

NIH Consensus Statement

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Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes

NATIONAL INSTITUTES OF HEALTH
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This statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

Abstract

The National Institutes of Health Consensus Development Conference on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes brought together specialists in obstetrics, neonatology, pharmacology, epidemiology, and nursing; basic scientists in physiology and cellular biology; and the public to address the following questions: (1) For what conditions and purposes are antenatal corticosteroids used, and what is the scientific basis for that use? (2) What are the short-term and long-term benefits of antenatal corticosteroid treatment? (3) What are the short-term and long-term adverse effects for the infant and mother? (4) What is the influence of the type of corticosteroid, dosage, timing and circumstances of administration, and associated therapy on treatment outcome? (5) What are the economic consequences of this treatment? (6) What are the recommendations for use of antenatal corticosteroids? and (7) What research is needed to guide clinical care? Following 1½ days of presentations by experts and discussion by the audience, a consensus panel weighed the evidence and prepared their consensus statement.

The consensus panel concluded that antenatal corticosteroid therapy for fetal maturation reduces mortality, respiratory distress syndrome, and intraventricular hemorrhage in preterm infants. These benefits extend to a broad range of gestational ages (24–34 weeks) and are not limited by gender or race. Although the beneficial effects of corticosteroids are greatest more than 24 hours after beginning treatment, treatment less than 24 hours in duration may also improve outcomes. The benefits of antenatal corticosteroids are additive to those derived from surfactant therapy.

In the presence of preterm premature rupture of the membranes, antenatal corticosteroid therapy reduces the frequency of respiratory distress syndrome, intraventricular hemorrhage, and neonatal death, although to a lesser extent than with intact membranes. Whether this therapy

increases either neonatal or maternal infection is unclear. However, the risk of intraventricular hemorrhage and death from prematurity is greater than the risk from infection.

Data from trials with followup of children up to 12 years indicate that antenatal corticosteroid therapy does not adversely affect physical growth or psychomotor development.

Antenatal corticosteroid therapy is indicated for women at risk of premature delivery with few exceptions and will result in a substantial decrease in neonatal morbidity and mortality, as well as substantial savings in health care costs. The use of antenatal corticosteroids for fetal maturation is a rare example of a technology that yields substantial cost savings in addition to improving health.

The full text of the consensus panel's statement follows.

Introduction

Preterm delivery occurs in 7–10 percent of all pregnancies and is a major cause of infant mortality and morbidity. In addition, preterm births are associated with more than \$2 billion in health care costs annually. Preterm infants account for the majority of all neonatal deaths. Immature infants may have numerous complications including respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), sepsis, patent ductus arteriosus (PDA), and retinopathy of prematurity. RDS is often the most acute problem of the very immature infant and, along with IVH, accounts for a significant proportion of neonatal deaths. Although most premature infants survive without major sequelae, some require rehospitalization and special services.

Corticosteroid treatment of pregnant women delivering prematurely was first introduced in 1972 to enhance fetal lung maturity. A recent meta-analysis concluded that corticosteroid administration prior to anticipated preterm delivery is associated with a large reduction in the incidence of early neonatal death, RDS, IVH, and NEC.

Despite evidence of beneficial effects from both experimental models and randomized controlled trials in humans, a minority of women delivering prematurely receive antenatal corticosteroid treatment. In reports from approximately 500 perinatal centers, only 12–18 percent of women who deliver preterm infants of 501–1,500 grams birthweight are treated with antenatal corticosteroids. Clinicians are not treating many patients who might benefit because of concerns about the efficacy of corticosteroids and the potential complications of treatment in certain conditions. Use of this therapy is further impeded by lack of access to prenatal care and to appropriate delivery services.

