No. 122, January 2003

Antenatal Corticosteroid Therapy for Fetal Maturation

This Committee Opinion has been approved by the Executive Committee of the Society of Obstetricians and Gynaecologists of Canada and replaces Committee Opinion No. 53 dated December 1995.

PRINCIPAL AUTHOR
Joan Crane, MD, FRCSC, St. John's NL

MATERNAL-FETAL MEDICINE COMMITTEE
Joan Crane, MD, FRCSC (Chair), St. John's NL
Anthony Armson, MD, FRCSC, Halifax NS
Monica Brunner, MD, Montreal QC
Sandra de la Ronde, MD, FRCSC, Calgary AB
Dan Farine, MD, FRCSC, Toronto ON
Lisa Keenan-Lindsay, RN, Oakville ON
Line Leduc, MD, FRCSC, Montreal QC
Carol Schneider, MD, FRCSC, Winnipeg MB
John Van Aerde, MD, FRCPC, Edmonton AB

Abstract

Objectives: To assess the benefits and risks of antenatal corticosteroid therapy for fetal maturation.

Options: To administer antenatal corticosteroids or not to women at risk of preterm birth.

Outcomes: Perinatal morbidity, including: respiratory distress syndrome, intraventricular hemorrhage, infection, adrenal suppression, somatic and brain growth; perinatal mortality; and maternal morbidity, including infection and adrenal suppression.

Evidence: MEDLINE and PubMed searches 1996 to August 2002 for English-language articles related to antenatal corticosteroid therapy for fetal maturation, the Cochrane Library, and national statements including that of the National Institutes of Health (NIH), the American College of Obstetricians and Gynecologists, and the Royal College of Obstetricians and Gynaecologists.

Values: The evidence obtained was reviewed and evaluated by the Maternal-Fetal Medicine Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC) and recommendations were made according to guidelines developed by the Canadian Task Force on the Periodic Health Exam.

Benefits and Harms: A single course of corticosteroids reduces perinatal mortality, respiratory distress syndrome, and intraventricular hemorrhage. Information regarding repeat courses of corticosteroids is limited and conflicting, with many studies being retrospective and non-randomized. Some studies suggested a reduction in respiratory distress syndrome with repeat courses, but some found increased rates of neonatal and maternal infection; fetal, neonatal, and maternal adrenal suppression; decreased fetal or neonatal somatic and brain growth; and increased perinatal mortality.

Recommendations: The SOGC supports the recommendations of the NIH Consensus Development Panel:

1. All pregnant women between 24 and 34 weeks' gestation who are at risk of preterm delivery within 7 days should be considered candidates for antenatal treatment with a single course of corticosteroids. (I-A)
2. Treatment should consist of two 12 mg doses of betamethasone given IM 24 hours apart, or four 6 mg doses of dexamethasone given IM 12 hours apart (I-A). There is no proof of efficacy for any other regimen.
3. Because of insufficient scientific data from randomized clinical trials regarding efficacy and safety, repeat courses of corticosteroids should not be used routinely (II-2E) but be reserved for women participating in randomized controlled trials.

Validation: This Committee Opinion has been reviewed and approved by the Maternal-Fetal Medicine Committee of the SOGC and approved by SOGC Council.

Key Words
Corticosteroid, preterm birth, respiratory distress syndrome, perinatal morbidity and mortality

J Obstet Gynaecol Can 2003;25(1):45–8.

INTRODUCTION

Preterm birth is a significant cause of perinatal morbidity and mortality,[1] accounting for up to 85% of neonatal mortality not caused by lethal malformations.[2] It is a major determinant of serious neonatal and infant morbidity including respiratory distress syndrome (RDS), necrotizing enterocolitis, intraventricular hemorrhage (IVH), and long-term neurodevelopmental handicap.[3]

In addition to its medical importance, preterm delivery has an important economic effect on both short- and long-term care of these preterm infants.[4] The lifetime cost of a surviving preterm infant weighing less than 2500 g, including initial hospitalization, rehospitalization in the first years of life, and long-term morbidity with and without institutionalization, is over $600,000, with an annual cost in Canada of over eight billion dollars attributed to prematurity.[5]

Despite improvements in perinatal care, the preterm birth rate in Canada has increased from 6.3% in 1981 to 6.8% in 1992 through 1994, a relative increase of 9%.[6]

The quality of evidence reported in this document has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam (Table).[7]

