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Committee on Obstetric Practice

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Antenatal Corticosteroid Therapy for Fetal Maturation

ABSTRACT: A single course of corticosteroids is recommended for pregnant women between 24 weeks and 34 weeks of gestation who are at risk of preterm delivery within 7 days. A single course of antenatal corticosteroids should be administered to women with premature rupture of membranes before 32 weeks of gestation to reduce the risks of respiratory distress syndrome, perinatal mortality, and other morbidities. The efficacy of corticosteroid use at 32–33 completed weeks of gestation for preterm premature rupture of membranes is unclear, but treatment may be beneficial, particularly if pulmonary immaturity is documented. Sparse data exist on the efficacy of corticosteroid use before fetal age of viability, and such use is not recommended. A single rescue course of antenatal corticosteroids may be considered if the antecedent treatment was given more than 2 weeks prior, the gestational age is less than 32 6/7 weeks, and the women are judged by the clinician to be likely to give birth within the next week. However, regularly scheduled repeat courses or multiple courses (more than two) are not recommended. Further research regarding the risks and benefits, optimal dose, and timing of a single rescue course of steroid treatment is needed.

In 2000, the National Institute of Child Health and Human Development and the Office of Medical Applications of Research of the National Institutes of Health convened a consensus conference on antenatal steroids, entitled "Consensus Development Conference on Antenatal Corticosteroids Revisited: Repeat Courses," to address the issue of repeated courses of corticosteroids for fetal maturation. The consensus panel from this conference reaffirmed the 1994 consensus panel's recommendation of giving a single course of corticosteroids to all pregnant women between 24 weeks and 34 weeks of gestation who are at risk of preterm delivery within 7 days (1). Because of insufficient scientific evidence, the panel also recommended that repeat corticosteroid courses, including so-called "rescue therapy," should not be routinely used but should be reserved for women enrolled in clinical trials.

Multiple Weekly or Every Other Week Courses

There is no convincing scientific evidence that antenatal corticosteroid therapy increases the risk of neonatal infection, although multiple courses have been associated with fetal adrenal suppression (2). Follow-up studies of adolescents aged 14 years who were exposed to at least one course of corticosteroid treatment indicate there is no apparent risk of an adverse neurodevelopmental outcome associated with antenatal corticosteroid use (3). In a randomized trial of single versus multiple courses of antenatal corticosteroids, a reduction in birth weight and an increase in the number of infants who were small for gestational age was found, especially after four courses of corticosteroids (4). Although not consistent, six studies found decreased birth weight and head circumference with repeat courses (4–10) and three studies did not (11–13). The 2000 consensus panel concluded that studies regarding the possible benefits and risks of repeat courses of antenatal corticosteroids are limited because of their study design and "methodologic inconsistencies." The 2000 consensus panel noted that, although there is a suggestion of possible benefit from repeated courses (especially in the reduction and severity of respiratory distress), there also are animal and human data that suggest deleterious effects on the fetus regarding cerebral myelination, lung growth, and function of the hypothalamic–pituitary–adrenal axis. Follow-up of children at 2 years of age exposed to repeat courses of antenatal corticosteroids showed no significant difference in physical or neurocognitive measures in two studies (14–15),

and the same outcome was found in younger children in a third study (16). Although not statistically significant, the relative risk of cerebral palsy in infants exposed to multiple courses of antenatal corticosteroids (relative risk, 5.7; 95% confidence interval, 0.7–46.7; P=0.12) in one study is of concern and warrants further study (14). Maternal effects include increased risk of infection and suppression of the hypothalamic–pituitary–adrenal axis (6, 17).

