Bipolar Disorder and Pregnancy: Risks Revealed

In this issue of the *Journal*, Viguera et al. report findings from a prospective study of the course of bipolar disorder during pregnancy. Retrospective studies have identified the postpartum period as a particularly high-risk time for relapse in women with bipolar disorder (1, 2). A prospective study by Cohen et al. demonstrated that the postpartum is a period of high risk for mood episodes in women with bipolar disorder, with markedly higher rates of mood episodes in women who were not treated with mood stabilizers compared with those who continued or restarted medication (3). Mood stabilizers are a complicated class of medication to consider using during pregnancy, due to the known teratogenic risks posed by some and the lack of safety data for use in pregnancy for others (4). Presently, due to inadequate data, it is difficult to offer patients who are pregnant a definitive and comprehensive account of the risks of untreated bipolar disorder, the risks and benefits of medication, and the predictors of relapse during pregnancy.

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In general, untreated maternal mood disorders during pregnancy are serious risk factors for the fetus, with impacts on pregnancy outcomes and infant/child development. Untreated depressive episodes are known to pose risks to the fetus (5). The specific risks of untreated maternal bipolar disorder are poorly understood and have received little study. By definition, untreated mania poses clear risk to the individual due to impulsivity and impaired judgment. Mania often results in poor self-care, which is dangerous to both mother and child.

In their current article, Viguera et al. compare relapse rates and time to recurrence for mood episodes between women who continue taking mood stabilizers during pregnancy and women who discontinue medication. The investigators enrolled 89 women with bipolar I or bipolar II disorder who were planning pregnancy and seeking psychiatric consultation in a specialized perinatal psychiatry program. Pregnant women were enrolled prior to 24 weeks gestation and included if they 1) were euthymic for at least 1 month prior to conception, 2) were receiving treatment with a mood stabilizer, or 3) had discontinued pharmacotherapy at least 6 months prior to pregnancy or within the first trimester. Women were followed through pregnancy and the postpartum year, and patients decided themselves whether to continue or discontinue medication. A majority of women experienced at least one mood episode during pregnancy (70.8%). The risk of recurrence was significantly higher in women who discontinued treatment with mood stabilizers. Women who discontinued medication also spent more time ill during pregnancy compared with women who continued medication. Several history of illness and treatment factors were associated with relapse during pregnancy. One of the treatment factors associated with increased relapse rates was rapid mood stabilizer discontinuation. The only pregnancy-related predictor of relapse was if the pregnancy was unplanned.

This study is groundbreaking, in that it is the largest prospective study of the course of bipolar disorder during pregnancy to our knowledge. The risk of recurrence was

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demonstrated to be extremely high during pregnancy, and greatest when medications were discontinued.

The finding that relapse rates were higher after rapid versus slow discontinuation of mood stabilizers is not surprising and is consistent with the literature in this area, including Viguera et al.'s previous retrospective study of relapse rates in pregnancy and the postpartum (1). However, this finding is profoundly relevant to clinical practice and invites us to consider a paradigm shift in the treatment of women with bipolar disorder of reproductive age. A large number of women suffer from bipolar disorders, as bipolar I disorder generally affects women and men with equal prevalence and bipolar II disorder disproportionately affects women. The onset of bipolar disorder is frequently in childhood and adolescence. When considering the chronic and recurrent course of bipolar disorder, optimal treatment for most women with this illness includes mood stabilizing medications for most, if not all, of their reproductive years.

Viguera et al. also found that rapid discontinuation of medication was associated with unplanned pregnancies, a scenario often seen in clinical practice. The authors take the well supported position that the practice of rapid discontinuation of psychotropic medication needs to be reassessed. The implications of this study affect most practicing psychiatrists. Assuming that women with bipolar disorder are similar to the general population, the great majority of patients with bipolar disorder of reproductive age will experience pregnancy and childbirth and will be faced with decisions about treatment during pregnancy. Psychiatrists should anticipate that unplanned pregnancies will occur during the course of treatment of women with chronic disorders such as bipolar disorder.

Pregnancies, including those that are not planned, need to be conceptualized as expected events that intersect with treatment course. Unfortunately, most health care providers are not trained to consider pregnancy as an expected event that is likely to occur during the course of treatment of a chronic and/or recurrent illness. Instead, psychiatrists and patients alike are frequently overwhelmed with fear and panic when a woman with bipolar disorder discovers she is pregnant. Concern about medication exposure for the fetus often precipitates abrupt discontinuation of mood stabilizers, with or without physician input. There are known teratogenic risks from treatment with some commonly utilized mood stabilizers in the first trimester, such as neural tube defects with valproate and carbamazepine and cardiovascular malformations such as Ebstein's anomaly with lithium (4). Especially in the case of neural tube defects with the use of anticonvulsants, the window of greatest concern is very early in pregnancy; by the time a woman discovers she is pregnant, the most serious period of risk for the fetus has frequently already passed. Therefore, by abruptly discontinuing medication in an attempt to protect her baby, a woman or her physician may unwittingly increase the risk of relapse for mood episodes, while having little impact on the teratogenic effects of medication exposure.

Routine treatment planning for female patients should systematically include a discussion regarding the scenario of unplanned pregnancy. In the case of an unplanned pregnancy, information from the treating physician about the risks of medication, as well as the risks of untreated bipolar disorder, would help avoid the panicked and fear-based decision making that typically occurs in this situation. This strategy may decrease the number of women who are subject to abrupt discontinuation of mood stabilizers during pregnancy.

As Viguera and colleagues acknowledge, their findings may not generalize to other clinical populations. This study was conducted in a specialty research program by leaders in the field. As it was a specialty program, patients either were referred by obstetricians or were self-referred. An overwhelming majority were Caucasian, educated, married, and employed outside the home. As noted by the investigators, despite these demographic characteristics, which may be associated with greater access to care and resources, patients still experienced a high relapse rate. Therefore, the reported risk of

recurrence during pregnancy in this study may actually underrepresent the risk in the broader population. In other clinical and more diverse populations of pregnant women with bipolar disorder, rates of relapse may indeed be much higher.

This study represents an excellent step forward in the understanding of bipolar disorder in women. This observational prospective study provides a greater understanding of the serious risk of relapse during pregnancy. As the authors state, they will present the postpartum data from the study population in a forthcoming report, which is expected to add further valuable insights into this important and understudied area of psychiatry.

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