To address these issues, the National Institute of Child Health and Human Development, together with the Office of Medical Applications of Research of the National Institutes of Health, convened a Consensus Development Conference on the Effect of Corticosteroids for Fetal Maturation on

Perinatal Outcomes. The conference was cosponsored by the National Heart, Lung, and Blood Institute and the National Institute of Nursing Research. After a year of study and preparation concluding with 1½ days presentations by experts in the relevant fields and discussion from the audience, an independent consensus panel composed of representatives from the medical and related scientific disciplines, as well as representatives from the public, considered the evidence and formulated a consensus statement in response to the following key questions:

- For what conditions and purposes are antenatal corticosteroids used, and what is the scientific basis for that use?
- What are the short-term and long-term benefits of antenatal corticosteroid treatment?
- What are the short-term and long-term adverse effects for the infant and mother?
- What is the influence of the type of corticosteroid, dosage, timing and circumstances of administration, and associated therapy on treatment outcome?
- What are the economic consequences of this treatment?
- What are the recommendations for use of antenatal corticosteroids?
- What research is needed to guide clinical care?

For What Conditions and Purposes Are Antenatal Corticosteroids Used, and What Is the Scientific Basis for That Use?

Animal studies conducted in the 1950's and 1960's showed that the pituitary adrenal system affected differentiation of the intestine and lung. Later studies found physiologic surges in corticosteroids just before term or preterm delivery, and a relationship between fetal cortisol levels at delivery and lung maturity. Since then, randomized controlled trials in women have confirmed the maturational effects of corticosteroids on fetal organ systems such as the cardiovascular, respiratory, nervous, and gastrointestinal systems. As a result, antenatal corticosteroids are now administered for the purpose of hastening maturation of the preterm infant's organs and tissues, thus reducing morbidity and mortality related to prematurity.

The clinical conditions under which antenatal corticosteroid administration has been investigated are those associated with threatened or inevitable preterm delivery. These include (1) preterm labor, which accounts for 30–50 percent of all preterm deliveries; (2) preterm premature rupture of membranes, which accounts for 20–50 percent of all preterm deliveries; (3) preeclampsia, which is associated with 10–25 percent of preterm deliveries; and (4) other conditions, such as diabetes mellitus, third-trimester bleeding, fetal distress, or isoimmunization necessitating preterm delivery, which account for up to 10 percent of preterm deliveries. The use of antenatal corticosteroid therapy has been studied in relatively few pregnancies less than 24 weeks' or greater than 34 weeks' gestation.

Additional issues that have been investigated include duration of the "treatment window," the gender and race of the fetus, the relationship of gestational age to the risks and benefits of treatment, and the use of antenatal corticosteroids along with other treatments, such as postnatal pulmonary surfactant and tocolytic administration.

Scientific Basis

Studies of antenatal corticosteroid treatment were evaluated with the grading system developed by the Canadian Task Force on the Periodic Health Examination and adapted by the U.S. Preventive Services Task Force (Table 1). The ratings reflect both the quality of evidence and the strength of the recommendations that can be based on that evidence. For most of these conditions or outcomes, at least some data were available from randomized controlled trials. For some outcomes, such as RDS, data were extensive. For other maternal conditions or neonatal outcomes, though derived from randomized controlled trials, data were limited. Hence, for some conditions or outcomes, although grade I evidence was available, this evidence was judged insufficient to allow a recommendation concerning the use of corticosteroids.

Quality of Evidence

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940's) could also be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Strength of Recommendation Regarding Corticosteroid Administration

- A. There is good evidence to support use.
- B. There is fair evidence to support use.
- C. There is inadequate evidence to argue for or against use.
- D. There is fair evidence to avoid use.
- E. There is good evidence to avoid use.

Table 1. Evidence of efficacy of corticosteroids and strength of recommendation according to delivery interval, gestational age, status of membranes, and neonatal outcome

	Quality of evidence for benefit	Strength of recommendation
Interval from treatment to delivery		
<24 hours	I	B
24 hours to 7 days	I	A
>7 days	I	C
Gestational age		
Delivery age 24–28 weeks	I	A
Delivery at 29–34 weeks	I	A
Delivery at >34 weeks	I	C
Preterm premature rupture of membranes		
	I	B
Neonatal outcomes		
Mortality	I	A
Respiratory distress syndrome	I	A
Intraventricular hemorrhage	I	A

What Are the Short-Term and Long-Term Benefits of Antenatal Corticosteroid Treatment?

