Prenatal Corticosteroids — Early Gain, Long-Term Questions
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A single course of prenatal corticosteroid therapy has been shown to accelerate fetal lung maturation when premature delivery is imminent. This therapy reduces morbidity and mortality in premature newborns by reducing the incidence of respiratory disease and dependence on mechanical respiratory support. Longer-term follow-up has revealed no adverse effects on neurodevelopmental outcomes or growth, and this treatment is routinely recommended for women at risk for premature delivery between 24 weeks and 33 weeks of gestation.

Prenatal corticosteroid therapy accelerates fetal lung maturation through a complex interaction of hormonal and intercellular signaling that leads to differentiation of the surfactant lipid–protein pathways and through less well-defined increases in lung compliance. These effects depend on the susceptibility of fetal lung cells to corticosteroids, which relates to the presence of appropriate receptors and other humoral and structural factors in the fetal lung. In other words, the fetal lung must be biologically ready for a corticosteroid “trigger” in order to mature. In humans, this window of biologic readiness of the lungs for corticosteroids seems to occur most often between 26 weeks and 33 weeks of gestation, though it may begin earlier in some fetuses.

Increasing success in extending pregnancy nearer to term (by means of tocolysis, prevention of infection, and careful ongoing evaluation) and observations that the biologic effects of prenatal corticosteroids were sustained for up to 1 week after prenatal corticosteroid therapy inevitably led to the question of whether repeat courses of corticosteroids might be effective in women who remained at risk for premature delivery after a single course. Anecdotal reports of the efficacy and safety of multiple courses of prenatal corticosteroids led to broad adoption of their use in practice without data from large randomized trials or study of long-term outcomes. Of serious concern were studies in animals of repeat courses of prenatal corticosteroids, which demonstrated delays in structural brain development and reductions in body size, suggesting the possibility of harm from this intervention. Thus, a National Institutes of Health Consensus Panel recommended in 2000 that weekly courses of corticosteroids be reserved for controlled studies assessing their effects, limiting broad use in practice until results were available.

The Australian Collaborative Trial of Repeat Doses of Steroids (ACTORDS) and a National Institute of Child Health and Human Development’s Maternal–Fetal Medicine Units (MFMU) Network study were designed to compare weekly courses of corticosteroids with a single course in women at risk for preterm delivery. In reports assessing short-term outcomes, both trials showed better results after repeat courses than after a single course, including less need for mechanical respiratory support and surfactant use (MFMU report) and less respiratory distress syndrome, severe neonatal lung disease, and serious neonatal morbidity (ACTORDS report). Both trials, however, raised concerns about lower birth weights in the repeat-corticosteroids groups, and the ACTORDS study also found smaller head circumferences in the repeat-corticosteroid group. Did these early reports suggest that repeat courses of corticosteroids would lead to short-term benefits in lung maturation at the expense of healthy long-term neurologic development and somatic growth?

In this issue of the Journal, Crowther et al.
(for the ACTORDS study group) and Wapner et al.\textsuperscript{13} (for the MFMU network) report the longer-term neurodevelopmental and somatic-growth outcomes of children whose mothers were randomly assigned to either weekly courses of prenatal corticosteroids or a single course. Both studies report no significant differences in body-size measurements, blood pressure, or Bayley Developmental Index scores between the single-course and multiple-course groups at 24 to 36 months of age. The ACTORDS study also included assessments of emotional reactivity, sleep and attention problems, and aggressive behaviors; the only significant difference between groups was in attention problems, which were slightly more common in children in the repeat-corticosteroid group, but the difference was small.

Neither study found significant differences in rates of major neurodevelopmental complications such as blindness and deafness (assessed in ACTORDS) or in the occurrence of cerebral palsy (assessed in both studies), although the MFMU trial\textsuperscript{13} reported a trend to a higher rate of cerebral palsy in the repeat-course group than in the single-course group (2.9% vs. 0.5%, $P=0.12$). The differences in rates of cerebral palsy in the MFMU trial might have occurred by chance, but it is also possible that the finding is real and would have been statistically significant in a larger trial.

The number of weekly courses and the total dose of betamethasone used per course differed between the trials. The MFMU trial limited repeat courses to four early in the trial because of concern about harm from further courses,\textsuperscript{11} whereas the ACTORDS study\textsuperscript{10} did not limit the number of courses. In the MFMU trial, five of the six infants with cerebral palsy in the repeat-corticosteroid group were exposed to four or more courses, although the number of courses did not significantly affect the rate of cerebral palsy in the ACTORDS study. The total weekly dose of betamethasone in the MFMU trial (24 mg, given in two 12-mg doses 24 hours apart\textsuperscript{11}) was greater than that in the ACTORDS study (a single weekly dose of 11.4 mg of betamethasone\textsuperscript{10}). These differences in trial protocols raise questions about whether higher corticosteroid doses may increase risks for adverse outcomes, although more data are needed.

