Does a second course of antenatal corticosteroids offer benefit in the setting of preterm PROM?

No. Among 1,641 women in this secondary analysis of a prominent randomized controlled trial (RCT), there was no demonstrated benefit for a second course of antenatal corticosteroids (ACS) in the setting of preterm premature rupture of membranes (PROM). When a second course of corticosteroids was given, the rate of neonatal or maternal infection did not increase.

FAST TRACK

The lack of association between a second dose of antenatal corticosteroids and neonatal sepsis is not justification to use a rescue course of antenatal steroids in women with preterm PROM

Gyamfi-Bannerman C, Son M. Preterm premature rupture of membranes and the rate of neonatal sepsis after two courses of antenatal corticosteroids. Obstet Gynecol. 2014;124(5):999–1003.

EXPERT COMMENTARY

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Gyamfi-Bannerman and Son report their secondary analysis of a randomized controlled trial (RCT) conducted through the Eunice Kennedy Shriver National Institute of Child Health and Human Development's Maternal-Fetal Medicine Units Network. The aim of the parent RCT was to determine whether antenatal administration of magnesium sulfate decreases the rate of cerebral palsy or death in children delivered preterm. More than 80% of the women enrolled in this RCT had preterm PROM. Of these women, 98% were given antenatal corticosteroids for fetal maturation, and 9% received two courses. This aspect of the RCT provided an opportunity for Gyamfi-Bannerman and Son to study the comparative effects of one course versus two courses of ACS in the setting of preterm PROM.

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Background of the study

Concern about the declining efficacy of ACS when the interval between administration and delivery exceeds 7 days prompted several

WHAT THIS EVIDENCE MEANS FOR PRACTICE

We must always remain cautious about basing policy or clinical decisions on cohort studies. It has been argued that basing a change in clinical practice on the findings of subgroup analyses is a deviation from fundamental scientific truth.[13] Such findings should be regarded as hypothesis testing only and considered exploratory in nature.

This study's abstract conclusion that there is a lack of association between a second dose of ACS and neonatal sepsis should not be regarded as justification to use a rescue course of ACS in women with preterm PROM. We recommend that such a practice be avoided outside the context of an approved research protocol.

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randomized trials exploring the safety and efficacy of multiple ACS courses. Multiple courses were ultimately deemed to be inadvisable because of an association with reduced birth weight and neonatal head circumference.[1,2] However, the unfavorable effects of ACS on anthropometrics was observed when more than three courses were administered, leaving open the possibility of giving only one additional course when needed as a "rescue" dose. Indeed, the use of a single rescue course of ACS in women with intact membranes had a favorable impact on neonatal respiratory function in two RCTs.[3,4]

The best available evidence (Level 1) demonstrates that the use of a single course of ACS in preterm PROM does not increase the risk of neonatal or maternal infection even in the setting of prolonged rupture of membranes.[5] However, pregnant women with preterm PROM were excluded from trials of repetitive ACS dosing because earlier observational studies had suggested that they would experience a substantially increased risk of infectious morbidity when three or more courses of ACS are given.[6–8] What remained debatable on a scientific level was whether a single rescue dose of ACS in women with preterm PROM would be safe and beneficial.

Findings of the analysis

Compared with a single course of ACS, exposure to two courses did not influence the rate of neonatal sepsis or chorioamnionitis. As reassuring as that finding may be, the study found no benefit for the additional course, although it was powered to do so. There was no difference in the rates of respiratory distress syndrome between the study groups.

The findings of Gyamfi-Bannerman and Son replicate those of a subgroup analysis of women in an RCT comparing weekly and single-course ACS.[9] In that study, weekly courses of ACS in women with preterm PROM did not improve neonatal outcomes beyond what was achieved with single-course therapy. Similar findings have been reported by the Cochrane database.[10]

Ruptured versus intact membranes: When is the benefit of ACS greater?

The improvement in neonatal outcomes observed with ACS in pregnancies complicated by preterm PROM is not as pronounced as it is in gestations with intact membranes. In preterm PROM, fetuses reportedly are stressed by the presence of intrauterine inflammation or infection, or both, which accelerates lung maturity by encouraging the secretion of endogenous corticosteroids, resulting in the production of surfactant and eliminating the potential benefit of exogenous ACS.[11] This theoretical consideration has not been verified in a systematic analysis of accumulated data,[5] and the administration of a single course of ACS in preterm PROM now has been shown clearly to improve neonatal outcomes.[12] As Gyamfi-Bannerman and Son demonstrate, the same cannot be said about the administration of a rescue dose of ACS.

Strengths and limitations of the trial

Gyamfi-Bannerman and Son did not address the same interaction as the parent study. The exposure of interest was ACS, an event that occurred in a manner unrelated to the randomization for magnesium sulfate administration. Therefore, the outcome data are no longer randomized in nature, and the study becomes a retrospective cohort analysis.

Gyamfi-Bannerman and Son recognize the limitations of such a study, especially the lack of standardization in the intervention (exact timing of intervention or type of formulation). As with any nonrandomized experiment, the potential for unintended systematic bias is present.

This study, in particular, was subject to "survivor bias," as reflected in the significantly different intervals between membrane rupture and delivery in the two groups.

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FAST TRACK

A single course of antenatal corticosteroids in preterm PROM clearly improves neonatal outcomes

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