreased rapidly, and the side effects are more clinically discernible. Both carbamazepine and valproic acid have the potential for serious or possibly lethal side effects, such as leukopenia and hepatitis, that, while admittedly rare, are difficult to detect prior to clinical symptomatology. The authors of this article typically do not encourage breastfeeding while taking mood stabilizers because of the need for invasive infant monitoring. When any psychotropic medication is used during lactation, the infant should be routinely monitored at a minimum frequency as often as an adult would be monitored since the infant is also exposed to the medication. The need to gather data on lithium excretion into breast milk, including time course of excretion, infant serum concentration, and incidence, if any, of adverse effects in the absence of in utero exposure, is underscored by the clinical data. The available data would indicate that the use of valproic acid during lactation is preferable to both carbamazepine and lithium. The use of novel agents or switching to a second agent with purportedly greater relative safety during lactation is not without risk. First, such changes may result in exposing the developing infant to a second medication (e.g., lithium in pregnancy and valproic acid for lactation), and there are no data on the safety of such multiple exposures. Changing the mother to a novel medication during the high-risk period may enhance the possibility of recurrent symptoms, thus increasing the risk by having both medication and mental illness exposure for the infant.

If medications are used in women who are breastfeeding, the infant is exposed and should have routine monitoring of the indices affected by the individual medication. The frequency of infant monitoring is unstudied; a reasonable approach would be monthly monitoring for 2 to 3 months, after any increase in maternal daily dose, or if side effects are observed in the infant. Despite the benefits of breastfeeding, a low threshold for suspending breastfeeding or complete weaning is recommended. The reports of recurrent psychotic symptoms in women who have postpartum-onset psychosis with return of the menstrual cycle underscore the need to monitor women closely throughout the first postpartum year.[60–62] Finally, postpartum women should be cautioned about subsequent conception while breastfeeding.

TREATMENT GUIDELINES

There are no risk-free treatment options for women requiring pharmacotherapy during pregnancy and lactation. The role of psychotherapy for the treatment of affective disorders during these periods is markedly understudied. The following guidelines for treatment of women with bipolar disorder during pregnancy and lactation are designed to minimize the risk of fetal/infant complications and maintain maternal mental health.

Treatment Begins Prior to Conception

Over 50% of pregnancies are unplanned. The easiest method of minimizing the risk of pregnancy exposure to medications is to assume that pregnancy is imminent if the reproductive system is intact. The treatment plan for women with bipolar disorder who are of reproductive potential should include the risk/benefit assessment for pregnancy. Regardless of medication choice, the clinician should (1) document the patient's birth control method, (2) document discussion of potential risks for pregnancy exposure, (3) encourage proper nutrition, exercise, and vitamin supplementation, (4) discourage the use of tobacco, alcohol, or excessive caffeine (> 300 mg/day), (5) inquire about the use of purportedly natural supplements and educate the patient about the lack of pregnancy outcome data on the majority of these agents, and (6) inquire about any plans for pregnancy and emphasize the need for prepregnancy consultation in the future. Medications such as lithium, carbamazepine, and valproic acid have well-documented clinical efficacy and data on their use during pregnancy and should be considered as first-line treatments for bipolar women who are of reproductive potential. The use of more novel agents, as first-line treatment or in polypharmacy, may increase the risk liability for pregnancy, and a personal or familial history of an affective disorder after childbirth should prompt the clinician to consider lithium as a first-line choice on the basis of the clinical data concerning prevention strategies.

The clinician should document the education of the prospective parents about the risk of mental illness in their offspring. The treatment plan for managing a woman with bipolar disorder during pregnancy needs to include a plan for the emergence of manic and/or depressive symptoms

in pregnancy and the postpartum period. The most important facet of preconception counseling is the patient's history including (1) severity of illness and impairment, (2) duration of remission, (3) information on medication-free periods, including duration of euthymia and/or factors precipitating recurrence or medication restart, (4) all prior treatments and response, (5) documentation of the patient's minimum effective serum concentration of antimanic agents, and (6) identification of symptoms or life events that have preceded prior episodes. Unfortunately, there are limited data about the course of bipolar disorder during pregnancy. In all cases, prenatal care, prenatal vitamins, proper nutrition, and strategies to eliminate toxic exposures should be initiated and the risk/benefit assessment documented. The clinician should discuss the treatment plan and rationale for decisions with the patient's obstetrical group to avoid conflicting information and establish a liaison with them for management.

Planned Conceptions

In women who have had either isolated episodes of mild-to-moderate severity or those with bipolar II disorder, medication discontinuation prior to conception may be a reasonable option. The medication should be tapered over 7 to 10 days after onset of the last menses preceding the desired conception time to avoid confusion with any premenstrual symptoms. Utereoplacental circulation is not established until Day 13 postconception; therefore, the risk of fetal exposure is minimal.[20]

Some women may be concerned about the risk of relapse if they do not conceive in the first month they are off medicine or if they have histories that do not support medication discontinuation. The clinician should make every effort to minimize fetal risks and document all discussions in the patient's medical record. Taking lithium affords an advantage over the anticonvulsants. Women can remain on lithium and monitor pregnancy status with home pregnancy tests weekly after ovulation. Once a positive pregnancy test is observed, the medication can be tapered over 3 to 5 days, thereby minimizing fetal exposure during cardiovascular development.

Women with brittle or recalcitrant bipolar disorder, for whom medication discontinuation and ECT are not reasonable options, should be maintained on the minimum effective dose. If possible, monotherapy is preferable; if supplemental medications are needed, there is some experience with the use of adjunctive haloperidol and clonazepam (Stowe ZN, 1997. Unpublished observation).

