ANTENATAL CORTICOSTEROIDS REVISITED

REPEAT COURSES

NIH Consensus Development Conference

PROGRAM

Office of the Director

National Institutes of Health

NIH Consensus Development Conference on

ANTENATAL CORTICOSTEROIDS REVISITED

REPEAT COURSES

August 17–18, 2000
Masur Auditorium
National Institutes of Health
Bethesda, Maryland

Sponsored by:
National Institute of Child Health and Human Development
NIH Office of Medical Applications of Research

Cosponsored by:
National Institute of Nursing Research
National Heart, Lung, and Blood Institute

National Institutes Of Health

CONTENTS

INTRODUCTION

Preterm delivery is a major cause of death and illness in infants. Corticosteroid treatment of pregnant women delivering prematurely was first introduced in 1972 to enhance fetal lung maturity. Subsequent research has focused on the ability of glucocorticoids to reduce mortality and brain injury in preterm neonates.

In 1994, the National Institutes of Health sponsored a Consensus Development Conference on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes to assess the effectiveness of antenatal glucocorticoid therapy. The consensus panel concluded, in part, that giving corticosteroids to pregnant women at risk for preterm delivery reduces the risk of death, respiratory distress syndrome, and intraventricular hemorrhage in their preterm infants.

The 1994 panel noted that optimal benefit of antenatal corticosteroid therapy lasts 7 days. The panel also noted that the potential benefits and risks of repeated administration of antenatal corticosteroids 7 days after the initial course are unknown and called for additional research on this issue.

The NIH is organizing this 1½ day conference to present research on repeat courses of antenatal corticosteroid therapy. After a day of presentations and audience discussion, an independent, non-Federal consensus development panel will weigh the scientific evidence and write a draft statement that will be presented to the audience on the second day. The panel's statement will address these questions:

- Is the evidence on benefits and risks of repeat courses of antenatal corticosteroids sufficient to permit consensus recommendations?

- If so, what are the recommendations?
- If not, what additional information should be obtained?

General Information

Conference sessions will be held in the Masur Auditorium of the Clinical Center (Building 10), National Institutes of Health, Bethesda, Maryland. Sessions will run from 8 a.m. to 3 p.m. on Thursday and from 8:30 a.m. to 12:30 p.m. on Friday. The telephone number for the message center is (301) 496-2520.

Cafeteria

The cafeteria in the Clinical Center is located one floor below the auditorium in the basement of the building. It is open from 7 a.m. to 2:30 p.m., serving breakfast and lunch.

Sponsors

The primary sponsors of this conference are the National Institute of Child Health and Human Development and the NIH Office of Medical Applications of Research. Additional sponsors are the National Institute of Nursing Research and the National Heart, Lung, and Blood Institute.

Statement of Interest

In accordance with ACCME requirements, each speaker presenting at this conference has been asked to submit documentation outlining all outside involvement pertaining to the subject area. Please refer to the chart in your participant packet for details.

AGENDA

THURSDAY, AUGUST 17, 2000

8:00 a.m. Opening Remarks and Acknowledgements
Duane Alexander, M.D., Director
National Institute of Child Health
and Human Development

8:10 a.m. Charge to the Panel
Barnett Kramer, M.D., M.P.H., Director
Office of Medical Applications of Research

8:20 a.m. Conference Overview
Larry C. Gilstrap III, M.D.
Emma Sue Hightower Chairman and Professor
Department of Obstetrics, Gynecology, and
Reproductive Sciences
University of Texas-Houston Medical School

I. Overview

8:25 a.m. Criteria for Evaluating the Quality of Evidence
John C. Sinclair, M.D., Professor
Department of Pediatrics
McMaster University Medical Center

8:40 a.m. Pharmacology of Corticosteroids
Robert M. Ward, M.D., FAAP, F.C.P., Professor
Department of Pediatrics
University of Utah School of Medicine

