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Affective Disorders and Lithium Use During Pregnancy

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Affective disorders are classified into two major categories, unipolar and bipolar. Unipolar disorders have recurrent major depressive episodes. Bipolar disorders involve recurrent periods of depression and mania (manic-depressive illness). The latter psychosis tends to be episodic, with a propensity for depression, but also exhibits one or more striking periods of enhanced alertness, great energy, flights of fancy, and other typical symptoms of mania. This RISK||NEWSLETTER will discuss the differences between unipolar and bipolar disorders and then focus on the effects that lithium may have on a pregnancy.

GENETIC EVIDENCE

Although the mode of inheritance for affective disorders is unknown, family studies clearly differentiate the bipolar from the unipolar type and indicate a strong genetic predisposition for affective disorders.

Relatives of a bipolar proband have a higher risk of affective disorders than the general population; some will be bipolar, though most will be unipolar. Affected relatives of a unipolar proband will almost always be bipolar. Relatives of an early-onset proband are at greater risk than relatives of late-onset. Female first degree relatives of a bipolar proband are 1.5-2.0 times more frequently affected than male first degree relatives. No difference between the sexes in frequency of disease is observed in relatives with unipolar disorders. When both parents are affected with a bipolar disorder, each child is at a 50-75% risk of developing an affective disorder. Genetic counseling of individuals at risk for affective disorders is done using empiric recurrence risks (see table below).

LITHIUM

The effect of lithium during pregnancy on the developing fetus is a concern because of its increasing use as a treatment of bipolar disorder. In 1968, a registry of lithium exposed pregnancies was established in Denmark. This registry was later extended internationally and revealed a possible association between lithium exposure and congenital heart disease (Weinstein, 1976;

Schere, 1973). Nora et al (1974) first described the association of Ebstein's anomaly with antepartum lithium exposure. Ebstein's anomaly is the congenital downward displacement of the tricuspid valve into the right ventricle. In their study of 733 women, there were only 2 women on lithium and both delivered children with Ebstein's anomaly. These results proved to be significant and unlikely due to coincidence, since the incidence of this anomaly is 1 in 20,000. These results suggest that infants of women treated with lithium during pregnancy are at risk for Ebstein's anomaly approximately 400 times greater than the general population. Another report from the international registry included data

on a total of 225 infants born to women treated with lithium at least during the first trimester of pregnancy (Weinstein, 1976). Congenital anomalies were apparent in 25 (11.1%) of these children, including 18 (8.0%) infants with cardiovascular defects and 6 (2.7%) with Ebstein's anomaly. The data from the registry is biased toward the overestimation of adverse outcome according to Cohen et al but this information has been used to guide clinical practice for the last 20 years (Cohen et al, 1994). A prospective multicenter study conducted in Canada followed 138 first trimester lithium exposed pregnancies. There was no overall increase in birth defects, but one case of Ebstein's anomaly was found among the exposed fetuses (Jacobson, 1992).

EMPIRIC RISKS FOR AFFECTIVE DISORDERS GENERAL POPULATION(%)

Unipolar Bipolar

Female 5-9 1

Male 3-4 1

FIRST DEGREE RELATIVES

Risk to Relatives(%)

