Steroids In Utero Don't Derail T Cells Long Term

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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.

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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.

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.

"We didn't observe any signs of neuropsychiatric impairment in a series of nine children treated with dexamethasone in utero for neonatal lupus," he said. ■