Delving Further Into Discontinuation Risk: Addressing the Use of Mood Stabilizers During Pregnancy

TO THE EDITOR: We commend Adele C. Viguera, M.D., et al. for their excellent, much-needed study, published in the December 2007 issue of the *Journal*, on the risk of mood episode relapse in bipolar disorder during pregnancy (1). The study adds to their previous important contributions to the field and demonstrates the value of careful observational studies when obtaining randomized evidence is not feasible. In the spirit of wanting to glean as much clinically relevant information as possible from their valuable cohort, we have several questions regarding their findings.

First, the study cohort included women who discontinued the use of a mood stabilizer up to 6 months before conception. However, these women may have been substantially different from those who discontinued the use of mood stabilizers only after becoming pregnant. Furthermore, the total medication-free period for these women differs from the women who discontinued the use of medication after conception. Would it be possible to conduct a subanalysis to determine whether relapse rates differ among women who discontinue medication before versus after conception? Although sample size and statistical power might be diminished, such an analysis may provide some tentative information for women who are interested in discontinuing mood stabilizers proactively in order to minimize the risk of first-trimester exposure to the fetus (the period during which such medications appear to increase the risk of fetal malformations [2]). The results might also help researchers determine whether these two groups of women should be combined or separated in future studies.

In addition, the authors did not report the number of patients who discontinued medication before conception and also relapsed before conception. Was this number actually zero? If so, this suggests that the period around conception and beyond may be uniquely stressful for women with bipolar disorder.

Second, we applaud the authors for their thorough analysis of factors predicting relapse during pregnancy. However, their analysis appeared to combine women who discontinued the use of a mood stabilizer with those who continued receiving treatment. It seems that the more clinically relevant analysis (albeit less powered) would involve the investigation of predictors of relapse specifically among those subjects who discontinue the use of mood stabilizers. The results might help clinicians to more specifically counsel women who are interested in discontinuing mood stabilizers about their individual risk of mood episode recurrence.

Last, as the authors pointed out, there were differences among the two groups of women that potentially inflated the risk of discontinuing mood stabilizers. Although the authors controlled for some of these differences, there remained a significant difference between the groups in the number of psychotropic medications used, which suggests that there were potentially greater levels of relatively treatment-refractory illness in the group discontinuing medication. Is it likely that residual differences in the severity of bipolar disorder between those subjects who continued and discontinued mood stabilizers may explain some of the risk associated with mood stabilizer discontinuation in this study?

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Mood Stabilizer Discontinuation in Pregnant Women With Bipolar Disorder

TO THE EDITOR: In their article, Dr. Viguera et al. concluded that the overall risk of at least one recurrence of a new mood episode during pregnancy was 71% among women who discontinued the use of a mood stabilizer 6 months prior to conception to 12 weeks postconception (relative to women who continued treatment with a mood stabilizer). As indicated in the article, the two groups of women differed with regard to several characteristics.

In the multivariate modeling or risk-factors-adjusted analysis, only some of the predictors of recurrence were included. It is not clear to us whether all the statistically significant predictors were covaried. For example, rapid cycling, which is a predictor of recurrence, was not entered as a covariate, although it did differ between the two groups at baseline.

We are also puzzled by the way the authors presented the issue of current adjunctive antipsychotic use. There was a large difference between the two groups of women. The use of current adjunctive antipsychotics was reported in 21% of subjects who discontinued the use of a mood stabilizer and in 41% of those who continued treatment. This difference is close to significance (p=0.07). The list of predictors of recurrence did not include the adjunctive use of antipsychotics, nor was it mentioned whether adjunctive use was associated with the risk of recurrence. Given the likelihood that antipsychotics may be mood stabilizers, should not this factor have received attention in the data analysis?

Additionally, it would be necessary to know which subjects discontinued the use of a mood stabilizer more than 1 month