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The Last Therapeutic Orphan: The Pregnant Woman

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The pregnant woman is perhaps the last true therapeutic orphan. Because of the ethical, medicolegal, and fetal safety concerns regarding pregnant women, few pharmacokinetic, pharmacodynamic, or clinical trials are conducted during pregnancy.

—Stika and Frederiksen (1)

Episodes of bipolar disorder or psychosis during pregnancy present substantial risks to the woman, her fetus, and her family (2). Pharmacotherapy is the mainstay of treatment for these disorders (2). The clinical challenge is to judge whether the disease burden is reduced sufficiently by pharmacotherapy to offset the risks of drug exposure and support a more favorable reproductive outcome. This assessment is established by risk-benefit decision making that is individualized for the woman on the basis of her unique clinical course, including responsiveness to drug treatment and the frequency and severity of the mood and cognitive instability and the resulting functional impairment (3). Information from case series or grouped data must be utilized to estimate the risk for the individual woman.

Bergink and colleagues (3) provide novel data from a naturalistic study of women seeking consultation for the treatment of serious mental illness during childbearing. Seventy women seen at their specialized perinatal psychiatry service had either bipolar disorder (N=41) or psychotic episodes only in the postpartum period (N=29) according to the DSM-IV definition of onset within 4 weeks of birth. The women with a history of postpartum psychosis had no manic or psychotic symptoms outside the postpartum period. However, having depressive episodes did not exclude women from this category, and six of the 29 women with postpartum psychosis also experienced depressive episodes (V. Bergink, personal communication, 2012). The investigators constructed treatment plans for the two groups of women and prospectively collected information on their illness courses across pregnancy and after birth.

None of the 29 women with past episodes of postpartum psychosis experienced recurrences during pregnancy, even though they were not prophylactically treated with medication. In contrast, the 41 women with bipolar disorder experienced double the rate of recurrence when untreated (four of 10, or 40.0%) as when treated (six of 31, or 19.4%). Conversely, about 80% of the treated women and 60% of the untreated women with bipolar disorder *remained well* during pregnancy. After childbirth, all women with a history of postpartum psychosis

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(100.0%) remained well if they elected drug prophylaxis at delivery (20 of 29) and 55.6% (five of nine) of the women who declined prophylaxis were episode free. Among the 31 bipolar women who remained stable during pregnancy, 24 of 26 (92.3%) of those who used prophylaxis upon delivery remained well, and four of the remaining five women (80.0%) who declined prophylaxis remained well.

The observations of Bergink et al. (3) and the literature (2, 4) support their recommendation that women with postpartum psychosis be monitored without medication through pregnancy for recurrence and provided with preventive pharmacotherapy at delivery. However, the authors' data compel tempering their contention that "patients with bipolar disorder require continuous prophylaxis throughout pregnancy and the postpartum period to effectively reduce their peripartum relapse risk." Preventive pharmacotherapy invokes a tension between providing medication to all patients, many of whom would not become ill if unmedicated, and preventing episodes in the ones who would become ill without prophylaxis. Routine prophylactic medication during pregnancy for women with bipolar disorder would result in 100% of women being exposed when 60% would have remained well without treatment. The strength of the case for preventive drug treatment depends on its efficacy in reducing the clinical and functional severity of the disorder balanced with the reproductive risks of the pharmacotherapy offered.

Further advancement of the care for pregnant women with serious mental illness involves identification of the clinical, biological, and/or genetic characteristics of women who are at higher (and lower) risk for recurrence during pregnancy, to allow targeting of prophylactic treatment for the most vulnerable candidates. Some investigators have observed a subgroup of women who experience mood stabilization of bipolar disorder during pregnancy (2), while others have reported that pregnancy has no protective effect on the risk for episodes (5). A useful subgroup observation made by Bergink et al. (3) is that women with both bipolar disorder and episodes of postbirth psychosis had a higher risk for peripartum recurrence (50.0%) than women with bipolar disorder who had no previous postpartum episodes (27.3%).

For American psychiatrists, the prevention program provided by Bergink et al. (3) to their patients is enviable! The new mothers were hospitalized for the first week postpartum in a private room and monitored for symptom recurrence daily. Night-time newborn feedings were provided by staff to promote uninterrupted sleep, with lorazepam prescribed at bedtime. The infants of women receiving prophylaxis were fed formula because of the "current uncertainty regarding breast-feeding during maternal lithium treatment." Certainly breast-feeding, with its inherent sleep disruption, is a modifiable risk factor that contributes to mood destabilization. However, an unanswered question is whether the provision of lithium fully or partially offsets this risk. Five of the nine women with postpartum psychosis who declined prophylaxis (and presumably breast-fed their infants) remained well; how many of the four women who had recurrences might have remained well with lithium prophylaxis?

Published case series provide data to inform lithium treatment for women during lactation. The percentage of the mother's maternal serum level that appeared in the infant ranged from

10% to 17% (6) and 11% to 56% (7) in a total of 14 pairs, and infant development was normal. The infants in these series were also exposed continuously to lithium during fetal life. The breast-fed babies of women with postpartum psychosis who are treated prophylactically only after birth would have substantially less lithium exposure through breast milk alone. Additionally, research on the myriad short- and long-term health benefits of breast-feeding for both mother and child is accumulating. Major public health campaigns, such as the recent Surgeon General's Call to Action to Support Breastfeeding (<http://www.surgeongeneral.gov/topics/breastfeeding/index.html>), educate women about the multiple risks of formula feeding. An example is that hospitalization for lower respiratory tract disease in the first year of life is more than 250% higher among formula-fed infants than among babies exclusively breast-fed at least 4 months.

When women elect maintenance medication across childbearing, optimal dosing of lithium is critical to maximize symptom reduction, but it is also challenging because of the rapidly changing metabolic states during pregnancy and immediately after birth (1, 2). Pharmacokinetic and pharmacodynamic studies have been encouraged by the Food and Drug Administration (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072133.pdf>) to guide evidence-based dose management during pregnancy with the goal of improving outcomes for women with serious illnesses and their offspring.

Writing a prescription for a pregnant woman results from the physician's judgment that her health is best served by treatment of the disorder, yet our literature is largely focused on negative outcomes related to drug treatment, rather than its positive impact on disease (2, 8). The work of Hunter et al. (9) in this issue demonstrates that infants born to mothers with anxiety disorders have impaired P50 auditory gating, a marker of attentional processing in young infants. The intriguing finding was that maternal antidepressant treatment improved sensory gating in the offspring of anxious mothers. Elsewhere in the issue, Karlsson et al. (10) describe an association between high levels of maternal antibodies directed at gliadin (from wheat) and later nonaffective psychoses in offspring. This observation suggests the possibility that a dietary intervention, limiting gluten intake during pregnancy, might prevent serious mental illness in offspring. Clearly, the inclusion of pregnant women in observational and therapeutic medical research has largely untapped public health potential for society (8).

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