BY WILLIAM H. CLEWELL, MD

Antenatal corticoids: optimal timing and dosing

This simple and inexpensive treatment can cut neonatal mortality rates in half, but not all common regimens are supported by evidence. The author reviews the literature and summarizes recommendations from the NIH.

Premature birth is the largest unsolved problem in obstetrics today and the single most significant cause of neonatal morbidity and mortality.[1] And although clinicians have been largely unable to reduce the incidence of preterm deliveries, the introduction of maternal antenatal glucocorticoid treatment to accelerate fetal lung maturity has allowed us to significantly reduce associated mortality and morbidity.

Research shows that this simple and inexpensive treatment can cut the neonatal mortality rate by about 50%, substantially lower the incidence of neonatal intracranial hemorrhage and diminish the cost of neonatal care. But following the first Consensus Development Conference on this therapy by the National Institutes of Health (NIH), held in 1994, many physicians became overly enthusiastic in their administration of antepartum steroids, often prescribing regimens and dose schedules not yet subjected to clinical trials.

Here, I review the literature on this therapy, looking at what we know and what is still being examined, and detail how clini-

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KEY POINTS

- Antepartum glucocorticoids are highly effective in reducing neonatal morbidity and mortality in prematurely born infants.
- Single courses have shown no adverse effect on the mother or newborn.
- Data on the risks and benefits of repeat courses are inconclusive.
- Repeat courses should not be used.
- Since optimal benefit occurs when the drug is given between 2 and 7 days before delivery, every attempt should be made to time administration accordingly.

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cians should administer antepartum corticosteroids based on current evidence.

The history

Glucocorticoids function as "switch" triggers in biology. In other words, they change cell behavior—often in dramatic ways. One effect is to "turn off" cell proliferation and initiate mature cell function. It is this mechanism that is believed to be instrumental in fetal pulmonary development. The agents stimulate the maturation of alveolar type 2 cells to begin surfactant production and trigger architectural maturation of the fetal lung, thereby reducing the thickness of the alveolar membrane as well as the diffusion distance between alveolar gas and pulmonary capillary.[2]

While studying the mechanism of parturition in sheep, Liggins observed that an intravenous injection of dexamethasone to a ewe's fetus could induce labor at immature gestational ages. Delivery generally occurred about 50 hours after injection. Further, these lambs did not succumb to respiratory distress syndrome (RDS), while those delivered by cesarean section at comparable gestational ages died of respiratory immaturity.[3]

With Howie, Liggins later reported on a similar effect in humans treated with antepartum glucocorticoids.[4] In their study, gravidas admitted in preterm labor were randomized to treatment with either placebo or 12 mg of a betamethasone phosphate/sulfate mixture. Patients received 2 doses intramuscularly (IM) 24 hours apart. Among women who received corticosteroids and delivered between 48 hours and 7 days after the first injection, there was a 50% reduction in neonatal mortality, compared with controls. In patients with hypertension, however, the authors noted an increased fetal death rate among treated patients compared with controls.

Other researchers sought to investigate this treatment further, and by 1994 a total of 17 prospective, randomized, controlled studies on antenatal glucocorticoids had been performed, most of which showed similar improvement in neonatal survival. Despite this overwhelming evidence, only an estimated 12% to 18% of infants born prematurely in the United States and United Kingdom received this treatment.[5] This low utilization rate seemed to be due to general conservatism on the part of obstetricians, concern about potential long-term adverse effects, and specific risks in some circumstances (such as hypertension and premature rupture of membranes [PROM]). As a result, the NIH convened a Consensus Development Conference on the topic.

TABLE 1

Effective doses of antepartum corticoids for fetal maturation

BETAMETHASONE	**12 mg IM every 24 hours for 2 doses***
DEXAMETHASONE	**6 mg IM every 12 hours for 4 doses***

*Optimal timing is to start treatment between 2 and 7 days before delivery.

NIH Consensus Statement, 1994

The consensus panel reviewed the published literature and commissioned a study on the cost-effectiveness of antenatal glucocorticoids. It also asked Dr. Patricia Crowley to update a 1990 meta-analysis of 12 controlled trials on this therapy.[6] Her revised report included all randomized trials published from 1972 to 1994.[7] With this information in hand, the panel then held a conference at which experts and the public could comment on the topic.

The resulting report, published in November 1994, concluded that antenatal glucocorticoids significantly reduced the risk of mortality, RDS, and intraventricular hemorrhage in infants born between 24 and 34

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weeks' gestation.[5] Maximum benefit was achieved when administration of the drug was initiated more than 48 hours prior to delivery. There appeared to be no difference in benefit based on the gender or race of the fetus.

Two drug regimens were tested in the various prospective trials: 12 mg of betamethasone, given IM in 2 doses 24 hours apart; and 6 mg of dexamethasone, given IM in 4 doses 12 hours apart (**TABLE 1**). While these doses were chosen arbitrarily, multiple clinical trials showed them to be effective. Studies of umbilical cord blood-drug levels also noted that these doses achieved steroid concentrations in the fetus comparable to that found during a neonatal stress response.[8] No other drug or dose regimen has been studied as thoroughly or shown to be effective for preventing neonatal morbidity and mortality in premature infants.