Short-Term Benefits for the Infant

Antenatal corticosteroid therapy in the preterm fetus in many randomized controlled trials has reduced neonatal mortality and the incidence of RDS. A meta-analysis based on 15 such trials showed a reduction in the incidence of RDS with a typical odds ratio of 0.5 (95% CI = 0.4–0.6)¹ and a reduction of neonatal mortality with a typical odds ratio of 0.6 (95% CI = 0.5–0.8). These data are not only statistically significant but also clinically compelling. In subgroup analysis, these benefits were confirmed regardless of the infant's gender or race.

One recent randomized controlled trial showed a significant reduction in IVH with antenatal corticosteroid treatment. Secondary outcome variables reported in the meta-analysis of randomized controlled trials also showed a significant reduction in the incidence of IVH with an odds ratio of 0.5 (95% CI = 0.3–0.9). This reduction in IVH is supported by the results of the observational database, information prospectively collected in five registries involving more than 30,000 low birthweight infants. Since IVH is an important contributor to mortality and serious long-term neuro-developmental disability, this reduction is a major benefit.

Improved circulatory stability and reduced requirements for oxygen and ventilatory support were additional benefits identified in randomized controlled trials. Data are conflicting for NEC and PDA. The meta-analysis of the randomized

¹ A meta-analysis uses quantitative methods to summarize results derived from a systematic review of randomized controlled trials. Results of meta-analyses are customarily reported in terms of odds ratios and 95 percent confidence intervals (CIs). Odds ratios of 1.0 indicate no effect; those below 1.0 imply protective effect; and those above 1.0 an increased risk. Ninety-five percent CIs that exclude 1.0 are considered significant at the $p < .05$ level.

controlled trials revealed a reduction of the incidence of NEC however; this finding was not corroborated by the observational database. Conversely, the incidence of PDA was not found to be reduced in the meta-analysis but was significantly reduced in the observational database.

Long-Term Benefits for the Infant

Several studies have followed infants from the randomized trials for as long as 12 years. The increased survival of treated infants has not resulted in the appearance of adverse long-term effects.

What Are the Short-Term and Long-Term Adverse Effects for the Infant and Mother?

Short-Term Adverse Effects for the Infant

Short-term adverse effects of antenatal corticosteroid administration of greatest concern in the neonate include infection and adrenal suppression. The evidence presented to date shows no increase in infection in treated infants, no clinically important adrenal suppression, and rapid return of adrenal function when antenatal corticosteroids are discontinued.

Some animal studies have suggested that antenatal corticosteroid treatment might promote maladaptive responses to hypoxia. Other animal studies have shown that corticosteroids in doses similar to those used in humans antenatally provide protection against hypoxic-ischemic brain injury. More data are needed from human studies in this area of research.

Long-Term Adverse Effects for the Infant

Studies initiated in the 1970's, which followed the development of children treated antenatally with corticosteroids up to the age of 12 years, showed no adverse outcomes in the areas of motor skills, language, cognition, memory, concentration, or scholastic achievement. The possibility of adverse, long-term neurodevelopmental outcomes has been suggested by studies of corticosteroid administration in animals. These studies were conducted using doses approximately 10 times the doses used in human clinical trials. There does not seem to be an increased risk in children of long-term neurodevelopmental impairment, as reflected in any greater prevalence of learning, behavioral, motor, or sensory disturbances. Long-term effects of antenatal corticosteroids on growth and the onset of puberty are not fully known.

Short-Term and Long-Term Adverse Maternal Effects

Maternal pulmonary edema can occur when antenatal corticosteroids are used in combination with tocolytic agents. This complication is more commonly associated with maternal infection, fluid overload, and multiple gestation. Pulmonary edema has not been reported when antenatal corticosteroids are used alone.

