Study Probes Safety of Biologics in Pregnancy

BY AMY ROTHMAN SCHONFELD

PHILADELPHIA — Women with rheumatic disease who took etanercept during pregnancy were three times more likely to have a child with a major malformation than a disease-matched comparison group, judging from interim results from a small sample.

Most of the malformations were isolated, and no patterns of birth defect were apparent, according to Christina Chambers, Ph.D., who presented the findings from the Autoimmune Diseases in Pregnancy Project being conducted by the Organization of Teratology Information Specialists (OTIS) at the annual meeting of the American College of Rheumatology.

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DR. CHAMBERS

The OTIS Study is a prospective observational cohort study with the purpose of evaluating effects of autoimmune diseases and their treatment on pregnancy outcomes and fetal development. Recruitment of pregnant women began in 2000, and is projected to continue through 2015. Current recruitment stands at 944, with a goal of 1,500, explained Dr. Chambers, an associate professor of pediatrics and family and preventive medicine at the University of California in San Diego.

To be enrolled, the women must have current diagnoses of rheumatoid arthritis (RA), juvenile rheumatoid arthritis, ankylosing spondylitis, psoriasis and psoriatic arthritis, or Crohn's disease. After birth, the infants are followed for up to a year.

"Evaluating pregnancy outcomes following medication exposure is a not a situation that lends itself to conducting a randomized controlled trial for obvious ethical reasons," said Dr. Chambers. While the literature contains case reports, the OTIS Project is designed to give clinicians the evidence-based information they need to counsel patients who are pregnant or considering becoming pregnant.

At the time of this progress report, outcome was available for 115 women with RA who had been exposed to etanercept, compared to 55 disease-comparison controls. Outcome was available for 42 women with RA who were exposed to adalimumab, compared with 58 disease-matched women and 84 healthy controls.

The percent of live births was higher in those treated with etanercept compared with those with similar rheumatic diseases (92% vs. 85%) and fewer spontaneous abortions occurred in the etanercept-treated group (4% vs. 11%). There were no ectopic pregnancies in either group. One stillbirth was reported in the etanercept cohort and none in the controls. Preterm deliveries were more common in women who were taking etanercept (23% vs. 13%). Taking the drug did not seem to be related to the average birth weight in full-term infants.

Of the major malformations among all pregnancies enrolled in OTIS, 12% (14 of 114) were reported in the etanercept group, compared with 3.8% (2 of 53) in the disease-matched controls. "Typically we would see a specific pattern of malformation with a medication that truly causes defects, but our results indicate that most of the defects were isolated with no apparent patterns," she said.

For those exposed to adalimumab, the percentage of live births was lower in those receiving the drug (88%) compared with those with similar autoimmune illnesses (93%) and healthy controls (92%). The rate of spontaneous abortions also was higher in the adalimumab-treated cohort (12%) compared with the disease-matched (5%) and healthy cohorts (1%).

Preterm delivery was higher in both the adalimumab-treated (14%) and disease-matched comparison (17%) groups versus healthy controls (4%). Mean birth weight was approximately 300 grams less in full term infants whose mothers had received adalimumab compared with healthy controls but similar to full-term infants in the disease-matched comparison group. Rates of major malformations were similar (4%-5%) in all groups.

"Firm conclusions await the accumulation of target sample size for adalimumab and etanercept and multivariate analysis," she said. ■

DRUGS, PREGNANCY, AND LACTATION

Fetal Safety of Paroxetine

For at least a decade after approval in the United States in 1992, the selective serotonin reuptake inhibitor (SSRI) paroxetine (Paxil) was believed to be safe during pregnancy, based on data from studies of a small number of patients. The studies included one of women from teratogen information services in North America, including Motherisk, which did not find an increase in major malformations among 267 women who took paroxetine, fluvoxamine, or sertraline during pregnancy compared with controls (JAMA 1998;279:609-10).

Over the next several years, more studies on pregnancy outcomes after in utero exposure to paroxetine were reported, with no dramatically different conclusions. In 2005, however, the manufacturer came to the Food and Drug Administration with data from a registry that appeared to suggest an association between prenatal exposure to paroxetine and a higher-than-expected rate of congenital cardiac malformations.

BY GIDEON KOREN, M.D.

Considering the common occurrence of depression in pregnancy and the potential for the dire consequences of untreated depression during pregnancy, it is critical for clinicians to examine the emerging evidence closely.

When considering the reproductive safety data on paroxetine specifically, the earlier data were from teratogen information services, where pregnant women who contacted the services were followed prospectively for birth outcomes. These were relatively small studies lacking the statistical power to show small increases in malformation rates.

More recent studies using administrative databases, linking claims information on drugs prescribed during pregnancy to records of pregnancy outcomes, provide much larger numbers of patients, but with the cost of poorer quality of data, as discussed here.

With these types of studies that looked at outcomes associated with first-trimester exposure to paroxetine and to other SSRIs, we began to see some different and contradictory results: Some studies found an association between paroxetine exposure and an increased risk of cardiac malformations, in particular ventricular septal defects (VSD). But others did not find this association, and in fact suggested an increased risk for cardiac malformations with other SSRIs, such as sertraline or citalopram. There have also been several meta-analyses, again with mixed results.

Therefore, the picture is very confusing. But there is consensus on one point: If there is a risk, it is very small.

I am among those researchers who have doubts about the veracity of the signals generated from administrative databases, which I believe suffer from major sources of uncontrolled bias, such as ascertainment bias. Consider the following example: While all SSRIs are used to treat depression, paroxetine has been used preferentially to also treat anxiety disorder. There are studies showing that the children of women with anxiety are much more likely to be tested for malformations, and hence, more likely to find the most common of them all—the ventricular septal defect.

In a meta-analysis of literature between 1985 and 2006, my associates and I determined that first-trimester use of paroxetine was associated with a slight increase in cardiac malformations. The use of ultrasound during pregnancy, however, was 30% higher among the women who were on antidepressants during pregnancy, and the babies of women who were on SSRIs had about twice as many echocardiograms during their first year of life than the babies of women who were not on an SSRI during pregnancy. In addition, about four times as many women on paroxetine were using it to treat anxiety than were women on other SSRIs (Clin. Ther. 2007;29:918-26).

Until we settle this issue of ascertainment bias in this situation, we cannot be certain that in utero exposure to paroxetine is associated with an increased risk of cardiac malformations.

What also needs to be considered is that VSDs are the most common congenital malformation in nature and most VSDs close spontaneously, so when children in the control groups are examined later, because their parents are less concerned, the malformation may not be detected.

For me, the most convincing evidence that paroxetine does not increase the risk of cardiovascular malformations comes from an international study of infants exposed to paroxetine in the first trimester—cases that had been prospectively followed at teratogen information services around the world, including Motherisk. The cardiovascular malformation rate among the 1,174 infants exposed to paroxetine in utero and among an unexposed group of infants was the same—0.7%—approaching the rate of 1% in the general population (Am. J. Psychiatry 2008;165:749-52). This prospective study obviated the uncontrolled biases of administrative databases.

Women who may be treated with paroxetine during pregnancy should know that the possible risk associated with paroxetine is controversial and that there is no question they should be treated if they need treatment. In addition, cardiovascular malformations during pregnancy can be ruled out with appropriate testing.

At Motherisk, we are following women who have taken paroxetine during pregnancy, and we point out to them and to their treating physicians that untreated depression carries with it serious maternal and fetal risks, including higher rates of life-threatening postpartum depression. ■

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