Biologics in Pregnancy Up Malformation Risk

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.

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 began in 2000, and is projected to continue through 2015. Current recruitment stands at 944, with a goal of 1,500, said Dr. Chambers, an associate professor of pediatrics and family and preventive medicine at the University of California in San Diego.

Pregnant women are typically enrolled in the study before they reach 20 weeks of gestation. 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.

Many participants are referred to the OTIS coordinating center, where they undergo multiple interviews and review of their symptom management. After birth, the infants are followed for up to a year, during which time they are assessed by their pediatricians, undergo blinded dysmorphological examination by OTIS physicians, and are photographed.

"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 with 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%). 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%).

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. The defects included displaced stomach with epispadias and congenital eye defect; ventricular septal defect with peripheral pulmonic stenosis; pyloric stenosis; hypospadias; ventricular septal defect with patent foramen ovale and patent ductus arteriosus; volvulus; patent foramen ovale; atrial septal defect with patent ductus arteriosus; microcephaly; congenital hypothyroidism; and an unspecified heart defect. Three abnormalities—Noonan syndrome, Turner syndrome, and Down syndrome—were genetic or chromosomal. "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," Dr. Chambers 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%). There were no ectopic pregnancies or stillbirths in the drug-treated group.

Preterm delivery was higher in both the adalimumab-treated (14%) and disease-matched comparison (17%) groups compared with 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 (from 4% to 5%) in all groups and within the range of expected numbers in the general population, said Dr. Chambers. ■

MY TAKE

Answering Your Patient's Questions

There are really sparse data on the safety of biologic agents in women who are pregnant. We currently are in a situation where controlled randomized trials typically are not appropriate, yet pregnant women are using these medications. The OTIS project is a prospective, observational cohort study that should shed light on whether biologics are safe for women who are pregnant. However, it will still be several years before all results are in and the data can be statistically analyzed. In the meantime, what can you tell your patients about the use of biologics if they are pregnant or plan to become pregnant?

BY CHRISTINA CHAMBERS, PH.D.

Q: If I take a biologic, will it be more difficult to become pregnant?

A: Information is very limited, but to date neither preclinical data nor clinical data indicate that becoming pregnant is more difficult.

Q. If I do become pregnant while on a biologic drug, do I have a chance of having a baby with a birth defect?

A. One of the principles of teratology is that known teratogens tend to cause specific patterns of malformations. To date with the limited information available, neither animal nor human data suggest that the risk for a specific pattern of defects is increased over baseline if you take a biologic agent while pregnant. While preliminary results from the OTIS project have noted that more malformations occurred in the offspring of women taking etanercept, the defects were varied and isolated.

Q. If I do become pregnant while taking this drug, will my child's immune system be compromised?

A. There are limited human data available for rituximab. To date, the results of the OTIS study do not indicate an increase in opportunistic infections, hospitalizations, or malignancies in the infants of women who have taken etanercept or adalimumab.

Q. If I do become pregnant while taking a biologic agent, do I have to discontinue the drug or can I safely continue to take the drug throughout pregnancy?

A. We really don't know the answer. In the OTIS project, approximately half of women on etanercept or adalimumab remain on the medication into the second or third trimester.

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