Fetal T Cells Unaffected by Intrauterine Steroid Exposure

BY BRUCE JANCIN
Denver Bureau

VIENNA — Prolonged intrauterine exposure to high-dose dexamethasone appears to be largely devoid of clinically significant adverse effects on normal T-cell development when evaluated up to a dozen years later, Paolo Airo, M.D., said at the annual European congress of rheumatology.

This has been a controversial issue. Some physicians are concerned that prolonged intrauterine exposure to corticosteroids might steer T-cell differentiation within the fetal thymus in a direction that predisposes to clinical immune dysfunction. They point to an increased rate of hospitalizations for infectious diseases during the first years of life in children with a history of prenatal steroid therapy for prematurity.

But a corticosteroid effect is only one of a number of plausible explanations for such an association, said Dr. Airo of the University of Brescia (Italy).

To examine the effect of prenatal high-dose steroids on the T-cell component of the immune system, he and his coinvestigators studied eight children with a history of such therapy given after they were diagnosed in utero with neonatal lupus.

Neonatal lupus, he explained, is a serious condition occurring in children whose mothers have anti-Rho/SSA antibodies, which can cross the placenta. The most important clinical manifestation is congenital heart block; it is associated with significant mortality and permanent morbidity.

When affected fetuses are identified they are typically treated with several weeks of a high-dose steroid given to the mother. Dexamethasone is the agent used most widely. Since it is a fluorinated corticosteroid, it is not inactivated by placental enzymes, so it can reach the fetus in its active form. The purpose of this therapy is to slow the inflammatory process to prevent progression of incomplete to complete congenital heart block, as well as to treat fetal hydrops and/or myocarditis.

The mean age of the eight children studied was 6.6 years, with a range of 2-12 years. All had a pacemaker. None had clinical or laboratory indications of autoimmune disease. A total of 31 age-matched healthy children served as controls, he said at the congress, sponsored by the European League Against Rheumatism.

The results showed that the children with a history of in utero steroid therapy had no abnormalities in the various measures of T-cell number or function that have the most clear-cut potential clinical consequences.

Thymic output—a key study end point—was normal in children with prolonged fetal exposure to steroids; this was shown by the number of T-cell receptor excision circles (TRECs) in their peripheral blood mononuclear cells, which were measured by real-time polymerase chain reaction. The total number of T cells circulating in peripheral blood was similar to that of controls, as was T-cell subset diversity. Nor did the patients' lymphocyte proliferative response to mitogens differ from that seen in control subjects. Peripheral blood mononuclear cell interferon-γ production and apoptotic response were also similar to that in controls.

The one abnormality seen in children with a history of fetal exposure to steroids involved evidence of oligoclonal T-cell expansion. Similar changes have been reported in animals with in utero exposure to high-dose steroids. However, such changes also can be readily observed in humans after a viral infection. And the clinical significance of this sort of alteration in T-cell repertoire remains unclear, the rheumatologist said.

"We don't know if there is a link between these kinds of changes in PCR repertoire and autoimmunity, but we know that this kind of restriction is frequently detected in patients with rheumatoid arthritis and other autoimmune disorders. And it has been reported that children with neonatal lupus are at increased risk of developing autoimmune disorders in their first years," he explained.

Aside from the question of the effects on T cells of intrauterine steroid exposure, other adverse consequences have been reported by various investigators. These include increased rates of obstetric complications, adrenal insufficiency, hypertension, and neuropsychiatric impairment.

"Although it's not really the topic of this presentation, I will say that we didn't observe any signs of neuropsychiatric impairment in a series of nine children treated with dexamethasone in utero for neonatal lupus in our hospital," Dr. Airo said. ■

Hysterectomy in Fibroid Patients Studied

BETHESDA, MD. — Persistence of symptoms and dissatisfaction with their health are significant predictors of hysterectomy in women with fibroids.

A total of 633 ethnically diverse women with fibroids who sought care were followed for 2 years. They completed questionnaires about quality of life and their interest in a hysterectomy, investigators wrote in a poster presented at a conference on uterine leiomyoma research sponsored by the National Institutes of Health. A total of 58 women had undergone a hysterectomy by the end of 2 years. Overall, baseline dissatisfaction with health and persistence of symptoms were highly predictive of hysterectomy in a multivariate analysis, with odds ratios of 2.54 and 3.11, respectively.