Rescue Courses

The utility of a rescue course of steroids remains questionable for those patients who received treatment early in pregnancy and present again after more than 1–2 weeks with a recurrent or new risk of preterm birth. Although the initial data (18) suggested the benefit of steroids may decrease after 7 days, the duration of steroid benefit remains controversial (19). A multicenter randomized trial of a single rescue course was performed in 437 patients without preterm premature rupture of membranes (PROM) who had completed a single course of antenatal steroids before 30 weeks of gestation and at least 14 days before inclusion, and were judged to have a recurring threat of preterm birth in the coming week before 33 weeks of gestation (20). The investigators found a significant reduction in respiratory distress syndrome, the need for surfactant, and composite morbidity for those giving birth before 34 weeks of gestation and for the overall cohort. No increase in newborn complications or intrauterine growth restriction was identified, although the power to evaluate these individual outcomes was low. Long-term outcome data are not available for these patients.

Betamethasone Versus Dexamethasone

Betamethasone and dexamethasone are the most widely studied corticosteroids and they generally have been preferred for antenatal treatment to accelerate fetal organ maturation. Both cross the placenta in their active form and have nearly identical biologic activity. Both lack mineralocorticoid activity and have relatively weak immunosuppressive activity with short-term use. Although betamethasone and dexamethasone differ only by a single methyl group, betamethasone has a longer half-life because of its decreased clearance and larger volume of distribution (21). The 2000 consensus panel reviewed all available reports on the safety and efficacy of betamethasone and dexamethasone. It did not find significant scientific evidence to support a recommendation that betamethasone should be used preferentially instead of dexamethasone. Of the 10 trials included in a Cochrane review on this issue, there were no differences in perinatal death or alterations in biophysical activity, but there was a decreased incidence of intraventricular hemorrhage with dexamethasone treatment (22). Alternatively, an observational study reported less frequent adverse neurological outcome at 18–22 months after betamethasone exposure (23). These inconsistent and limited data are not considered sufficient to recommend one steroid regimen over the other.

Recommendations

The Committee on Obstetric Practice recommends either of the following corticosteroid courses:

- Betamethasone (12 mg) given intramuscularly 24 hours apart for two doses
- Dexamethasone (6 mg) given intramuscularly every 12 hours for four doses

A single course of corticosteroids is recommended for pregnant women between 24 weeks and 34 weeks of gestation who are at risk of preterm delivery within 7 days (24). A single course of antenatal corticosteroids should be administered to women with PROM before 32 weeks of gestation to reduce the risks of respiratory distress syndrome, perinatal mortality, and other morbidities. The efficacy of corticosteroid use at 32–33 completed weeks of gestation for preterm PROM is unclear based on available evidence, but treatment may be beneficial, particularly if pulmonary immaturity is documented. There are no data regarding the efficacy of corticosteroid use before viability, and it is not recommended. A single rescue course of antenatal corticosteroids may be considered if the antecedent treatment was given more than 2 weeks prior, the gestational age is less than 32 6/7 weeks, and the women are judged by the clinician to be likely to give birth within the next week (20). However, regularly scheduled repeat courses or multiple courses (more than two) are not recommended. Further research regarding the risks and benefits, optimal dose, and timing of a single rescue course of steroid treatment is needed.

References

1. Antenatal corticosteroids revisited: repeat courses. NIH Consens Statement 2000;17(2):1–18.
2. Kairalla AB. Hypothalamic-pituitary-adrenal axis function in premature neonates after extensive prenatal treatment with betamethasone: a case history. Am J Perinatol 1992;9:428–30.
3. Doyle LW, Ford GW, Rickards AL, Kelly EA, Davis NM, Callanan C, et al. Antenatal corticosteroids and outcome at 14 years of age in children with birth weight less than 1501 grams. Pediatrics 2000;106:E2.
4. Wapner RJ, Sorokin Y, Thom EA, Johnson F, Dudley DJ, Spong CY, et al. Single versus weekly courses of antenatal corticosteroids: evaluation of safety and efficacy. National Institute of Child Health and Human Development Maternal Fetal Medicine Units Network. Am J Obstet Gynecol 2006;195:633–42.
5. French NP, Hagan R, Evans SF, Godfrey M, Newnham JP. Repeated antenatal corticosteroids: size at birth and subsequent development. Am J Obstet Gynecol 1999;180:114–21.