Patient Unipolar Bipolar

Unipolar 7-19 0.3-2

Twins Unipolar Bipolar

Identical 40 65

Fraternal 11 15

In contrast, there are studies which suggest that lithium exposure does not seem to cause Ebstein's anomaly (Kallen, 1988; Zalstein, 1990). At the Fourth International Conference of Teratogen Information Services Jacobson et al (1991) presented their results of a prospective study on lithium exposure during first trimester and pregnancy outcome. They reported that of the 122 pregnant women who consulted teratogen information services because of their lithium exposure, there was no increase in incidence of adverse pregnancy outcome compared to a control population. None of these children were born with any form of congenital heart disease (Jacobson et al, 1991). Four case control studies testing the possible association between in utero exposure to lithium and Ebstein's anomaly did not demonstrate an increased incidence of cardiovascular deformities. These studies were performed with cases of Ebstein's anomaly identified through the International Clearinghouse for Birth Defects Monitoring Systems, the U.S. Center for Disease Control and Prevention's Birth Defects Monitoring Program, the Hospital for Sick Children, Toronto, Ontario, and the Motol Teaching Hospital in Prague, Czechoslovakia. Controls were drawn from the same resources. None of the mothers of the 207 children with Ebstein's anomaly were exposed to lithium during pregnancy. Each of these studies had the statistical power of 97% or greater to detect a 400-fold increase in the risk of Ebstein's anomaly in association with maternal exposure during pregnancy. The fact that no association was observed suggests that the initial estimate of the teratogenic risk to the fetus was inflated, and that the true risk is lower than previously suggested (Cohen et al, 1994).

CLINICAL IMPLICATIONS

Bipolar disorders affect approximately 1% of the general population. Women are at greatest risk during childbearing years (Reifman, 1980). Women with severe illness must make the decision either to take a medication that potentially could be teratogenic to their fetus or to suffer the morbidity of their disorder. The previous mentioned studies have prompted clinicians to reevaluate the guidelines of treatment for these women.

Cohen et al (1994) suggested that the following guidelines be considered for treating women with lithium. He recommended that careful contraceptive practices for all women of childbearing age should be encouraged and the need for lithium prophylaxis be evaluated. In women with single episodes of

affective instability and long intervening periods of well-being, tapering and discontinuation of lithium prophylaxis prior to pregnancy should be attempted. If possible, lithium-free well-being should be maintained for the entire pregnancy with the reintroduction of lithium during the second and third trimester, if necessary.

In women with severe bipolar disorder in whom discontinuation of lithium prophylaxis poses a substantial risk of increased morbidity, Cohen et al suggests that one temporarily discontinue lithium therapy for a period coinciding as closely as possible with that of embryogenesis. Reintroduction of lithium and/or treatment with antipsychotic agents should be considered if clinical deterioration occurs.

In women with severe bipolar disorder in whom discontinuation of lithium prophylaxis poses an unacceptable risk of increased morbidity, it may be necessary to maintain lithium therapy throughout pregnancy.

Other considerations for women who take lithium during all or part of the first trimester of pregnancy include the provision of reproductive genetic risk counseling as early in pregnancy as possible. Furthermore, prenatal diagnosis by fetal echocardiography and high-resolution ultrasound examination at 16-18 weeks gestation should be offered.

SUMMARY

Careful family planning and proper genetic counseling on the risks of lithium therapy during pregnancy are essential components in the care of women who have bipolar disorder and wish to conceive. Gradual tapering of the lithium dose is advisable as recent data has shown that a relapse is delayed if dosage is reduced slowly rather than abruptly (Faedda, 1993). If discontinuation of lithium is undesirable to pregnant women due to the morbidity risk, then appropriate reproductive genetic counseling and prenatal diagnosis should be offered. Lithium treatment during the second and third trimesters is not expected to be associated with an increased risk of malformations. For patients who discontinue use of lithium during the first trimester and whose condition begins to deteriorate, reintroduction of the drug for the remainder of the pregnancy is acceptable. High-resolution ultrasound examination and fetal echocardiography at 16-18 weeks gestation should be available for women who were treated with lithium during their first trimester. Patients should be made aware that the risk of fetal malformations with first trimester lithium treatment is somewhat greater than the general population risk. The best estimate of the risk of major congenital malformations among offspring of lithium treated women was approximately 4-12%, as observed in cohort studies (Kallen, 1988; Jacobson, 1992). In contrast, the prevalence of congenital anomalies in the untreated control group in these studies was 2-4%. Women being treated with lithium because of an affective disorder have frequently been counseled to avoid pregnancy or terminate pregnancies that do occur. Recent research in this area points to a more modest risk of teratogenic effects with first trimester exposure than originally estimated. Based on the updated risk estimates, with proper counseling and prenatal testing, many patients and physicians may want to reevaluate their options.