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EDITORIALS



Antenatal Glucocorticoids for Late Preterm Birth?

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Late preterm infants (born between 34 weeks and 36 weeks 5 days of gestation) make up the largest proportion of preterm births and are at higher risk for neonatal death and complications including respiratory disease than are infants born at term (at least 37 weeks of gestation).¹ Late preterm survivors are also at risk for lifelong health problems, including cerebral palsy and learning difficulties.² Personal and societal costs of these births are substantial.³

A single course of antenatal glucocorticoids given to mothers at risk for preterm birth is now standard prophylactic treatment against the respiratory distress syndrome and other serious neonatal complications.⁴ A recent systematic review of 26 randomized trials involving 4469 women and 4853 infants indicated that antenatal glucocorticoids administered between 24 weeks and 34 weeks 6 days of gestation reduced rates of infant death and the respiratory distress syndrome.⁵ However, the range of gestational ages for which antenatal glucocorticoids are recommended varies among current international clinical practice guidelines, with U.S. guidelines recommending their use up to 33 completed weeks of gestation⁶ and others, including those of the World Health Organization, recommending their use up to 34 completed weeks of gestation.^{5,7}

There has been limited evidence to guide these recommendations. The three trials that have specifically assessed the use of glucocorticoids for late preterm gestation had low event rates and imprecision in or lack of reporting of neonatal deaths and respiratory distress outcomes.⁴

In this issue of the *Journal*, Gyamfi-Bannerman et al.⁸ report the results of a multicenter, placebo-controlled, randomized trial in which 2831 women between 34 weeks and 36 weeks 5 days of gestation and at high risk for late preterm birth were randomly assigned to receive two injections of betamethasone or placebo 24 hours apart. Women who were expected to give birth in less than 12 hours or who had a multiple gestation or pregestational diabetes were not eligible. Strengths of this trial are the similarity of the study groups at randomization, the use of placebo and masking of study-group assignments, and the nearly complete availability of data for the primary outcome (99.9%).

The study showed a significantly lower risk of the composite primary outcome (stillbirth or neonatal death before 72 hours or need for respiratory support by 72 hours of age) in the betamethasone group than in the placebo group. The estimated number of women who would need to be treated to avoid one infant requiring respiratory support was 35, with a lower 95% confidence interval of 19 but an upper level of 259.

In keeping with the reduced need for respiratory support, there were significantly lower risks of several secondary outcomes in the betamethasone group than in the placebo group. These risks included severe respiratory complications, transient tachypnea of the newborn, and bronchopulmonary dysplasia but not the respiratory distress syndrome. There were no stillbirths or neonatal deaths before 72 hours. However, there was a higher incidence of neonatal hypoglycemia (relative risk, 1.60; 95% confidence interval, 1.37 to 1.87) among the infants of mothers in

the betamethasone group. Injection-related adverse maternal effects were more common in the placebo group.

Thus, do the benefits of using antenatal glucocorticoids before late preterm birth outweigh the risks? The answer depends in part on whether these findings can be generalized to the wider population of women at risk for late preterm birth. Since women whose babies were at highest risk for neonatal complications (i.e., those with multiple gestations or diabetes) were excluded from this trial, the potential benefits may be underestimated.

Although there was no mortality benefit, none was expected in a population at very low risk for death. Rather, the main benefits were reduced complications (primarily respiratory-related, but also a small reduction in the time until the first feeding and in the risk of a stay in an intermediate or intensive care nursery for more than 3 days). These improved outcomes were probably associated with reduced costs, although the present report did not include an economic analysis.

An important question is whether these short-term benefits may be associated with any long-term benefits or risks. In this context, the increase in the incidence of neonatal hypoglycemia is particularly worrisome, especially since neonatal hypoglycemia has been reported to be the only independent risk factor for later developmental delay among moderate or late preterm infants.⁹

The trial protocol suggests that follow-up is planned up to 6 months of age, but much longer developmental follow-up will be essential to assess whether the neonatal respiratory benefits translate into later health and developmental benefits without harm, as has been shown in other trials.^{4,10}

A meta-analysis of individual participant data from the total of six trials that have used antenatal glucocorticoids in mothers with late preterm gestation^{4,5} may help to guide clinical recommendations as to the range of gestational ages in which antenatal glucocorticoids are most

effective and to identify future research questions. In the meantime, data from this trial provide further evidence of short-term benefits for the use of antenatal glucocorticoids up to 34 weeks 6 days of gestation, findings that are consistent with many existing recommendations^{5,7} and that may help clinicians and pregnant women make informed decisions about the use of glucocorticoids beyond this gestation.

Disclosure forms provided by the authors are available with the full text of this article at www.nejm.org.

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