Methotrexate May Curb Girls' Ovarian Function

BY BRUCE JANCIN

FROM THE ANNUAL MEETING OF THE AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

DENVER – Chronic methotrexate therapy may harm the future fertility of girls and young women being treated for rheumatoid arthritis or juvenile idiopathic arthritis, based on preliminary findings from an observational study.

'As early as 1 year of age, these girls are placed on methotrexate weekly for years and years and years.'

DR. COOPER

"The biggest issue is that rheumatologists have become much more aggressive in their therapy for these young girls with juvenile idiopathic arthritis in the last 5-10 years. As early as 1 year of age, these girls are placed on methotrexate weekly for years and years and years," Dr. Amber R. Cooper said at the meeting.

The study findings suggest a need to alter how physicians counsel patients and their families on this score in light of emerging evidence that long-term cytotoxic therapy with methotrexate may threaten the oocyte pool, she said.

Thus far, 168 females aged 4-49 years have been recruited for the ongoing study from pediatric and adult rheumatology clinics. Every 3-4 months they undergo measurement of serum anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), inhibin B, and other indicators of ovarian reserve. In addition, transabdominal ultrasound is performed annually by sonographers blinded as to the patients' treatment regimen in order to assess ovarian volume and antral follicle count, explained Dr. Cooper of Washington University in St. Louis.

Among the study participants, 55% have juvenile idiopathic arthritis, formerly called juvenile rheumatoid arthritis, and 43% have rheumatoid arthritis. The rest have psoriatic arthritis or undifferentiated spondyloarthropathies. The subjects' mean age at diagnosis was 18.6 years, while at enrollment in the fertility study they averaged 25.4 years of age. Forty-three percent were on methotrexate or the related drug leflunomide, 12% were on a tumor necrosis factor (TNF) antagonist, 30% were on both, and 15% were on other agents, mainly corticosteroids, hydroxychloroquine, or sulfasalazine.

The primary study end point was change over time in AMH level, widely considered to be the best indicator of ovarian reserve. At enrollment, the median AMH level was 2.25 ng/mL in patients on methotrexate or leflunomide, 1.65 ng/mL in those on a TNF antagonist, 2.42 ng/mL in patients on both, and 2.54 ng/mL in patients on other agents.

A multifactorial analysis showed that patients on methotrexate/leflunomide were the only ones who showed a progressive decline in AMH with increasing time on therapy. In addition, patients on methotrexate or methotrexate plus an anti-TNF biologic had significantly lower antral follicle counts than did other patients.

A key question is whether patients on chronic therapy take an irreversible hit to the primordial oocyte pool, or if their oocyte count will eventually recover after they come off methotrexate, Dr. Cooper said.

Dr. Cooper's study is funded by a grant from the Society for Reproductive Endocrinology and Infertility. She had no other relevant financial disclosures. ■

Type 1 Genetic Variants Also Tied to Juvenile Arthritis

BY MICHELE G. SULLIVAN

FROM THE ANNALS OF THE RHEUMATIC DISEASES

Two genetic polymorphisms now appear to be associated with juvenile idiopathic arthritis as well as type 1 diabetes or celiac disease.

The finding lends credence to a growing idea that genetic variability in common loci can predispose a child to different autoimmune disorders, wrote Dr. Anne Hinks of the University of Manchester, England, and colleagues.

"The approach of targeting variants associated with other autoimmune diseases is already yielding insights into the genetic complexity underlying susceptibility to this serious childhood disease," Dr. Hinks and her coauthors wrote (Ann. Rheum. Dis. 2010;69:2169-72).

The researchers compared DNA from 1,054 patients with juvenile idiopathic arthritis with that of 3,129 healthy controls. All the subjects were white. The study focused on 13 single nucleotide polymorphisms (SNPs) that had already had confirmed associations with type 1 diabetes or celiac disease.

One SNP on the preferred translocation partner in lipoma (LPP) gene (rs1464510) was significantly associated with juvenile idiopathic arthritis. Another SNP located in the ataxin 2 (ATXN2) gene was marginally associated with JIA, but the association was not significant.

