T-Cell Development Deemed OK After Prenatal Steroids

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 woman. 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 children 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 having 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, Dr. Airo 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," according to the rheumatologist.

Putting aside 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.

"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," the physician said. ■

Pregnancy Often Triggers Bipolar Relapse, Studies Show

BY MITCHEL L. ZOLER
Philadelphia Bureau

PITTSBURGH — Pregnancy can trigger a relapse in women with bipolar disorder, especially if they stop their mood-stabilizing treatment.

Although data from several studies are conflicting, a prospective study showed that about two-thirds of women with a history of bipolar disorder had a relapse during pregnancy, Adele C. Viguera, M.D., said at the Sixth International Conference on Bipolar Disorder.

Although data from several studies are conflicting, a prospective study showed that two-thirds of women with bipolar disorder relapsed during pregnancy.

In that study, about half of the women had relapsed before their 18th week of pregnancy. Relapse was even more rapid in the postpartum period, with about half of the women studied having a return of their bipolar disorder within 6 weeks after delivery, said Dr. Viguera, of the department of psychiatry at Massachusetts General Hospital in Boston.

Results from a separate study, led by Dr. Viguera and reported 2 years ago, showed that the majority of bipolar recurrences during pregnancy or postpartum involve either major depressive episodes or mixed states.

A major factor linked with recurrences is discontinuation of mood-stabilizing treatment, especially an abrupt stop. In Dr. Viguera's study which involved 82 women, the relapse rate among the women who stopped their mood-stabilizing medication was 75%, compared with a 35% relapse rate among women who continued their treatment.

Another important determinant of relapse is whether affective illness occurs during pregnancy. In Dr. Viguera's study, a total of 61% of the studied women had a postpartum relapse. More than 80% of the women with relapses had affective illness during pregnancy. As a result of this observation, "we're very aggressive about maintaining euthymia" during pregnancy, Dr. Viguera said at the meeting, also sponsored by the University of Pittsburgh.

But data are limited on the safety of mood stabilizers during and after pregnancy. A study reported this year showed that in a North American registry, treatment of pregnant women with valproic acid was linked with 16 fetal anomalies among 149 women treated, an 11% rate that was "much higher than expected," said Dr. Viguera. Additional findings from studies of valproic acid use in pregnant women with epilepsy also show a relatively high rate of major malformations, fetal death, and developmental delay.

Results from another registry showed that treatment with lamotrigine was associated with a 3% incidence of major malformations in a series of 414 treated women. Other studies have confirmed that lamotrigine treatment is linked with fewer serious effects during pregnancy than other anticonvulsants.

Results from a prospective study published this year showed a single major malformation among 151 women treated with an atypical antipsychotic in pregnancy. The drugs included in this study were olanzapine, risperidone, quetiapine, and clozapine. Although the low rate of fetal damage was reassuring, the number of women studied was too small to produce a definitive conclusion about safety, Dr. Viguera said. ■

Weight Gain in 5 Years Before Pregnancy May Increase GDM Risk

SAN DIEGO — Weight gain in the 5 years before pregnancy is associated with an increased risk for gestational diabetes, Monique Hedderson reported in a poster at the annual scientific sessions of the American Diabetes Association.

In a nested case-control study including 114 women with gestational diabetes mellitus (GDM) and 95 controls who were members of Kaiser Permanente of Northern California, those who had gained between 1.1 kg and 10.0 kg in the 5 years before their last menstrual period were nearly twice as likely (crude odds ratio 1.98) to have developed GDM during pregnancy than were those whose weight remained within 1 kg of baseline, said Ms. Hedderson, of Kaiser Permanente, Oakland, Calif., and her associates.

The women who developed GDM were older, more likely to be from an ethnic minority group, more likely to be overweight at baseline, and more likely to be primiparous or to have had at least two prior live births.

After adjustment for these factors, the relationship between prepregnancy weight gain and GDM was even stronger, with an odds ratio of 2.58. The relationship with weight loss was again insignificant (OR 0.9).

—Miriam Tucker

Maternal Obesity Linked to Increased Risk of Orofacial Clefts in Infants

Obese women are 30% more likely than women of normal weight to give birth to an infant with an orofacial cleft, investigators have reported.

"One possible explanation is undetected type 2 diabetes. Obese women, in the absence of overt diabetes, have been found to have an impaired glucose metabolism, which may be associated with an increased risk for orofacial clefts," wrote Marie Cedergren, M.D., of the University of Linköping, and her coinvestigator, Bengt Kallen, M.D., of Tornblad Institute at the University of Lund (Cleft Palate Craniofac. J. 2005;42:367-71).

Of almost 1 million infants born in Sweden from 1992 to 2001, 1,686 infants were born with orofacial clefts; 84% of the clefts were not associated with another major congenital malformation. Compared with infants born of normal weight mothers, infants of obese mothers had their risk increase by 28% for cleft palate, 14% for cleft lip, and 31% for both abnormalities.

The risk of orofacial clefting among these infants was significantly higher (odds ratio 1.88) when associated with other congential defects, but still elevated (OR 1.20) when clefting was the only defect.

—Michele G. Sullivan