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## DRUGS, PREGNANCY, AND LACTATION

# Yet More Reproductive Safety Data on SSRIs

Over the last 5 years, several studies analyzing the reproductive safety of the SSRIs, individually and as a group, have been published in the United States and elsewhere. Earlier studies that failed to show an association between first-trimester exposure to SSRIs and an overall increased risk of major congenital malformations were typically small cohort studies; subsequent meta-analyses of the cohort studies have also failed to show an increased risk, which has been reassuring.

The cohort study is the gold standard for evaluating the teratogenic potential of drugs. However, such a study is limited by the difficulty in enrolling enough exposed subjects to demonstrate a statistically significant difference between the two groups (which is particularly true for relatively rare outcomes that can easily be missed).

Recently, several large case-control studies have questioned the safety of SSRIs with respect to teratogenic risk. These case-control studies have included an analysis of records from a large managed care organization, which found an increased risk of heart defects in the babies of women who were prescribed paroxetine (Paxil) during pregnancy, compared with the babies of women prescribed other antidepressants during pregnancy. Another study, using data from the Swedish Medical Birth Registry, also found an increased risk of cardiac defects among infants with first-trimester exposure to paroxetine.

Two large case-control studies published in June represent the latest efforts to use birth defect surveillance programs to refine our understanding of the reproductive safety of SSRIs. Based on their size, these studies might be expected to refine the risk estimate for congenital malformations following fetal exposure to SSRIs, but these investigations had divergent results.

The National Birth Defects Prevention Study compared 9,622 infants with birth defects with 4,092 control infants born in the United States from 1997 to 2003 and found no significant association between use of any SSRI from 1 month before to 3 months after conception and congenital heart defects or most other birth defects analyzed.

There was, however, a significantly increased risk for anencephaly (odds ratio 2.4), craniosynostosis (OR 2.5), and omphalocele (OR 2.8) associated with SSRI use in early pregnancy; these are birth defects that have not been associated with in utero exposure to SSRIs in previous studies. The relationship was particularly strong with paroxetine (N. Engl. J. Med. 2007;356:2684-92).

But no associations were identified between maternal SSRI use in early pregnancy and these three anomalies or congenital heart defects overall in the accompanying

# Diabetes Not Linked to Specific Birth Defects

CHICAGO — Pregnant women with diabetes have a two- to four-times higher risk of having a child with a birth defect, but a review of a national birth defects registry does not show that any one type of defect is associated with diabetes, Dr. Adolfo Correa said at the annual scientific sessions of the American Diabetes Association.

The review looked at data from the National Birth Defects Prevention Study, which had reports on 9,778 cases of live births with birth defects and 4,086 control live births, said Dr. Correa of the division of birth defects and developmental disabilities at the Centers for Disease Control and Prevention, Atlanta.

The analysis found a significantly increased risk in 25 of 37 categories of defects, with odds ratios of 5.0 or higher for 17 categories. However, no one category stood out. The highest odds ratio was for sacral agenesis, but out of 25 cases, only 9 involved mothers with diabetes.

"Pregestational diabetes is associated with an increased risk for a wide variety of defects," but the study found only weak associations, he said.

**—Timothy F. Kirn**

case-control study of 9,849 infants with birth defects and 5,860 infants with no birth defects enrolled in the Slone Epidemiology Center Birth Defects Study, at Boston University (N. Engl. J. Med. 2007;356:2675-83). However, there was a significant association between the use of sertraline (Zoloft) specifically and both omphalocele (odds ratio 5.7) and septal defects (2.0).There was also a significant association between paroxetine exposure and right-ventricular outflow tract obstruction defects (odds ratio of 3.3). It should be noted that the number of actual exposures in these studies to a specific SSRI was particularly small, fewer than 10 actual reported exposures.

Where do these two important studies leave the patient and the clinician? Despite the divergent findings, both studies suggest that the absolute risk of overall major congenital malformations or even particularly rare malformations is extremely small, as pointed out by the respective authors and the accompanying editorial (N. Engl. J. Med. 2007;356:2732-3). For example, the Slone study authors point out that the estimated prevalence of right-ventricular outflow tract obstruction defects is about 5.5 cases per 10,000 live births, so the risk of this defect would be only 0.2% if an SSRI increased the risk fourfold. It also has been noted that in such studies the search for numerous outcomes associated with potentially numerous exposures may result in a finding by chance.

Clinicians and patients deciding about treatment during pregnancy will need to continue to make decisions on a case by case basis, weighing the risks and benefits using the available, incomplete data on the relative risks of exposure to the medicine or to depression, and the patient's wishes.

In addition, clinicians and patients should consider that, while we have not yet absolutely quantified the risk of prenatal exposure of SSRIs (which might not be achievable), a critical finding influencing treatment decisions is that untreated depression during pregnancy dramatically increases risk for postpartum psychiatric relapse. In fact, perhaps nothing trumps the importance of sustaining maternal emotional well-being during pregnancy, even given the small absolute risks that may be associated with an individual SSRI during pregnancy. ■

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