No definite adverse effects on mother or infant were observed in any of the studies, though concerns remained—and, indeed, still exist—about an increased risk of infection in women with PROM. Of note, no studies published after the original Liggins and Howie article demonstrated an increased risk for the infants of hypertensive mothers.

It became common practice at many centers to repeat **weekly steroid courses**, so the fetus was never more than **7 days** from treatment.

Very little data exist on the long-term development of children treated with these drugs. One study followed children who received glucocorticoids and those who were given placebo up to the age of 12 years.[9] Of 102 survivors in the study, 90 were available for follow up. The result: Antenatal corticosteroid therapy appeared to have no adverse effects on growth or development in these children, though there was a trend toward delayed pubertal development in treated males.

Effects of the NIH report

Following the 1994 report, antepartum corticoid use greatly increased. In many areas, up to 60% of infants delivered prematurely were receiving treatment. But a crucial question remained unanswered by the consensus panel: How soon after the first injection would the infant have to be delivered in order for the glucocorticoids to maintain a protective effect?

In their original article, Liggins and Howie noted they could not demonstrate a statistically significant reduction in mortality or in the incidence or severity of RDS for neonates born more than 7 days after treatment.[3] Unfortunately, many readers mistakenly assumed no statistically significant benefit meant there was no benefit at all. This error was eventually developed into the concept of the "steroid window": a period extending from 48 hours to 7 days after the first steroid injection, during which the fetus would derive benefit from treatment.

What some clinicians failed to consider was that by 1 week after admission to the study, many women in both the control group and the treated group had delivered. As a result, the analysis for infants born more than 7 days after treatment were based on less data than the statistics for those delivered earlier in the study. Also, because these fetuses experienced an extra week of gestational development, they were not at as high a risk for morbidity and mortality as those born closer to the time of treatment initiation. Therefore, the statistical improvements would not be as dramatic. Nevertheless, once this "window of benefit" concept was accepted, it became common practice at many centers to repeat weekly steroid courses, so the fetus was never more than 7 days from steroid treatment. These weekly courses were continued until the fetus reached the gestational age of presumed pulmonary maturity.

Many institutions also expanded the

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indications for glucocorticoid treatment. At some hospitals, patients with a history of preterm delivery were started on weekly courses of steroids as early as 24 weeks into the pregnancy, to "keep them in the window" in case of premature delivery. Patients admitted to a hospital with a placenta previa were put on similar treatment regimens. Although this liberal use of therapy benefited many neonates, it also exposed numerous patients to repeated courses for which there was no scientific evidence. This led the NIH to reconvene the Consensus Development Conference in 2000 to consider the issue of repeat courses.

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Updated conclusions, protocols

The reconvened consensus panel reviewed the available published human and animal studies, as well as information presented at both consensus conferences.[10]

At least one animal study suggested that repeat courses resulted in improved lung mechanics and gas exchange compared to single courses,[11] though others demonstrated that repeat courses had deleterious effects on somatic and brain growth, lung growth and organization, and retinal development.[12-14]

No randomized controlled human studies addressing this question were available, and data from nonrandomized human studies, all of which were retrospective and inadequately controlled, were of limited quality. These studies suggested that repeat courses resulted in a reduction in the severity of respiratory disease,[15] but did not show convincing evidence of reduced mortality or lower long-term morbidity. Of note, none of the humans studies included infants who had multiple courses of antepartum steroids and then delivered near term. All told, conclusions were inconsistent and often conflicting, with some suggesting adverse effects while others found none.

Since repeat courses did not offer a clearly demonstrated benefit and were associated with potential adverse effects in both animal and human studies, the consensus report concluded that repeat courses of antepartum corticosteroids for fetal maturation should only be used in the context of randomized clinical trials.

At the time of the consensus conference, 4 such trials were underway or planned. Thus far, only 1 has been completed. Guinn and colleagues conducted a randomized, double-blind, placebo-controlled, intention-to-treat trial at 13 US institutions from February 1996 through April 2000. They found that weekly doses of antenatal corticosteroids did not reduce composite neonatal morbidity compared with a single course of treatment, and therefore concluded that weekly regimens should not be routinely prescribed for women at risk for preterm delivery.[16]

The remaining 3 studies comparing single- and multiple-dose courses of antenatal corticosteroids are expected to be completed in 2004. A randomized, double-blind, placebo-controlled trial started in March 2000 and sponsored by the NIH Maternal Fetal Medicine Units Network will involve 2,400 women. The Multiple Antenatal Corticosteroid Study (MACS)—a randomized, controlled trial funded by the Canadian Health Research Institute and launched in March 2001—will report on 1,900 American and Canadian women. Finally, the Trial of the Effects of Antenatal Multiple Courses of Steroids (TEAMS), organized by England's National Perinatal Epidemiology Unit, will look at the regimens in 4,000 women.

Conclusion

Until these randomized clinical trials have been completed and can offer

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conclusive results, physicians must administer antenatal glucocorticoids only in contexts supported by the evidence. To that end, only women who are clearly in preterm labor should receive this treatment, and then only in the doses outlined in the table. Since the fetus gets the most benefit from antenatal corticosteroid treatment when the drug is given between 2 and 7 days before delivery, clinicians should make every attempt to administer therapy in that time frame. ■

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Dr. Clewell reports no affiliation or financial arrangement with any of the companies that manufacture drugs or devices in any of the product classes mentioned in this article.