

# **Lithium Use in Pregnancy and the Risk of Cardiac Malformations**

Hello! Jim Phelps here with a Quick Take for the Psychopharmacology Institute. Our next clinical question is: How safe is lithium in early pregnancy?

We have 2 new large studies that appeared in the last year to examine this question. It's an important clinical question because recent guidelines from the CANMAT—the Canadian Mood and Anxiety Disorders Treatment Program—and the International Society for Bipolar Disorders placed lithium very high on the list of treatments for acute mania and maintenance.

I think the context is important as well. Up until further recently, as many as 50% of all pregnancies were unplanned in the United States, and recent data from the Centers for Disease Control and Prevention show that figure is improving. It's down to, in some regions of the country, one-third of pregnancies, but in other parts of the country it is even a little higher than 50% of unplanned pregnancies. So, we can help patients plan their pregnancies and their treatments when they anticipate those pregnancies. These new data help us understand the risk that lithium presents when we're having those discussions. We've been telling patients that there is a risk of cardiac malformations, including Ebstein's anomaly, when lithium is present in the first trimester of pregnancy. It's still true, but both studies suggest that the risk is lower than previously suggested. So, when we were using figures, for example, on the order of a 1 in 1000 increased risk, we were in the right ballpark, and we can continue to stay in that ballpark.

A few details from the studies. The first, from Elisabetta Paterno and colleagues published in the *New England Journal* in the middle of 2017, looked at a large database, the Medicaid database in the United States, over 10 years. Of 1.3

million pregnancies, 650 included lithium in the first trimester. And their bottom line is, there is a signal, but it's smaller than previously thought. Importantly, they pointed out what appears to be a dose-relationship with lithium: At doses greater than 900 mg, it is associated with a 3 times increase in risk and in doses of 600 mg or less, no increase in risk relative to when there is no lithium present.

The second study has basically the same results but much more recent, August 2018, in *\*Lancet Psychiatry\** from Trine Munk-Olsen and colleagues. This is a meta-analysis of 6 countries' data. And, again, there is a signal, but it's a risk that is smaller than previously thought. I'll summarize with a quote from those authors: "Our results and those of Patorno, et al., jointly suggest that the absolute risk of malformations is much smaller than reported in earlier studies."

I think, interestingly, before their own paper came out in *\*Lancet Psychiatry\**, Dr. Munk-Olsen and colleagues wrote a letter to the editor in reply to the *\*New England Journal\** article from Patorno. And they emphasized then, I'll quote this as well, "These findings do not imply or support discontinuation of lithium if pregnant or planning pregnancy." In other words, these findings—meaning those of Patorno—and the subsequent findings from their own group do not suggest that we should be telling patients to discontinue lithium if they're planning on becoming pregnant.

Now, I know that, clinically, that's a different matter. Talking with a patient, we try to present some data around risk and then assess the patient's level of concern. These risk data are just a part of that conversation. But the good news is that the new data support our previous conception of lithium having a very low risk in this setting, though not zero.

## **Abstract**

## **Lithium Use in Pregnancy and the Risk of Cardiac Malformations**

Elisabetta Patorno, M.D., Dr.P.H., Krista F. Huybrechts, Ph.D., Brian T. Bateman, M.D., Jacqueline M. Cohen, Ph.D., Rishi J. Desai, Ph.D., Helen Mogun, M.S., Lee S. Cohen, M.D., and Sonia Hernandez-Diaz, M.D., Dr.P.H.

**BACKGROUND:** There has been concern that exposure to lithium early in pregnancy may be associated with a marked increase in the risk of Ebstein's anomaly (a right ventricular outflow tract obstruction defect) in infants and overall congenital cardiac defects, but data are conflicting and limited.

**METHODS:** We conducted a cohort study involving 1,325,563 pregnancies in women who were enrolled in Medicaid and who delivered a live-born infant between 2000 and 2010. We examined the risk of cardiac malformations among infants exposed to lithium during the first trimester as compared with unexposed infants and, in secondary analyses, with infants exposed to another commonly used mood stabilizer, lamotrigine. Risk ratios and 95% confidence intervals were estimated with control for psychiatric and medical conditions, medications, and other potential confounders.

**RESULTS:** Cardiac malformations were present in 16 of the 663 infants exposed to lithium (2.41%), 15,251 of the 1,322,955 nonexposed infants (1.15%), and 27 of the 1945 infants exposed to lamotrigine (1.39%). The adjusted risk ratio for cardiac malformations among infants exposed to lithium as compared with unexposed infants was 1.65 (95% confidence interval [CI], 1.02 to 2.68). The risk ratio was 1.11 (95% CI, 0.46 to 2.64) for a daily dose of 600 mg or less, 1.60 (95% CI, 0.67 to 3.80) for 601 to 900 mg, and 3.22 (95% CI, 1.47 to 7.02) for more than 900 mg. The prevalence of right ventricular outflow tract obstruction defects was 0.60% among lithium-exposed infants versus 0.18% among unexposed infants (adjusted

risk ratio, 2.66; 95% CI, 1.00 to 7.06). Results were similar when lamotrigine-exposed infants were used as the reference group.

**CONCLUSIONS:** Maternal use of lithium during the first trimester was associated with an increased risk of cardiac malformations, including Ebstein's anomaly; the magnitude of this effect was smaller than had been previously postulated. (Funded by the National Institute of Mental Health.)

### **Reference**

Paterno, E., Huybrechts, K. F., Bateman, B. T., Cohen, J. M., Desai, R. J., Mogun, H., Cohen, L. S., & Hernandez-Diaz, S. (2017). [Lithium use in pregnancy and the risk of cardiac malformations.](#) *New England Journal of Medicine*, 376(23), 2245-2254.