EVIDENCE AND OPINION

A meta-analysis of studies evaluating the use of corticosteroids in women at increased risk of preterm birth has concluded that a single course of corticosteriods reduced perinatal mortality (OR 0.60, 95% CI 0.48–0.75), respiratory distress syndrome (OR 0.53, 95% CI 0.44–0.63), and intraventricular hemorrhage (OR 0.48, 95% CI 0.32–0.72).[8] In 1994, the National Institutes of Health (NIH) sponsored a Consensus Development Conference on the effect of corticosteroids for fetal lung maturation on perinatal outcomes, concluding that a single course of corticosteroids should be considered for women at risk of preterm delivery.[9] It concluded that the optimal benefit of corticosteroids lasted for 7 days, and further research was needed to determine the possible benefit of repeat corticosteroid doses 7 days after the initial course.[9] Despite this call for further research, repeat and "rescue" courses of corticosteroids have been increasingly used in clinical practice outside of clinical trials.[9-14]

The NIH again convened a consensus panel in 2000 to address the issue of antenatal corticosteroid use for preterm women, reaffirming the benefit of a single course of corticosteroids, but concluding that current data did not support the routine use of repeat courses.[14]

Previous studies in animal models have tried to evaluate the benefits and risks of repeat courses of corticosteroids. The findings include improved lung mechanics, gas exchange, and maturation,[15-17] but also increased risk of reduced lung, brain, and overall body growth,[14-30] delayed cerebral myelination,[20] as well as deleterious effects on the hypothalamic-pituitary-adrenal axis.[17,21,26,27,30]

Studies in humans of repeat corticosteroids use are limited, many being non-randomized and retrospective, and therefore subject to methodologic problems.[15,30] Some studies suggested a reduction in the incidence and severity of RDS,[30-34] increased

QUALITY OF EVIDENCE ASSESSMENT	CLASSIFICATION OF RECOMMENDATIONS
The quality of evidence reported in this document has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam.[7] I: Evidence obtained from at least one properly randomized controlled trial. II-1: Evidence from well-designed controlled trials without randomization. II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group. II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category. III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.	Recommendations included in this document have been adapted from the ranking method described in the Classification of Recommendations found in the Report of the Canadian Task Force on the Periodic Health Exam.[7] A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination. B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination. C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination, but recommendations may be made on other grounds. D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination. E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

rates of maternal and neonatal infection,[30,31,35,37] maternal and fetal adrenal suppression,[38-40] decreased fetal or neonatal somatic and brain growth,[31,38,41] and increased perinatal mortality.[36,38]

A randomized trial of single versus weekly courses of antenatal corticosteroids for women at risk of preterm delivery was stopped after an interim analysis found that weekly courses did not reduce composite neonatal morbidity (RR 0.80, 95% CI 0.59–1.10), but resulted in a trend toward more cases of severe IVH (9 vs 2 cases, $p = 0.06$) and chorioamnionitis (24.1% vs 17.8%, $p = 0.09$) in the weekly group.[42] This study has been criticized for being terminated before its calculated sample size could have adequate power to find possible reduction in adverse perinatal outcome.[43,44]

Both betamethasone and dexamethasone have been shown to have benefit for the fetus.[8,14] A recent retrospective study comparing betamethasone and dexamethasone found that betamethasone, but not dexamethasone, reduced the risk of periventricular leukomalacia.[45] This finding has not been reported by other investigators. The NIH consensus panel did not feel that there was enough evidence to recommend betamethasone over dexamethasone.[14] Betamethasone use has been associated with transient reduction in fetal heart rate variability and fetal movement.[46,47]

RECOMMENDATIONS

The SOGC Maternal-Fetal Medicine Committee, consistent with recommendations of the American College of Obstetricians and Gynecologists[48] and the Royal College of Obstetricians and Gynaecologists,[49] supports the recommendations of the NIH Consensus Development panel:[14]

1. **All pregnant women between 24 and 34 weeks' gestation who are at risk of preterm delivery within 7 days should be considered candidates for antenatal treatment with a single course of corticosteroids. (I-A)**
2. **Treatment should consist of two 12 mg doses of betamethasone given IM 24 hours apart, or four 6 mg doses of dexamethasone given IM 12 hours apart (I-A). There is no proof of efficacy for any other regimen.**
3. **Because of insufficient scientific data from randomized clinical trials regarding efficacy and safety, repeat courses of corticosteroids should not be used routinely (II-2E) but be reserved for women participating in randomized controlled trials.**

