ASK THE EXPERT

Much to Learn About Biologics in Pregnancy

Biological targeted therapies have revolutionized the treatment of autoimmune diseases in recent years, leading to significant improvements in the quality of life and clinical outcomes of patients with such conditions as rheumatoid arthritis, ankylosing spondylitis, psoriasis, Crohn's disease, and others. And while the safety of these agents has been the focus of multiple randomized controlled trials, one of the most vulnerable segments of the patient population—pregnant women—have been "orphaned" with respect to this issue, according to Christina D. Chambers, Ph.D.

CHRISTINA D. CHAMBERS, PH.D.

"There are really sparse data on the safety of biologic agents in women who are pregnant. We are currently in a situation where controlled randomized trials are not appropriate typically, yet pregnant women with autoimmune diseases are using these medications," Dr. Chambers said. The lack of adequate pregnancy safety information for these medications, together with the need to make appropriate treatment decisions and to communicate risk information to pregnant women are among the most challenging and critical issues in women's health, she said.

In an effort to shed light on the safety of all medications in pregnant women, the Organization of Teratology Information Specialists (OTIS), a non-profit organization made up of individual teratology information services located throughout the United States and Canada, is dedicated to providing accurate evidence-based, clinical information to patients and health care professionals about exposures during pregnancy and lactation, Dr. Chambers noted (www.otispregnancy.org).

In particular, the OTIS Autoimmune Diseases in Pregnancy Project, a prospective, observational cohort study designed to evaluate the effects of autoimmune diseases and treatment on pregnancy outcomes and fetal development, promises to answer many questions about the safety of biologic agents during pregnancy, Dr. Chambers said. She noted that the current recruitment for the project, which began in 2000 and will continue through 2015, is close to 950, with an ultimate goal of 1,500.

The primary objective of the OTIS autoimmune study is to evaluate the effect of certain autoimmune disease medications when used in the first trimester of pregnancy with respect to major structural birth defects of newborns, said Dr. Chambers. Secondary outcome measures include the assessment of effects of autoimmune disease medications with respect to potential minor malformations, spontaneous abortion, stillbirth, and preterm delivery; the measurement of pre- and post-natal fetal and infant growth and developmental milestones up to 1 year of life; and the evaluation of risk for malignancies and serious opportunistic infections in offspring up to 1 year of life, she explained.

Although some interim data from the OTIS autoimmune study have been made available, "it will be several years before all results are in and the data can be statistically analyzed," Dr. Chambers stressed. In the meantime, women with rheumatologic diseases are taking biologic drugs, and those who are pregnant or planning to become pregnant have many questions about their safety.

In this month's column, Dr. Chambers offers advice about how to answer patients' questions based on the safety information available to date.

Rheumatology News: Is there an increased risk of birth defects in babies exposed in utero to a biologic drug?
Dr. Chambers: 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 one takes a biologic agent while pregnant. While preliminary results from the OTIS autoimmune study have noted that more malformations occurred in the offspring of women taking etanercept, the defects were varied and isolated. I am aware of one case out of 41 etanercept- or infliximab-exposed pregnancies that were identified in a published analysis of the U.S. Food and Drug Administration Adverse Event Reporting database that involved the VACTERL (vertebral anomalies, anal atresia, cardiovascular anomalies, tracheoesophageal fistula, esophageal atresia, renal and or radial anomalies, limb abnormalities) pattern of malformations. Fortunately, we have identified no cases of VACTERL association in any infants born to women enrolled in the OTIS Autoimmune Diseases Pregnancy Project.

RN: Should women whose rheumatologic disease is well controlled with a biologic agent who are planning to conceive discontinue the drug?
Dr. Chambers: There are no compelling data to suggest that many of these medications pose a risk, and there are also insufficient data to date to establish pregnancy safety. For this reason, the decision regarding discontinuation of medication must be made in conjunction with the woman's health care provider in order to weigh the benefits of continuing the medication or risks of discontinuation against any risks to the pregnancy that are yet unknown. Additionally, for many women, conception can take months. The risk of uncontrolled or poorly controlled disease during this pre-pregnancy period should be taken into consideration.

RN: For women taking biologic agents who do become pregnant, can the drug be safely continued throughout the pregnancy?
Dr. Chambers: We do not know the answer to this. In the OTIS study, approximately half of women on etanercept or adalimumab remain on the medication into the second or third trimester.

RN: Will in utero exposure to a biologic compromise the baby's the immune systems?
Dr. Chambers: There is limited human data available to answer this question for women taking rituximab. For women who have taken etanercept or adalimumab, the results of the OTIS study to date do not indicate an increase in opportunistic infections, hospitalizations, or malignancies in their infants.

RN: Is it advisable for women to take, or restart taking, a biologic drug while breastfeeding?
Dr. Chambers: There are preclinical data that suggests biologics can be detected in breast milk. There are limited human data on this. In the few case reports in the literature, levels of etanercept, adalimumab, and infliximab have either been undetectable in human milk, or undetectable in infant sera once transplacental dosing was cleared. There has been no suggestion that biologics taken by the mother cause developmental problems in children.

RN: What, if any, are the known long-term consequences of exposure to biologics in utero or during breastfeeding?
Dr. Chambers: This is currently unknown. In the OTIS project, developmental milestones up to 1 year of age are being followed.

—Diana Mahoney

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Vitamin D Deficiency Found to Be Prevalent in RA

BY MITCHEL L. ZOLER

PHILADELPHIA — Patients with moderately active rheumatoid arthritis had a high prevalence of vitamin D insufficiency and deficiency in a prospective study of 1,160 patients in the Veterans Health Administration system.

Based on this finding, the "testing of vitamin D levels is mandatory" in patients with RA, Dr. Gail S. Kerr said at the annual meeting of the American College of Rheumatology.

In addition, although "more evidence is needed to determine the exact role of vitamin D in patients with rheumatoid arthritis, we advocate vitamin D replacement as an additional, non-DMARD [disease-modifying antirheumatic drug] component of RA management," said Dr. Kerr, chief of rheumatology at the Washington D.C. VA Medical Center.

The study used patients who were enrolled in the U.S. VARA (Veterans With RA) registry, which began in 2002 at eight VHA centers around the United States. The registry protocol included drawing a blood specimen from patients at the time of their enrollment. Patients entered the registry at similar rates throughout the year, which meant that no seasonal bias skewed their vitamin D levels.

The VHA provides medical care to more than 67,000 people with RA. Investigators plan to expand the registry to enroll 12,000 patients eventually.

The current analysis focused on the 1,160 enrolled patients for whom vitamin D levels were available. Measurement of serum vitamin D was by a radioimmunoassay. Insufficiency was defined as a level of 30 ng/mL or lower; deficiency was 20 ng/mL or lower.

Patients' average age was 64 years; 91% were men, 77% were white, and 17% were black. Their average duration of RA was 12 years, and they generally had moderately active disease. Their average body mass index was 28 kg/m^2.

Low vitamin D levels were common, with 85% of the patients meeting the definition of insufficiency, and 45% with a deficient level.

The average vitamin D level for the entire group was 22 ng/mL.

A multivariate analysis showed that patients who were younger and not white, as well as those with higher tender joint counts and higher body mass index, had a higher risk for having vitamin D insufficiency or deficiency.

Low vitamin D levels were also significantly linked with being positive for anti–cyclic citrullinated protein antibodies, and with a higher number of comorbidities, Dr. Kerr concluded. ■

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