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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Dr. Isakovich reports no competing interests. Dr. Smith receives funding from Forest Research Institute for two research studies on antidepressant medication; he has also received an award from the American Psychiatric Institute for Research and Education/Janssen Scholar Program; and he is currently receiving funds from a pilot grant from the American Foundation for Suicide Prevention.

This letter (doi: 10.1176/appi.ajp.2008.08010072) was accepted for publication in February 2008.

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

prior to conception, since the natural course of the illness would likely suggest that the longer period of time an individual is medication free, the higher the likelihood of recurrence. It can be hypothesized that if the data analysis had taken into consideration the length of time since discontinuation, the results might have shown that discontinuing the use of a mood stabilizer close to conception may produce different recurrence rates.

Symptoms of change in energy level, appetite, concentration, and psychomotor retardation may all occur in normal, healthy pregnancies and may not be associated with major depression. How did the analysis adjust for this potential confounder? This may explain the much greater frequency of depressive episodes relative to manic episodes. In addition, the nature of a woman's previous episode may predict the type of relapse experienced during pregnancy.

Finally, were there any untoward conditions in the newborn children that were part of this study? For many clinicians, the recommendation whether to discontinue or continue medication during the first trimester is influenced not only by the severity of maternal illness but also the perceived risk to the exposed fetus.

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This letter (doi: 10.1176/appi.ajp.2008.08010036) was accepted for publication in February 2008.

Dr. Viguera Replies

TO THE EDITOR: We thank Drs. Isakovich and Smith and Dr. Mazer-Poline et al. for providing us with the opportunity to clarify several points about our findings pertaining to illness recurrence in pregnant women with bipolar disorder. They raise the question of which variables were included in the multivariate model, including the proposed indices of illness severity. We used Cox modeling to adjust for covariates in our primary survival analysis in order to test our hypothesis that discontinuation of mood stabilizers was a strong predictor of time-to-recurrence. We reported using forward selection of covariates associated with recurrence or time-to-recurrence; however, many of these covariates were not sustained in multivariate modeling. Specifically, prior rapid cycling, adjunctive antipsychotic use, or use of ≥2 psychotropic agents did not remain significantly associated with recurrence latency in multivariate modeling, whereas discontinuation of a mood stabilizer remained strongly associated with shorter time-to-recurrence.

In regard to potential predictors of recurrence, specifically among women who discontinued the use of a mood stabilizer, our analysis yielded the same predictors of recurrence noted for the overall cohort, with the exception of past suicide attempts, which was no longer statistically significant. Similarly, results from multivariate regression modeling were unchanged. In addition, we found little difference in recurrence risk among women who discontinued the use of mood stabilizers before conception (N=19; 88.4% [95% CI=74.9%–96.1%; p=0.33]) versus after conception (N=43; 78.9% [95% CI= 54.4%–93.9%]; mean time off mood stabilizer=11.2 weeks). While the slightly lower recurrence risk among women who discontinued the use of a mood stabilizer before versus after conception may seem counterintuitive, it is important to consider the rate of taper during treatment discontinuation. Indeed, rapid discontinuation was a significant predictor of an even greater and earlier risk of recurrence compared with the gradual discontinuation of a mood stabilizer. At closer analysis, a higher proportion of women who discontinued the use of a mood stabilizer before conception gradually discontinued the use of medication compared with those who discontinued medication after conception (84% versus 26%, respectively). This difference is most likely attributable to whether the pregnancy was planned or unplanned. Not surprisingly, we found that unplanned pregnancy was associated with a greater likelihood of rapid discontinuation of treatment with a mood stabilizer (unplanned pregnancy: 23/24 [95.8%] versus planned pregnancy: 12/59 [20.3%]; Fisher's exact= p<0.0001).

Dr. Mazer-Poline et al. also raise the thought-provoking question regarding the extent to which somatic symptoms that are commonly encountered during pregnancy might account for the reported high rates of recurrences of bipolar disorder in early pregnancy, particularly of depressive and dysphoric mixed states. We acknowledge the challenges of differentiating the normative somatic complaints of pregnancy from symptoms of depression. Indeed, none of the available scales or diagnostic assessments for depression or mania has been validated in pregnant populations. However, a major strength of our study was the determination of the primary outcome variable (i.e., recurrence) using the Structured Clinical Interview for DSM-IV (SCID) mood module, which remains the current gold standard for diagnosing a new major depressive episode, mania, hypomania, or mixed states. In our study, the SCID mood module was administered by an experienced and trained rater, blinded to treatment status. As we commented in our article, some of the excess of depression we observed may have been accounted for by including subjects with bipolar II disorder, but we also reported a similar excess of depressive-dysphoric symptoms among bipolar I disorder subjects as well (depressive-dysphoric: 40.9% versus mania/hypomania: 19.6%). Alternatively, pregnancy itself may be a selective precipitant for depressive-dysphoric recurrences. A strong association of depressive morbidity in pregnancy among women with affective illness was observed by Louis-Victor Marcé more than150 years ago (1) as well as in more recent studies (2–4).

We agree that for many clinicians, whether to recommend the discontinuation or maintenance of any medication during the first trimester of pregnancy is strongly influenced by the potential risk to the fetus and associated liability risks to the clinician. Indeed, adverse outcomes of childbirth are not uncommon. In our study sample, which included 85 live births, there were two stillbirths. Both stillbirths involved the use of lithium throughout pregnancy, with one being the result of Ebstein's anomaly (a cardiac malformation associated with lithium exposure). However, no other occurrences of ob-