REFERENCES

1. Morrison JC. Preterm birth: a puzzle worth solving. Obstet Gynecol 1990;76:5S–12S.
2. Rush RW, Keirse MJNC, Howat P, Baum JD, Anderson ABM, Turnbull AC. Contribution of preterm delivery to perinatal mortality. Br Med J 1976;2:965–8.
3. McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. N Eng J Med 1985;312:82–90.
4. Creasy RK, Merkatz IR. Prevention of preterm birth: clinical opinion. Obstet Gynecol 1990;76:2S–4S.
5. Moutquin JM, Milot-Roy V, Irion O. Preterm birth prevention: effectiveness of current strategies. J Soc Obstet Gynaecol Can 1996;18:571–88.
6. Joseph KS, Kramer MS, Marcoux S, Ohlsson A, Wen SW, Allen A, et al. Determinants of preterm birth rates in Canada from 1981 through 1983 and from 1992 through 1994. N Engl J Med 1998;339:1434–9.
7. Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on the Periodic Health Exam. Ottawa: Canada Communication Group; 1994. p. xxxvii.
8. Crowley P. Prophylactic corticosteroids for preterm birth (Cochrane Review). In: The Cochrane Library. Issue 4. Oxford: Update Software; 2002.
9. National Institutes of Health Consensus Development Panel. National Institutes of Health Consensus Development Conference Statement. Effects of corticosteroid for fetal maturation on perinatal outcomes, February 28–March 2, 1994. J Am Med Assoc 1995;273:413–7.
10. Brocklehurst P, Gates S, McKenzie-McHarg K, Alfirevic Z, Chamberlain G. Are we prescribing multiple courses of antenatal corticosteroids? A survey of practice in the UK. Br J Obstet Gynaecol 1999;106(9):977–9.
11. O'Connell MP. Comment on: Brocklehurst P, et al. Are we prescribing multiple courses of antenatal corticosteroids? A survey of practice in the UK [Br J Obstet Gynaecol 1999;106(9):977–9]. Br J Obstet Gynaecol 2000;107(4):577–8.
12. Spencer C, Pakarian F. Comment on: Brocklehurst P, et al. Are we prescribing multiple courses of antenatal corticosteroids? A survey of practice in the UK [Br J Obstet Gynaecol 1999;106(9):977–9]. Br J Obstet Gynaecol 2000;107(3):434–5.
13. Quinlivan JA, Evans SF, Dunlop SA, Beazley LD, Newnham JP. Use of corticosteroids by Australian obstetricians – a survey of clinical practice. Aust N Z J Obstet Gynaecol 1998;38:1–7.
14. National Institutes of Health Consensus Development Panel. Antenatal corticosteroids revisited: repeat courses – National Institutes of Health Consensus Development Conference Statement, August 17–18, 2000. Obstet Gynecol 2001:98:144–50.
15. Smith GN, Kingdom JCP, Penning DH, Matthews SG. Antenatal corticosteroids: is more better? Lancet 2000;355:251–2.
16. Stewart JD, Sienko AE, Gonzalez CL, Christensen HD, Rayburn WF. Placebo-controlled comparison between a single dose and a multidose of betamethasone in accelerating lung maturation of mice offspring. Am J Obstet Gynecol 1998;179:1241–7.
17. Pratt L, Magness RR, Phernetton T, Hendricks SK, Abbott DH, Bird IM. Repeated use of betamethasone in rabbits: effect of treatment variation on adrenal suppression, pulmonary maturation, and pregnancy outcome. Am J Obstet Gynecol 1999;180:995–1005.
18. Jobe AH, Wada N, Berry LM, Ikegami M, Ervin MG. Single and repetitive maternal glucocorticoid exposures reduce fetal growth in sheep. Am J Obstet Gynecol 1998;178:880–5.
19. Huang WL, Beazley LD, Quinlivan JA, Evans SF, Newnham JP, Dunlop SA. Effect of corticosteroids on brain growth in fetal sheep. Obstet Gynecol 1999;94:213–8.
20. Quinlivan JA, Dunlop SA, Newnham J, Evans SF, Beazley LD. Repeated, but not single, maternal administration of corticosteroids delays myelination in the brain of fetal sheep. Prenat Neonat Med 1999;4:47–55.
21. Uno H, Lohmiller L, Thieme C, Kemnitz JW, Engle MJ, Roecker EB, et al. Brain damage induced by prenatal exposure to dexamethasone in fetal rhesus macaques, I: Hippocampus. Dev Brain Res 1990;53:157–67.
22. Uno H, Eisele S, Sakai A, Shelton S, Baker E, Dejesus O, et al. Neurotoxicity of glucocorticoids in the primate brain. Horm Behav 1994;28:336–48.
23. Stewart JD, Gonzalez CL, Christensen HD, Rayburn WF. Impact of multiple antenatal doses of betamethasone on growth and development of mice offspring. Am J Obstet Gynecol 1997;177:1138–44.
24. Jobe AH, Newnham J, Willet K, Sly P, Ikegami M. Fetal versus maternal and gestational age effects of repetitive antenatal glucocorticoids. Pediatrics 1998;102:1116–25.

