

Editorial

More Reasons to Hold on Additional Doses of Antenatal Steroids

L. M. Noguee, MD

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Almost 30 years have passed since Liggins and Howie reported the potential benefits of antenatal glucocorticoids given to mothers with threatened preterm delivery to reduce respiratory morbidity from respiratory distress syndrome (RDS) in their prematurely born infants.¹ Despite subsequent studies that supported the efficacy of antenatal steroids, antenatal glucocorticoid use remained low for over 20 years.^{2,3} In 1994, a National Institutes of Health (NIH) consensus conference recommended routine use of antenatal corticosteroids to advance lung maturity.⁴ The optimal benefits of steroids were felt to persist for 7 days, but uncertainty remained concerning the use of repeated doses of steroid in mothers whose pregnancies were able to be prolonged beyond a week, and this was an area for further investigation recommended by the NIH panel. Repeat doses of corticosteroids were observed to further improve lung function in preterm animals, particularly early in gestation, although they were also associated with decreased fetal growth.^{5,6} Despite a lack of data as to the efficacy and safety of repeated doses of steroids in human infants, multiple courses of steroids are often administered in this clinical context.^{7,8} Increasing concerns have been raised related to the deleterious effects of antenatal steroids on the fetus, and especially postnatal steroids given to premature infants with chronic lung disease, particularly with respect to the developing nervous system and neurodevelopmental outcome.⁹ In this issue of the *Journal*, Banks et al. provide further evidence to suggest that repeated doses of antenatal corticosteroids offer little benefit and may even be acutely harmful.¹⁰

In a previous analysis of the data from a prospective study of TRH administration to prevent RDS, Banks et al. found no benefits in terms of reduction in the incidences of RDS, intraventricular hemorrhage, or chronic lung disease in those infants whose mothers received multiple doses of antenatal steroids. Lower birth weights were observed in those infants that had received ≥ 2 courses, along with an increased mortality in infants whose mothers received ≥ 3 courses of steroids.¹¹ Those results were in accord with those of previous studies, which also found increased adverse effects in association with

multiple courses of prenatal steroids, including growth retardation and decreased head circumference.^{12,13} In their present study, Banks et al. found that the increased mortality was related to an increased incidence of severe respiratory disease in the first 24 hours of life, and not due to other maternal conditions or morbidities associated with prematurity. Thus, there was no apparent benefit in terms of acute pulmonary function associated with additional courses of corticosteroids, and possibly a detrimental effect.

As one of the principal reasons for administering antenatal steroids is to reduce the incidence of RDS, this apparent increased mortality due to acute, severe lung disease at first seems somewhat paradoxical. Reductions in both the overall incidence and severity of RDS have been observed in infants exposed to multiple courses of antenatal steroids in both retrospective and prospective studies.^{13,14} However, the severe lung disease in this study was not necessarily related to RDS and its complications. In the previously published study from this same group, pulmonary hypoplasia was thought to be a cause or contributing factor in the death of 5 of 13 infants who died after >3 courses of antenatal steroids. At least one of these infants had prolonged rupture of membranes, a condition known to be associated with pulmonary hypoplasia, but the underlying cause was less clear in others. Sepsis was a contributing factor in the death of 5 infants. Thus, the implication is that adverse effects of multiple doses of steroids with respect to lung development and risk for infection outweighed any benefits resulting from reduction in the severity of RDS. Unfortunately, autopsy data were not available to confirm the exact causes and mechanisms of death in these patients.

As the authors correctly point out, these findings do not necessarily indicate that the extra doses of steroids caused the severe lung disease. This was a post hoc analysis of data from a study meant to test a different hypothesis, and the reasons why some infants received multiple courses of steroids were not specified or controlled. Risk factors other than those examined may have resulted in fetuses that were more likely to have a poor outcome to receive additional courses of corticosteroids. In order for a mother to have received repetitive doses of corticosteroids, the pregnancy must have been successfully prolonged, and it is impossible to know whether exposure to steroids or factors associated with prolongation of the pregnancy contributed to the increased early severe lung disease and mortality.

However, although a causal mechanism has not been established, these observations are disturbing particularly in view of the growing body of evidence demonstrating adverse effects of prolonged postnatal doses of steroids on lung growth and alveolarization in experimental animals.^{15,16} Given the relatively long half-lives of betamethasone

Division of Neonatology, Johns Hopkins Hospital, 600 N. Wolfe Street, CMSC 6-104, Baltimore, MD, USA.

Address correspondence and reprint requests to L. M. Noguee, MD, Eudowood Neonatal Pulmonary Division, Johns Hopkins Hospital, 600 N. Wolfe Street, CMSC 6-104, Baltimore, MD 21287-3200, USA.

and dexamethasone, infants who received >3 courses of antenatal steroids had prolonged exposure during critical period of lung development. Taken in combination with the concern for pulmonary hypoplasia as a contributor to mortality in infants exposed to multiple doses of antenatal steroids, the risks of repeated courses of corticosteroids may outweigh the benefits with respect to pulmonary outcome.

Many questions remain unanswered. Drug interactions, particularly the interactions of steroids with tocolytic agents, deserve further study. Additional basic research is needed to better understand normal lung development and genetic and environmental causes of pulmonary hypoplasia. Identification of specific genetic factors contributing to the development of acute and chronic lung disease may identify which patients are likely to benefit from more or less aggressive therapy. In the interim, the findings of Banks et al. in this issue and other studies argue against the use of repeat courses of antenatal steroids. As has been stated elsewhere, including in the recommendation of the most recent NIH consensus conference, repeat doses of antenatal corticosteroids should only be administered in the context of prospective clinical trials.^{17–19} Unfortunately, such a recent prospective controlled trial was halted after half of the originally planned enrollment, because even though the severity of RDS was reduced in the group receiving multiple courses of antenatal steroids, no appreciable benefit was observed in terms of mortality. The potential risk/benefit ratio of repeat courses of antenatal steroids with respect to early, acute neonatal lung disease remains unknown.

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