8:55 a.m. Glucocorticoids and Normal Development
James F. Padbury, M.D., Professor and Vice Chairman
Department of Pediatrics
Brown University School of Medicine
Pediatrician-in-Chief
Women and Infants Hospital of Rhode Island

9:10 a.m. History of Repeat Courses and Patterns of Current Use in the United States, the United Kingdom, and Australia
Michael Socol, M.D., Professor
Section of Maternal-Fetal Medicine
Department of Obstetrics and Gynecology
Northwestern University Medical School

II. Preclinical Studies

9:30 a.m. Review of Effects of Repeat Courses of Antenatal Steroids in Animal Models
Alan Jobe, M.D., Ph.D., Professor of Pediatrics
Children's Hospital Medical Center of Cincinnati

III. Clinical Evidence

10:00 a.m. Multicenter Randomized Controlled Trial on Repeat Courses
Deborah Guinn, M.D., Assistant Professor
Department of Obstetrics and Gynecology
University of Colorado Health Sciences Center

10:15 a.m. Data on Repeat Courses of Antenatal Steroids From the TRH Trial
Beverly Banks, M.D., Ph.D., Neonatologist
Division of Neonatology
Children's Hospital of Philadelphia

10:30 a.m. Discussion

11:00 a.m. Long-Term Outcome After Repeat Courses:
French et al. Study
Noel French, MBChB, FRACP, Head of Neonatal Followup
King Edward Memorial Hospital, Australia

11:15 a.m. Long-Term Outcome After Repeat Courses:
Esplin et al. Study
M. Sean Esplin, M.D., Instructor
Division of Maternal-Fetal Medicine
Department of Obstetrics and Gynecology
University of Utah Health Sciences Center

11:30 a.m. Discussion

12:00 p.m. Lunch

1:00 p.m. Short-Term Outcome After Repeat Courses
James R. Scott, M.D., Professor
Department of Obstetrics and Gynecology
University of Utah Health Sciences Center

1:20 p.m. Review of Repeat Courses in Patients With Special Circumstances and Populations
Brian Mercer, M.D., Director, Maternal-Fetal Medicine
Department of Obstetrics and Gynecology
MetroHealth Medical Center

1:40 p.m. Review of Design of Ongoing Trials in the United States, the United Kingdom, Australia, and Canada
Ronald J. Wapner, M.D., Director
Division of Maternal-Fetal Medicine
Thomas Jefferson University Hospital

2:00 p.m. Discussion

2:30 p.m. Comments from Organizations

3:00 p.m. Adjournment (Panel Executive Session)

FRIDAY, AUGUST 18, 2000

8:30 a.m. Presentation of Consensus Statement
Larry C. Gilstrap III, M.D.
Emma Sue Hightower Chairman and Professor
Department of Obstetrics, Gynecology, and Reproductive Sciences
University of Texas-Houston Medical School

8:50 a.m. Discussion

10:00 a.m. Panel Meets in Executive Session

11:30 a.m. Press Conference

12:30 a.m. Adjournment

PANEL MEMBERS

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BIBLIOGRAPHY OF BACKGROUND MATERIALS

Abbasi S, Hirsch D, Davis J, Tolosa J, Sivieri E, Grous M, et al. Effect of single versus multiple courses of antenatal steroids on neonatal outcome of very low birthweight infants. Pediatr Res 1999;45:179A, abstract 1048.

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.

Abbasi S, Sivieri E, McGowan M, Gerdes J. Effects of multiple courses of antenatal steroids as compared to single course on neonatal lung mechanics. Pediatr Res 1999;45:292A, abstract 1721.

Allen VM, Allen AC, Usher RH, Liston RM. The effect of multiple courses of maternal antenatal steroids on the prevention of complications of prematurity. Am J Obstet Gynecol 1997;176:S48, abstract 136.

Andersen HF, Erhart B. Repeated corticosteroid doses have no effect on birth weight. Am J Obstet Gynecol 1998;178:S183, abstract 650.

