Lithium During Pregnancy

Lithium therapy is widely recommended as a first-line treatment for bipolar disorder, with demonstrated efficacy in both depression and mania, as well as in reducing the risk of suicide (1). During pregnancy, lithium is well established as an effective mood stabilizer and protective for women at high risk of relapse during the postpartum period (2–4). Among all mood stabilizers, lithium has the largest evidence base for efficacy in the peripartum period.

During pregnancy, the benefits of medication need to be carefully weighed against risks for the mother, for the fetus, and of neonatal complications, as well as risks during breast-feeding. Accordingly, significant efforts have been made to define these risks for all medications available to pregnant women, including psychopharmacological medications. For example, both valproate and carbamazepine have been clearly associated with congenital abnormalities (5). In contrast, the data regarding lithium have proven more difficult to interpret. Some studies have reported higher incidences of cardiotoxicity and Ebstein's anomaly in children born to women taking lithium during pregnancy, whereas this association was not observed in other studies (6–10). In 2012, McKnight et al. (11) reported the outcome of a meta-analysis, which concluded that the odds of lithium exposure in cases of Ebstein's anomaly were not significantly elevated. Specifically, they stated: "The evidence that exposure to lithium is teratogenic is quite weak, and our findings accord with the notion that the risk has been overestimated" (11). Importantly, however, the authors also cautioned that the strength of their conclusion was limited by the small number of cases and that further studies with larger numbers of cases would be needed to establish this result more definitively.

It is against the backdrop of this unresolved issue of paramount importance to peripartum mental health care that Diav-Citrin et al. (12), in this issue of the *Journal*, have now provided novel data from a prospective cohort study of lithium use during pregnancy. Pregnant women who contacted the Israeli Teratology Information Service were enrolled over a 6-year period. In total, 183 lithium-exposed pregnancies were included and prospectively followed during pregnancy and the postpartum period. The majority of patients had bipolar disorder or mania (67.4%), while the remaining patients were diagnosed with either unipolar depression or a primary psychotic disorder. Of these 183 patients, 121 women also used concurrent psychiatric medication. In the same time period, 72 disease-matched pregnant women were enrolled. These women with bipolar disorder were either untreated during pregnancy or taking antipsychotics and/or antidepressants. An additional comparison group consisted of 748 nonteratogenic-exposed pregnancies.

The rate of congenital anomalies did not differ between the three groups (lithium-exposed: N=8/140 [5.7%], bipolar disorder: N=3/61 [4.9%], and nonteratogenic exposure: N=24/711 [3.4%]). There was no evidence for an increase in persistent cardiovascular anomalies in the lithium-exposed group compared with the nonteratogenic exposure group. However, when spontaneously resolving cardiovascular anomalies were considered as well, the difference became significant. In total, there were five cardiovascular

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anomalies in the lithium-exposed group (N=5/123, of which two resolved spontaneously) compared with four anomalies among the nonexposed pregnancies (N=4/711, of which two resolved spontaneously).

In an attempt to increase the power of the study, the authors added 16 lithium-treated patients from Australia, 13 lithium-treated patients from Canada, and a combined 142 nonteratogenic exposure pregnancies from both centers. Upon integration of the combined data set, offspring from the lithium-exposed group had significantly higher incidences of serious cardiovascular and noncardiovascular anomalies. Importantly, however, the authors acknowledge that a disproportionate contribution of anomalies reported through the Australian service, suggestive of a detection bias, may have resulted in an overestimation of the risk of lithium during pregnancy.

Moreover, no differences in birth outcome were observed in lithium-exposed pregnancies compared with nonlithium-exposed pregnancies when considering only the subset of women with bipolar disorder. One possibility for this discrepancy might simply be the reduced statistical power of the bipolar subsample. Alternatively, the differential risk between lithium-exposed bipolar patients and nonlithium-exposed pregnancies might have resulted from the underlying bipolar disorder, rather than lithium. Supportive for the latter hypothesis, Bodén et al. (13) demonstrated in a population-based cohort study that bipolar disorder, whether treated or not, was associated with an increased risk of adverse pregnancy outcomes. In their study, there was no significant difference in birth outcome among 320 bipolar pregnant women treated with mood stabilizers, compared with 554 bipolar women without mood stabilization (13).

Evidence suggests that lithium should be the first choice in the prophylactic treatment of most patients with bipolar disorder, including women in their childbearing ages.

The association between lithium use and serious cardiovascular anomalies observed by Diav-Citrin et al. at the Israeli Teratology Information Service did not reach statistical significance. However, "not statistically significant" does not mean "not clinically relevant." A collaborative discussion is clearly required with every patient regarding the risks and benefits of lithium treatment during pregnancy, including both cardiovascular anomalies and neonatal complications, in order to establish a patient-centered treatment plan. The recommendation of Diav-Citrin et al. that all women receiving lithium during pregnancy should undergo fetal echocardiography and level-2 ultrasound examination appears very well justified given the current best evidence. Moreover, this research group adds considerable weight to the current literature in demonstrating a significantly higher rate of preterm delivery in lithium-exposed pregnancies, for which additional vigilance is warranted by psychiatrists and obstetricians during the third trimester (9, 10). Interestingly, preterm delivery has also been observed in untreated bipolar patients as well, in both the present study and the literature (13).

Some patients treated with lithium reported obstetric complications such as gestational diabetes, polyhydramnios, hypertension, toxemia, oligohydramnios, and polyuria/polydipsia. Unfortunately, these complications were not recorded for the comparison groups, and therefore the relative risk with lithium exposure cannot be assessed. Polyhydramnios and polyuria/polydipsia are well-known side effects of lithium during pregnancy; while for the other complications, the underlying bipolar disorder as well as polypharmacy are important confounding factors.

Notably, 66% of the women in the lithium group were taking concurrent psychiatric medication, despite the recommendation in the bipolar clinical guidelines for mood stabilization during pregnancy using a single medication.

In the present study, the total mean daily dose of lithium was 906 mg. However, information on the corresponding serum levels was not provided. In general, lithium blood levels should be maintained as low as possible and based on the personal history of the patient. Furthermore, and particularly during pregnancy, it might be useful to use twice-per-day dosing to avoid the higher peak lithium levels that result from once-daily dosing. The 2007 National Institute for Health and Care Excellence guidelines advise clinicians to monitor lithium levels monthly from the 20th week of gestation and then weekly beginning 4 weeks before delivery. There is no need to discontinue lithium in late pregnancy or during delivery, as long as the serum levels are within the therapeutic interval. Acute lithium toxicity of the neonate has been described in several case reports and observational studies. Therefore, pediatricians should carefully monitor babies during the first 48 hours for fetal goiter, hypotonia, bradycardia, arrhythmias, systolic murmur, hypothermia, cyanosis, tachypnea, and poor suck reflex, together known as "floppy baby syndrome" (14). Importantly, in all reports the infants recovered fully (5, 11).

After delivery, preconception dosing of lithium can be immediately resumed. There is a strong rationale for a relatively higher target plasma level (≥0.8 mmol/L) during the postpartum period because of the very high risk of bipolar relapse. Lithium levels should be monitored together closely with thyroid function. Breast-feeding during lithium use has been described only in small case series (15). The benefits of breast-feeding need to be weighed against the sleep disruption for the mother and the exposure of the child to lithium through breast milk.

Evidence suggests that lithium should be the first choice in the prophylactic treatment of most patients with bipolar disorder, including women in their childbearing ages (1, 16, 17). The ultimate decision regarding lithium treatment during pregnancy and the postpartum period should be made by the patient, following a collaborative discussion with her psychiatrist and obstetrician (18).

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