Both of the studies reported in this issue of the journal offer reassurance that weekly courses of prenatal corticosteroid therapy, now commonly used in practice, do not significantly increase risks for major adverse neurodevelopmental outcomes or sustained somatic growth delays. Yet the two sets of investigators offer different recommendations: Crowther et al. favor the use of repeat courses in women who remain at risk for preterm delivery, whereas Wapner et al. recommend caution in such practice, because of the higher rate of cerebral palsy observed in their repeat-course group than in their single-course group (although the difference was not significant). More information is needed before it will be clear which strategy is optimal. Further study of neurodevelopmental performance in school-age children is warranted, including the possible increased risk of cerebral palsy among these children, as well as among offspring of women in other trials of weekly corticosteroid therapy, with attention to the doses and regimens used. Pending the availability of such data, if a decision is made to give repeat courses of corticosteroids, it may be prudent to consider the use of lower doses (such as in the ACTORDS study); in all cases, we should inform parents of the limited data on long-term outcomes and should follow survivors for long-term neurodevelopmental outcomes.

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8. Uno H, Lohmiller L, Thieme C, et al. Brain damage induced by prenatal exposure to dexamethasone in fetal rhesus ma-
Lessons from a Genomewide Association Study of Rheumatoid Arthritis

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Rheumatoid arthritis is a chronic inflammatory disorder in which the articular joints are gradually destroyed. Occasionally there is systemic involvement, which can include vasculitis in various organs and pulmonary fibrosis. The disease has multifactorial causes to which genetic and environmental factors are thought to contribute. The presence of autoantibodies to cyclic citrullinated peptide (CCP) is specific to rheumatoid arthritis; although the mechanistic significance of these autoantibodies is obscure, their detection contributes both to the differential diagnosis and to a prediction of the severity of joint destruction. Rheumatoid arthritis causes substantial morbidity and mortality and is sometimes accompanied by severe infection or accelerated atherosclerosis.

During the past couple of decades, therapy for rheumatoid arthritis has been improved through the introduction of new antirheumatic drugs, such as the antimetabolite and antifolate drug methotrexate, and biologic therapeutics, such as antagonists to tumor necrosis factor (TNF). However, these treatments can have adverse effects, and responsiveness to these treatments varies considerably. Perhaps “personalized medicine” may one day address such variation. An improved understanding of the genetic causes of the disease represents a step toward this goal and the development of other therapeutic approaches.

The article by Plenge et al. in this issue of the Journal is therefore welcome. The authors report the results of a genomewide association study of an anti–CCP-positive subclass of rheumatoid arthritis. It is reassuring that the authors observed associations between rheumatoid arthritis and loci in and around HLA-DRB1 and PTPN22; these loci have been repeatedly implicated as genetic risk factors in persons of European descent. The authors also identified a new locus, containing TRAF1 and C5, through the use of a multistage study design with multiple samples. An earlier large-scale linkage-disequilibrium study and subsequent replication studies implicated a variant of PADI4 as a risk factor for rheumatoid arthritis. This variant would seem to have a more potent effect in Asian populations than in those of European descent. Variants of these genes are believed to confer a risk for the development of rheumatoid arthritis by affecting the presentation of autoantigens (in the case of HLA-DRB1), T-cell–receptor signal transduction (in the case of PTPN22), and the citrullination of proteins, targets of anti-CCP antibodies (in the case of PADI4). Variant TRAF1 may modify signal transduction through TNF receptors 1 and 2; variant C5 may amplify complement activation in the joints of patients with rheumatoid arthritis.

The genomewide association approach has yielded a wealth of new genetic susceptibility loci in other common and complex genetic disorders. The completion of the Human Genome Project and the development of large-scale public databases of human genetic heterogeneity and high-throughput genotyping technology have enabled researchers to carry out case–control association studies on thousands of samples with several hundreds of thousands of markers throughout the human genome. The scale of genomewide association studies continues to grow, and the number of markers used in such studies will soon approximate or exceed a million. It is not unrealistic to expect that the entire genome of all samples will be sequenced in the not-too-distant future.

An advantage of genomewide association stud-