Banks BA, Cnaan A, Morgan MA, Parer JT, Merrill JD, Ballard PL, et al. Multiple courses of antenatal corticosteroids and outcome of premature neonates. Am J Obstet Gynecol 1999;3:1-9.

Banks BA, Merrill, JD, Cnaan A, Macones G, Samilio D, Ballard R. Multiple courses of antenatal corticosteroids (ANCS): association with increased mortality and early severe lung disease (ESLD) in preterm neonates. Pediatrics 1999;104:739, abstract 8.

Bloom SL, Sheffield JS, Cox SM, McIntire DM, Leveno KJ. Is dexamethasone for fetal maturation associated with diminished fetal growth? Am J Obstet Gynecol 1999;180:S104, abstract 347.

Debbs R, Abbasi S, Tolosa J, Weiner S, Wapner R. Does serial versus single course betamethasone therapy increase neonatal morbidity? Am J Obstet Gynecol 1997;176:S47, abstract 129.

Demasio K, Benitz WE, Druzin M. Multiple course antenatal steroids in pregnancies delivering from 26-34 weeks decreases mean airway pressure. J Soc Gynecol Invest 1997;4:269A, abstract 754.

Dubiel M, Breborowicz GH, Gudmundsson S, Maršál K. Fetal lung power Doppler imaging and velocimetry before and after repeated betamethasone treatment. Prenat Neonat Med 1999;Jul 7:290-5.

Elimian A, Verma U, Visintainer P, Tejani N. Effectiveness of multidose antenatal steroids. Obstet Gynecol 2000;182:34-6.

Esplin MS, Fausett MB, Smith S, Oshiro BT, Porter TF, Branch DW, et al. Multiple courses of antenatal steroids are associated with a delay in long-term psychomotor development in children with birth weights <1,500 grams. Am J Obstet Gynecol 1999;180:S24, abstract 27.

Esters DM, Pass J, Egan JFX. Serial betamethasone use in a clinic practice: does it affect fetal growth? Am J Obstet Gynecol 2000; 182:abstract 122.

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.

Ghidini A, Salafia CM, Minior VK. Repeated courses of steroids in preterm membrane rupture do not increase the risk of histologic chorioamnionitis. Am J Perinatol 1997;14:309-13.

Guinn DA, BMZ study group. Multicenter randomized trial of single versus weekly courses of antenatal corticosteroids (ACS): interim analysis. Am J Obstet Gynecol Jan 2000;182:abstract 3.

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.

Jazayeri A, Gavrila D, Sincich T. Relationship between the number of antenatal steroid treatments for fetal lung maturity and neonatal morbidity. Am J Obstet Gynecol 2000;182:abstract 138.

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.

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;178:1-9.

Kirschbaum TH. Commentary on article by French NP, Hagan R, Evans SF, et al. Year Book of Obstetrics, Gynecology, and Women's Health 2000. Mosby; 2000.

Lescale K, Johnson LM, Dobtsis I, Divon MY. Weekly steroids as prophylaxis in preterm delivery: is there maternal adrenal suppression? Am J Obstet Gynecol 1999;180:S102, abstract 340.

Macones GA, Banks B, Cnaan D, Stamilio D, Merrill J, Morgan MA, et al. Multiple course antenatal steroids are independently associated with increased mortality in neonates born at less than 28 weeks gestation. Am J Obstet Gynecol 1999;180:S103, abstract 345.

Maher J, Collins J, Bowling S, Williamson K, Tolaymat L, McEvoy C. Timing of antenatal steroids and neonatal pulmonary mechanics. Am J Obstet Gynecol 2000;182:abstract 22.

McEvoy C, Bowling S, Sontage B, Stewart M. Timely repetitive antenatal steroids (AS) vs. single course AS: effect on functional residual capacity (FRC) and respiratory compliance (CRS) in preterm infants. Pediatr Res 1996;39:229A, abstract 1357.