Inadvertent Conception on Medication

The most important guideline when a woman conceives while taking medication is to avoid panic, as the exposure has already occurred during the highest risk period in the majority of cases. Review the history, as described above, and discuss the risk/benefit assessment while the patient is euthymic. If the decision is to discontinue medications, taper the medications over 3 to 5 days. Abruptly stopping medications only enhances the probability of relapse and may confound the clinical picture should the patient experience withdrawal symptoms. A time line, starting at the last menstrual cycle and continuing throughout the pregnancy, that documents exposures should include (1) all prescription, over-the-counter, and natural medications, (2) any alcohol, tobacco, drug, or caffeine use, (3) date of prenatal vitamin initiation, and (4) obstetrical visits and laboratory results.

Management During Pregnancy, Labor, and Delivery

In women who successfully discontinue medication, the decision whether to empirically restart medication after the first trimester remains controversial. More than 50% of these patients may experience a recurrence of symptoms during the pregnancy, and if the history includes a risk of self-harm, protracted recovery time, or evidence that the support system cannot tolerate another episode, empirical treatment may reduce overall risk to both mother and fetus.

If the clinical decision is to treat with medication, it is important to treat effectively. Partial treatment or symptom control only increases the risk to the fetus by having fetal exposure to both medication and maternal illness. During pregnancy, a woman's glomerular filtration rate increases with creatinine clearance typically doubling. Therefore, medications such as lithium may be excreted more rapidly, and if medication dosage is not increased, serum levels may fall and enhance the risk of bipolar relapse.[56] While some authors have suggested that serum lithium levels should be monitored weekly during pregnancy, a more reasonable approach is monthly monitoring of medication levels, along with serum electrolytes and a thyroid panel.[22,56] The alterations in the thyroid panel (e.g., thyroid-stimulating hormone increased) during pregnancy makes interpretation difficult and abnormalities should prompt an endocrinology consult. Clinical interview topics concerning lethargy, cold intolerance, constipation, and dry skin should also be included, and any symptoms deserve further exploration. Sodium restricted diets, diuretics, and nonsteroidal anti-inflammatory agents (NSAIDs) should be used cautiously if the patient is treated with lithium. With decreased sodium, there is potential for toxicity for those patients taking lithium due to reabsorption of lithium in the renal system. Lithium readily crosses the placenta, and fetal serum concentration is similar to mother's serum concentration. Thus, toxicity in mother equals toxicity in fetus.[23,38,53,63] Women with first trimester exposure to mood-stabilizing medication should have a perinatal consultation with a level II ultrasound performed at 16 to 18 weeks gestation to assess fetal heart and vertebral body development.

The duration of labor is highly variable and can result in dehydration. At delivery, there will be an acute volume

change of approximately 40%. These time periods represent a high risk for rapid increases in serum medication concentrations. In contrast to earlier reports recommending a discontinuation of lithium on the actual delivery day, a treatment plan consisting of hydration, intravenous fluids, or decrease in dosage is more reasonable considering the high risk of recurrence in the postpartum period.[22,32,56] Monitoring of maternal serum after delivery, continued hydration, and avoidance of NSAIDs for pain management will minimize the risk of maternal toxicity.

Treatment During Postpartum Period and Lactation

The high rate of recurrence in women with bipolar disorder during the postpartum period underscores the need to consider prophylaxis with lithium for women who have completed a pregnancy, either with or without medication. Women with previous histories of postpartum mental disturbance are at an increased risk for such problems in subsequent pregnancies. Several reports exist on the occurrence of prepartum psychosis in bipolar patients in pregnancy and even new-onset illness has been observed.[23,64,65] Women who have successfully abstained from lithium during all or most of their pregnancy need to consider the reinstitution of lithium for prophylaxis of postpartum bipolar illness. History and severity of prior episodes should be considered in this decision. In the absence of lithium prophylaxis, Targum et al., in 1979, found a high risk (two of three patients) for developing mania or depression in the postpartum period for bipolar patients.[5] Reports describe the postpartum relapse rate of mental illness as high as 30% to 50%.[18,66] Prophylaxis may be accomplished by restarting medication from 1 to 2 weeks before delivery or immediately after birth. Carbamazepine and valproic acid have not been proven effective in postpartum prophylaxis.[7,23,67]

CONCLUSIONS

The literature for the natural course of bipolar disorder during pregnancy and the impact of untreated maternal bipolar disorder during pregnancy remains obscure. The risk/benefit assessment for these women will remain a complex clinical question, as no decision is risk free. Individualized treatment planning with potential pregnancy in mind and a realistic appraisal of the teratogenic potential of all pharmacologic options will minimize the risk for both the mother and baby. As new agents are introduced, the clinician should be reminded that the lithium data provide a known risk where other agents do not yet possess such data. The chance of minimizing exposure during periods of greatest teratogenic risk, the ability to rapidly adjust serum concentrations by the use of hydration, knowledge of the typical side effects prior to toxicity, and availability of the largest dataset for treatment and prevention of postpartum mental illness support the use of lithium in women during the childbearing years. The key point for the clinician is documentation and education. There are also several reproductive psychiatry programs across the United States, and a second opinion or consultation is always a reasonable option.

Drug names: carbamazepine (Tegretol and others), clonazepam (Klonopin), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), lithium sustained-release (Lithobid, Eskalith CR), valproic acid (Depakene and others).

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