6. Abbasi S, Hirsch D, Davis J, Tolosa J, Stouffer N, Debbs R, et al. Effect of single versus multiple courses of antenatal corticosteroids on maternal and neonatal outcome. Am J Obstet Gynecol 2000;182:1243–9.
7. Banks BA, Cnaan A, Morgan MA, Parer JT, Merrill JD, Ballard PL, et al. Multiple courses of antenatal corticosteroids and outcome of premature neonates. North American Thyrotropin-Releasing Hormone Study Group. Am J Obstet Gynecol 1999;181:709–17.
8. Bloom SL, Sheffield JS, McIntire DD, Leveno KJ. Antenatal dexamethasone and decreased birth weight. Obstet Gynecol 2001;97:485–90.
9. Thorp JA, Jones PG, Knox E, Clark RH. Does antenatal corticosteroid therapy affect birth weight and head circumference? Obstet Gynecol 2002;99:101–8.
10. Murphy KE, Hannah ME, William AR, Hewson SA, et al. Multiple courses of antenatal corticosteroids for preterm birth (MACS): a randomised controlled trial. Lancet 2008;372:2143–9.
11. Guinn DA, Atkinson MW, Sullivan L, Lee M, MacGregor S, Parilla BV, et al. Single vs weekly courses of antenatal corticosteroids for women at risk of preterm delivery: A randomized controlled trial. JAMA 2001;286:1581–7.
12. Pratt L, Waschbusch L, Ladd W, Gangnon R, Hendricks SK. Multiple vs. single betamethasone therapy. Neonatal and maternal effects. J Reprod Med 1999;44:257–64.
13. Shelton SD, Boggess KA, Murtha AP, Groff AO, Herbert WN. Repeated fetal betamethasone treatment and birth weight and head circumference. Obstet Gynecol 2001; 97:301–4.
14. Wapner RJ, Sorokin Y, Mele L, Johnson F, Dudley DJ, Spong CY, et al. Long-term outcomes after repeat doses of antenatal corticosteroids. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. N Engl J Med 2007;357:1190–8.
15. Crowther CA, Doyle LW, Haslam RR, Hiller JE, Harding JE, Robinson JS. Outcomes at 2 years of age after repeat doses of antenatal corticosteroids. ACTORDS Study Group. N Engl J Med 2007;357:1179–89.
16. Asztalos EV, Murphy KE, Hannah ME, Willan AR, Matthews SG, Ohlsson A, et al. Multiple courses of antenatal corticosteroids for preterm birth study: 2-year outcomes. Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study Collaborative Group. Pediatrics 2010;126:e1045–55.
17. McKenna DS, Wittber GM, Nagaraja HN, Samuels P. The effects of repeat doses of antenatal corticosteroids on maternal adrenal function. Am J Obstet Gynecol 2000;183: 669–73.
18. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972; 50:515–25.
19. Peaceman AM, Bajaj K, Kumar P, Grobman WA. The interval between a single course of antenatal steroids and delivery and its association with neonatal outcomes. Am J Obstet Gynecol 2005;193:1165–9.
20. Garite TJ, Kurtzman J, Maurel K, Clark R. Impact of a 'rescue course' of antenatal corticosteroids: a multicenter randomized placebo-controlled trial. Obstetrix Collaborative Research Network [published erratum appears in Am J Obstet Gynecol 2009;201:428]. Am J Obstet Gynecol 2009; 200:248.e1–248.e9.
21. Fanaroff AA, Hack M. Periventricular leukomalacia—prospects for prevention. N Engl J Med 1999;341:1229–31.
22. Brownfoot FC, Crowther CA, Middleton P. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD006764. DOI: 10.1002/14651858.CD006764.pub2; 10.1002/14651858.CD006764.pub2.
23. Lee BH, Stoll BJ, McDonald SA, Higgins RD. Neurodevelopmental outcomes of extremely low birth weight infants exposed prenatally to dexamethasone versus betamethasone. National Institute of Child Health and Human Development Neonatal Research Network. Pediatrics 2008;121:289–96.
24. Roberts D, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD004454. DOI: 10.1002/14651858.CD004454.pub2; 10.1002/14651858.CD004454.pub2.

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