The SNP lying in the LPP domain is particularly interesting, the authors noted, because that gene has a confirmed association with celiac disease. LPP is integral in cell migration and adhesion and is a substrate of tyrosine phosphatase. It also has been linked to Ras signaling, a process important in cell growth, differentiation, and survival.

A third SNP (rs17810546) located in the interleukin 12A gene (IL12A) was significantly associated with enthesitis-related arthritis. The IL12A gene has already been associated with celiac disease. The association with arthritis was a strong one, Dr. Hinks and her colleagues noted, but there were no other associations with any other JIA subtype.

The IL12A gene exerts a number of important influences, including encoding a cytokine necessary for the differentiation of T cells and T cell–independent induction of interferon gamma, the authors noted. ■

VITALS

Major Finding: Two genetic variants with known associations to type 1 diabetes or celiac disease also predispose to juvenile idiopathic arthritis.

Data Source: DNA from 1,054 patients with juvenile idiopathic arthritis was compared with that of 3,129 healthy controls. Thirteen single nucleotide polymorphisms (SNPs) that already had confirmed associations with type 1 diabetes or celiac disease were investigated.

Disclosures: The study was sponsored by Arthritis Research U.K. and supported by the NIHR Manchester Biomedical Research Council. Genotype data used was funded by grants from the Medical Research Council and the Wellcome Trust. The authors said they had no relevant financial disclosures.

Cow's Milk Formula May Boost Later Risk of Type 1 Diabetes

BY MARY ANN MOON

FROM THE NEW ENGLAND JOURNAL OF MEDICINE

Children at risk for type 1 diabetes showed fewer signs of beta-cell autoimmunity for up to 10 years if they were fed a highly hydrolyzed casein formula rather than conventional cow's milk–based formula during infancy.

This indicates that "a preventive dietary intervention aimed at decreasing the risk of type 1 diabetes may be feasible," said Dr. Mikael Knip of the University of Helsinki, Finland, and his associates.

Their pilot study – the Trial to Reduce IDDM in the Genetically at Risk (TRIGR) – was not sufficiently powered to render a definitive conclusion about preventing progression to overt type 1 diabetes. However, a larger ongoing TRIGR study is now underway in 15 countries and is designed to address that issue, the investigators noted.

The pilot study involved 230 neonates born at 15 Finnish hospitals between 1995 and 1997 whose HLA genotypes showed susceptibility to type 1 diabetes and who had at least one first-degree relative with the disorder. The newborns were randomly assigned in a double-blind fashion to receive for at least 6 months either an extensively hydrolyzed casein-based formula (Nutramigen) or a control cow's milk–based formula made to smell and taste like the intervention formula.

Both formulas were offered only when breast milk was unavailable. Breast-feeding was encouraged, and mothers breast-fed at their own discretion and without modifying their diets.

Blood samples were obtained periodically to test for five autoantibodies.

The intervention formula was linked with a significant decrease in risk of seropositivity for islet-cell antibodies, the tyrosine phosphatase-related insulinoma-associated 2 molecule, or to at least one of the five autoantibodies assessed, which also included insulin antibodies, and antibodies to glutamic acid decarboxylase, and zinc transporter 8, Dr. Knip and his colleagues said (N. Engl. J. Med. 2010;363:1900-8).

By 10 years of age, 6% of children in the intervention group and 8% of those in the control group developed type 1 diabetes. This difference was nonsignificant, but the study was not designed to show significance of this measure, they added. ■

VITALS

Major Finding: Neonates who received casein-based formula were significantly less likely to develop signs of beta-cell autoimmunity by age 10 years than were those who received standard cow's milk–based formula.

Data Source: A multicenter Finnish pilot study in 230 neonates randomly assigned to receive an intervention or a control formula for at least 6 months, then followed for up to 10 years.

Disclosures: Funding was by the Academy of Finland, the European Commission, the Juvenile Diabetes Foundation, the Novo Nordisk Foundation, and several other nonindustry sources. Infant formulas were provided by Mead Johnson Nutrition. The researchers had no conflicts of interest.

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