25. Ikegami M, Jobe AH, Newnham J, Polk DH, Willet KE, Sly P. Repetitive prenatal glucocorticoids improve lung function and decrease growth in preterm lambs. Am J Respir Crit Care Med 1997;156:178–84.
26. Levitt NS, Lindsay RS, Holmes MC, Seckl JR. Dexamethasone in the last week of pregnancy attenuates hippocampal glucocorticoid receptor gene expression and elevates blood pressure in the adult offspring in the rat. Neuroendocrinology 1996;64:412–8.
27. Benediktsson R, Lindsay RS, Noble J, Seckl JR, Edwards CR. Glucocorticoid exposure in utero: new model for adult hypertension. Lancet 1993;341:339–41.
28. Pratt L, Magness RR, Phernetton T, Hendricks SK, Abbott DH, Bird IM. Repeated use of betamethasone in rabbits: effects of treatment variation on adrenal suppression, pulmonary maturation, and pregnancy outcome. Am J Obstet Gynecol 1999;180:995–1005.
29. Tabor BL, Rider ED, Ikegami M, Jobe AH, Lewis JF. Dose effects of antenatal corticosteroids for induction of lung maturation in preterm rabbits. Am J Obstet Gynecol 1991;164:675–81.
30. Walfisch A, Hallak M, Major M. Multiple courses of antenatal steroids: risks and benefits. Obstet Gynecol 2001;98:491–7.
31. Abbasi S, Hirsch D, Davis J, Tolasa 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.
32. Vermillion ST, Bland ML, Soper DE. Effectiveness of a rescue dose of antenatal betamethasone after an initial single course. Am J Obstet Gynecol 2001;185:1086–9.
33. 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.
34. Elimian A, Verma U, Visintainer P, Tejani N. Effectiveness of multidose antenatal steroids. Obstet Gynecol 2000;95:34–6.
35. Vermillion ST, Soper DE, Chasedunn-Roark J. Neonatal sepsis after betamethasone administration to patients with preterm premature rupture of membranes. Am J Obstet Gynecol 1999;181:320–7.
36. Vermillion ST, Soper DE, Newman RB. Neonatal sepsis and death after multiple courses of antenatal betamethasone therapy. Am J Obstet Gynecol 2000;183:810–4.
37. Rotmensch S, Vishne TH, Celentano C, Dan M, BenRafael Z. Maternal infectious morbidity following multiple courses of betamethasone. J Infect 1999;39:49–54.
38. 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.
39. Halel KJ, Gordon MC, Lightner CR, Barth WH Jr. Adrenal suppression induced by betamethasone in women at risk for premature delivery. Obstet Gynecol 2000;96:287–90.
40. McKenna DS, Wittber GM, Nagaraja HN, Samuels P. The effect of repeat doses of antenatal corticosteroids on maternal adrenal function. Am J Obstet Gynecol 2000;183:669–73.
41. 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.
42. Guinn DA, Atkinson MW, Sullivan L, Lee MJ, MacGregor S, Parilla BV, et al. Single vs weekly courses of antenatal corticosteroids for women at risk of preterm delivery. J Am Med Assoc 2001;286:1581–7.
43. Murphy KE, Hannah M, Brocklehurst P. Are weekly courses of antenatal steroids beneficial or dangerous [letter]. J Am Med Assoc 2002:287:188–90.
44. Jenkins TM, Wapner RJ, Thom EA, Spong CY. Are weekly courses of antenatal steroids beneficial or dangerous [letter]. J Am Med Assoc 2002;287:187–8.
45. Baud O, Foix-L'Helias L, Kaminski M, Audibert F, Jarreau PH, Papiernik E, et al. Antenatal glucocorticosteroid treatment and cystic periventricular leukomalacia in very premature infants. N Engl J Med 1999; 341:1190–6.
46. Senat MV, Minoui S, Multon O, Fernadez H, Frydonan R, Ville Y. Effect of dexamethasone and betamethasone on fetal heart rate variability in preterm labour: a randomised study. Br J Obstet Gynaecol 1998; 105:749–55.
47. Milder EJ, Derks JB, Visser GH. Antenatal corticosteroid therapy and fetal behavior: a randomised study of the effects of betamethasone and dexamethasone. Br J Obstet Gynaecol 1997;104:1239–47.
48. American College of Obstetricians and Gynecologists. Obstetric Practice Committee. Antenatal corticosteroid therapy for fetal maturation. ACOG Committee Opinion, No. 273. Obstet Gynecol 2002;99(5 Pt 1):871–3.
49. Penney GC, on behalf of the Guidelines and Audit Sub-Committee. Royal College of Obstetricians and Gynaecologists. Antenatal corticosteroids to prevent respiratory distress syndrome. RCOG; 1999. Available on-line at <http://www.rcog.org.uk/guidelines.asp?PageID=106&GuidelineID=3>. Cited November 25, 2002.