The most frequently reported symptoms were bleeding (58%), pressure (24%), and pain (19%), said Miriam Kuppermann, Ph.D., and her associates at the University of California, San Francisco.

—Heidi Splete

DRUGS, PREGNANCY, AND LACTATION

Ginger for Nausea and Vomiting

Ginger in many forms is taken by pregnant women, with the hopes of alleviating the nausea and vomiting of pregnancy. These forms range from ginger tea, cookies, crystals, and sugars to inhaled powder and capsules containing ginger, as well as fresh ginger.

In a recently published metaanalysis of studies on ginger's use as an antiemetic during pregnancy, the authors concluded that the herbal supplement may be safe and effective for managing the nausea and vomiting of pregnancy (NVP). They noted, however, that more observational studies and larger randomized trials were needed before a definitive statement on safety could be made (Obstet. Gynecol. 2005;105:849-56).

BY GIDEON KOREN, M.D.

The metaanalysis included six double-blind, randomized controlled trials of almost 700 women and an observational study that my colleagues and I conducted on 187 women taking ginger. This is the first metaanalysis of studies on the use of ginger as an antiemetic during pregnancy. In the six randomized controlled trials, 500-1,500 mg daily of ginger were used for 3 days to 3 weeks in women who were at less than 20 weeks' gestation (Am. J. Obstet. Gynecol. 2003;189:1374-7).

In four trials, ginger was more effective than placebo in controlling symptoms of NVP, and in the two remaining trials, ginger was as effective as vitamin B_6 although I would add that vitamin B_6—when used alone—is effective mostly for mild cases of NVP.

No serious adverse effects or pregnancy-related problems were detected in the five studies that looked at safety. The outcomes evaluated in the randomized trials included prepartum hemorrhage, preeclampsia, preterm birth, congential abnormalities, major malformations, perinatal and neonatal death, birth weights, and gestational age.

In the prospective observational study, we looked primarily at fetal safety, comparing outcomes in 187 pregnant women who took ginger in the first trimester with another 187 women who during the first trimester took drugs known to be nonteratogenic. With one exception, we found no significant differences in adverse pregnancy outcomes between the two groups.

The exception was that there were significantly more infants with birth weights of less than 2,500 g in the comparison group (6.4%, vs 1.6% in the ginger group), even though there were eight pairs of twins in the ginger group. There were two major malformations in the comparison group, and three in the ginger group (a ventricular septal defect, right lung abnormality, and kidney abnormality). At age 2, the daughter of a mother who took 1,000 mg of ginger per day from weeks 11-20 of gestation, as well as doxylamine/vitamin B_6 in the first trimester, was diagnosed with idiopathic central precocious puberty. This may be a random finding.

In a subgroup of 66 women, we evaluated the effectiveness of ginger by asking them to rank from 0 to 10 how well ginger controlled NVP, with 0 as no effect and 10 as a maximal effect. The mean score was 3.3, not a very strong effect. Moreover, when we considered the form of ginger used, only capsules containing ginger were associated with an effect significantly greater than zero.

Thus, our observational study put effectiveness against placebo into context: While it is helpful to show in randomized controlled trials that ginger has a better antiemetic effect than placebo, the effect is very mild. Needless to say, many pregnant women are much more comfortable taking a natural product than a medication because of the perception that natural products are safer. But they should be aware that these products are not necessarily as effective as medicinal products, which in the United States and Canada, include ondansetron and metoclopramide.

At Motherisk, we advise women who call about ginger that it is probably safe and may help ease mild NVP, but it is unlikely to help with moderate to severe NVP.

A precautionary note: Women should also be aware that since there are many formulations of ginger, the amount of ginger in a given form is almost never certain. This is because natural products are not regulated with the same scrutiny as drugs. At this point, more studies comparing ginger with placebo probably are not needed. What would make sense now is to compare the safety and effectiveness of ginger and drugs, such as ondansetron and doxylamine and vitamin B_6, medicinal products that have been proved to be safe and effective for nausea and vomiting in pregnant women.

DR. KOREN *is professor of pediatrics, pharmacology, pharmacy, medicine, and medical genetics at the University of Toronto, and holds the Ivey Chair in Molecular Toxicology at the University of Western Ontario, London. He heads the Research Leadership in Better Pharmacotherapy During Pregnancy and Lactation at the Hospital for Sick Children, Toronto, where he also serves as director of the Motherisk Program, a teratogen information service (www.motherisk.org).*