McEvoy C, Bowling S, Sontage B, Stewart M. Timely repetitive antenatal steroids (AS) vs. single course AS: effect on functional residual capacity (FRC) and respiratory compliance (CRS) in preterm infants. J Invest Med 1996;44:A44.

McKenna DS, Wittber GM, Samuels P. The effects of repeated doses of antenatal cortiocosteroids on maternal adrenal function. Am J Obstet Gynecol 1999;180:S15, abstract 35.

Mercer B, Egerman RS, Carr T, Sibai BM. Is there a need for serial corticosteroid administration before preterm delivery? Am J Obstet Gynecol 1998;178:S182, abstract 646.

Mirabile C, Draper M, Veille JC, Mueller-Heubach E. Single versus multiple course glucocorticoid administration and effects on fetal growth. Am J Obstet Gynecol 1998;178:S183, abstract 649.

Polk DH, Ikegami M, Jobe AH, Sly P, Kohan R, Newnham J. Preterm lung function after retreatment with antenatal betamethasone in preterm lambs. Am J Obstet Gynecol 1997;176:308-15.

Quinlivan JA, Beazley LD, Evans SF, Newnham JP, Dunlop SA. Retinal maturation is delayed by repeated, but not single, maternal injections of betamethasone in sheep. Eye 2000;14:93-8.

Quinlivan JA, Evans SF, Dunlop SA, Beazley LD, Newnham JP. Use of corticosteroids by Australian obstetricians – a survey of clinical practice. Aust NZ J Obstet Gynaecol 1998;38:1-7.

Rotmensch S, Vishne TH, Celentano C, Dan M, Ben-Rafael Z. Maternal infectious morbidity following multiple courses of betamethasone. J Infect 1999;39:49-54.

Sinervo K, Lange I. Maternal and neonatal outcomes following single versus multiple courses of corticosteroids. Am J Obstet Gynecol 2000;182:abstract 103.

Sinha A. Letter and comment. Are we prescribing multiple courses of antenatal corticosteroids? A survey of practice in the UK. Br J Obstet Gynaecol 2000;107:578.

Smith GN, Kingdom JC, Penning DH, Matthews SG. Antenatal corticosteroids: is more better? Lancet 2000;355:251-2.

Smith LM, Qureshi N, Chao CR. Effects of single and multiple courses of antenatal glucocorticoids in preterm newborns less than 30 weeks' gestation. J Matern Fetal Med 2000;9:131-5.

Spencer C, Neales K. Antenatal corticosteroids to prevent neonatal respiratory distress syndrome. BMJ 2000;320:325-6.

Spencer C, Pakarian F. Letter. Are we prescribing multiple courses of antenatal corticosteroids? A survey of practice in the UK. Br J Obstet Gynaecol 2000;107:434-5.

Stewart JD, Sienko AE, Gonzalez CL, Christensen HD, Rayburn WF. Is a multidose of betamethasone more beneficial than a single dose in accelerating fetal lung maturation? Am J Obstet Gynecol 1998;178:S182, abstract 647.

Stone J, Lapinski R, Eddleman K, Gallousis F, Berkowitz R. Single vs multiple courses of steroids for fetal maturation: is more better? Am J Obstet Gynecol Jan 1997;176:S48, abstract 134.

Thorp JA, Yeast JD, Cohen GR, Wickstrom EA, D'Angelo LJ. Repeated antenatal betamethasone and perinatal outcome. Am J Obstet Gynecol 1999;180:abstract 23.

Vermillion S, Soper D, Bland M, Newman R. Effectiveness of antenatal betamethasone after preterm premature rupture of the membranes. Am J Obstet Gynecol 2000;182:abstract 48.

Vermillion S, Soper D, Newman R. Neonatal sepsis and death after multiple doses of antenatal betamethasone. Am J Obstet Gynecol 1999;180:S24, abstract 28.

Walther FJ, Jobe AH, Ikegami M. Repetitive prenatal glucocorticoid therapy reduces oxidative stress in the lungs of preterm lambs. J Appl Physiol 1998;85:273-8.