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Appropriate Use of Antenatal Corticosteroid Prophylaxis

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Antenatal corticosteroids for women at risk of preterm delivery is one of the most important interventions described to date to reduce morbidity and mortality in preterm newborns. First described by Liggins and Howie in 1972[1] and confirmed in at least 20 other randomized studies and in several meta-analyses,[2,3] utilization in most high-income countries nevertheless remained low through the early 1990s. Because of the discrepancy between the high efficacy of corticosteroids and low use, in 1993 the National Institute of Child Health and Human Development (NICHD) convened a consensus conference on the effect of corticosteroids on perinatal outcomes. The panel concluded that antenatal corticosteroid therapy reduced neonatal mortality, respiratory distress syndrome, and intraventricular hemorrhage in preterm neonates at a broad range of gestational ages (24–34 weeks), especially with delivery after 24 hours of treatment but before 7 days. Later studies confirmed that necrotizing enterocolitis and long-term neurologic disability also were reduced. After the dissemination of the consensus conference results,[4] antenatal corticosteroid use increased substantially, reaching 80% or more of 24-week to 34-week preterm births in the United States and many other high-income countries; use in most low- and middle-income countries generally remained low.

However, less attention has been paid to the outcome of neonates who were delivered outside the 24-week to 34-week window and especially among those who were delivered at term; in one meta-analysis, of the three studies that reported outcomes of 500 neonates born at more than 36 weeks of gestation, antenatal corticosteroid administration was associated with a 2.6-fold increase in neonatal death (results that were not statistically significant).[2]

One of the major challenges facing the physician managing a pregnancy at risk to deliver preterm is that the precise timing of delivery is often unknown. Especially in cases of preterm labor or preterm premature rupture of membranes, the timing of delivery is often outside the control of the physician, and in indicated preterm delivery, that is, for severe preeclampsia or eclampsia, progression of the disease may require delivery before attaining 24 hours of corticosteroid use. Conversely, about half of women in preterm labor who appear to be at risk of imminent delivery may go on to deliver at term. The nature of these

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conditions leads to a considerable number of neonates born outside the ideal window for corticosteroid delivery.

In an attempt to ensure that all preterm newborns received corticosteroids, after the 1993 NICHD consensus conference, many U.S. physicians adopted the strategy of multiple or even weekly doses of corticosteroids so that the ideal window would not be missed. However, it soon became clear that this practice resulted in diminished fetal growth and head size. A follow-up NICHD consensus conference held in 2000 recommended against this practice.[5,6] Subsequent studies suggest the benefit of a single rescue dose.

To date, a number of unanswered questions remain related to corticosteroid use, including better defining the ideal window for administration in terms of gestational age and time of delivery after first dose, and whether there are benefits of corticosteroid administration at 35 weeks and 36 weeks of gestation or for neonates of women undergoing cesarean delivery at any gestational age. Several studies as well as subsequent analyses of completed trials are ongoing to answer these questions.

Major questions also relate to corticosteroid therapy in low-income countries, including why use remains low and whether the risks and benefits of corticosteroids in low-income countries are different than in high-income countries. These issues are important because virtually all corticosteroid research has been done in high-income or middle-income countries in modern hospitals with neonatal intensive care units. In low-income countries where there is little or no newborn care and the mothers are often malnourished and may have greater exposure to many pathogens, it is unclear whether the benefits and risks would be different than in high-income countries. A recently published study conducted in five low-income countries and one middle-income country found no survival benefit to antenatal corticosteroid therapy in the target preterm population, and, surprisingly, found increased mortality in those neonates who received corticosteroids and who ultimately were delivered at term.[7] Without ultrasonography for gestational age dating and trained physicians, administering corticosteroids in the ideal window proved even more difficult than in high-income countries; most women in this study who received corticosteroids delivered at term.

The study by Razaz et al (see page 288) touches on many of these issues in both high-income and low-income countries.[8] In a population-based observational study from Nova Scotia, among 246,459 live births between 1988 and 2012, 2.5% received a partial or full course of antenatal corticosteroids. The rate of antenatal corticosteroid exposure for neonates born between 28 weeks and 32 weeks of gestation increased from 39.5% in 1988–1992 to 79.3% in 2008–2012, and exposure for those born at 33–34 weeks increased from 14.3% to 49.7%. Clearly the usage in 33-week to 34-week preterm neonates was less than optimal, with much room for improvement. Another important finding was that, although optimal antenatal corticosteroid receipt (defined as within 24–34 weeks of gestation with delivery occurring between 24 hours and 7 days postinjection) increased from 10% in 1988 to 23% in 2012, success at hitting the target window was quite low. Suboptimal administration, defined as receiving corticosteroids at 24–34 weeks of gestation but delivering outside the 24-hour and 7-day postinjection window, increased from 7% to 34%. Whether those neonates who were delivered outside the ideal window received benefit from

corticosteroids is unknown, but some benefit is likely. Probably most important, of the women who received antenatal corticosteroids in 2012, 52% delivered at or after 35 weeks of gestation, when the evidence for benefit is less and some increased risk is possible.

With one exception, implications for practice from the Razaz et al study are difficult to determine. Clearly, all physicians working in facilities with newborn care should aim to increase corticosteroid use in appropriate patients within the appropriate window, with renewed focus at 33–34 weeks of gestation. Exactly how to accomplish this is less clear. If we knew with some assurance when women at risk for preterm birth would deliver, solving this issue would be easy, but we do not. A physician could aggressively give corticosteroids to all women suspected of risk for a preterm birth but would almost certainly have many cases in which the women deliver outside the ideal window, and often at term. On the other hand, if the physician is overly cautious and gives corticosteroids only to those women highly likely to deliver in the near future, many women will either not receive corticosteroids or receive them less than 24 hours before delivery. Unlike Goldilocks, who, when confronted with a choice among cereals of too hot, too cold, or just right, was able to sample her choices, physicians do not have the option to know the timing of delivery when choosing to administer or withhold corticosteroids. For any individual patient, it is often not clear whether aggressive or cautious use of corticosteroids will produce the optimal results. In the low-income countries study described above, an aggressive attempt to increase corticosteroid use was chosen and corticosteroid coverage increased substantially. Unfortunately, many of those treated delivered at term, and neonatal outcomes were worse in those neonates. Until recently, there did not appear to be any increased risk to the mother or neonate for corticosteroid use when the delivery occurred after 34 weeks of gestation and especially at term. With the magnitude of overtreatment described in the Razaz et al study and the potential for increased neonatal mortality in neonates who receive antenatal corticosteroids but subsequently are delivered at term, a more cautious approach to the administration of antenatal corticosteroids may be indicated.

Biographies

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