The risk of maternal infection may be increased when corticosteroids are used in preterm premature rupture of membranes (PPROM); however, the degree of this effect, if any, is unclear. Furthermore, there is no evidence that antenatal corticosteroid treatment interferes with the ability to diagnose maternal infection. When corticosteroids are administered to pregnant diabetic women, diabetic control may become more difficult and insulin may have to be adjusted accordingly. Screening for gestational diabetes may similarly be affected. In serious maternal medical conditions that necessitate premature delivery, the delay necessary to demonstrate maximal corticosteroid effects for the fetus may worsen the maternal medical status. A subgroup analysis in the first randomized trial suggested that antenatal corticosteroid administration might predispose to fetal death in hypertensive women. Subsequent trials failed to demonstrate this effect. No long-term maternal adverse effects have been reported.

What Is the Influence of the Type of Corticosteroid, Dosage, Timing and Circumstances of Administration, and Associated Therapy on Treatment Outcome?

Type of Corticosteroid

Dexamethasone and betamethasone are the preferred corticosteroids for antenatal therapy. These two compounds are identical in biological activity and readily cross the placenta in their biologically active forms. They are devoid of mineralocorticoid activity, relatively weak in immunosuppressive activity, and exert longer duration of action than cortisol and methylprednisolone. They also are the most extensively studied antenatal corticosteroids for accelerating fetal maturation.

Dose

Treatment of two doses of 12 mg of betamethasone given intramuscularly 24 hours apart or four doses of 6 mg of dexamethasone given intramuscularly 12 hours apart has been shown to be effective. Although these regimens were arbitrarily selected, they have subsequently been shown to deliver concentrations to the fetus that are comparable to physiologic stress levels of cortisol occurring after birth in untreated premature infants who develop RDS.

These regimens result in an estimated 75 percent occupancy of available corticosteroid receptors, which should provide a near maximal induction of antenatal corticosteroid receptor-mediated response in fetal target tissues. Higher or more frequent doses do not increase the benefits of antenatal corticosteroid therapy and may increase the likelihood of adverse effects.

Timing

Strong evidence exists for neonatal benefits from a complete course of antenatal corticosteroids starting at 24 hours and lasting up to 7 days after treatment.

Evidence suggests a reduction in mortality, RDS, and IVH, even with treatment initiated less than 24 hours prior to delivery. Both clinical and *in vitro* evidence suggest that the corticosteroid biological effects persist up to 7 days following initial treatment.

Data are inadequate to establish the clinical benefit beyond 7 days after antenatal corticosteroid therapy. The potential benefits or risks of repeated administration after 7 days are unknown. *In vitro* experiments in human fetal lung explants show that inducible biochemical effects have dissipated by 7 days, although structural changes persist.

Circumstances of Administration

Gestational Age

For infants born at 29–34 weeks' gestation, treatment with antenatal corticosteroids clearly reduces the incidence of RDS and overall mortality. Although antenatal corticosteroids do not clearly decrease the incidence of RDS in infants born at 24–28 weeks' gestation, they reduce its severity. More important, antenatal corticosteroids clearly reduce mortality and the incidence of IVH in this age group. All fetuses between 24 and 34 weeks' gestation threatened with premature delivery are candidates for treatment with antenatal corticosteroids.

In infants born beyond 34 weeks' gestation, the risk of neonatal mortality, RDS, and IVH is low. The evidence for significant improvement in outcomes in these infants with antenatal corticosteroid use is limited. Use of corticosteroids in mothers expected to deliver at greater than 34 weeks is, therefore, not recommended unless there is evidence of pulmonary immaturity.

Race and Sex

There is no convincing evidence from any of the clinical trials that either gender or race of the fetus affects the response to therapy with antenatal corticosteroids.

Preterm Premature Rupture of Membranes

The use of antenatal corticosteroids to reduce infant morbidity in the presence of PPROM remains controversial. Antenatal corticosteroids reduced the risk of RDS in PPROM in randomized controlled trials, although the magnitude of the reduction was not as great as when the membranes were intact. Strong evidence from observational studies suggests that, even in the presence of PPROM, the incidence of neonatal mortality and IVH is reduced when antenatal corticosteroids are used. Although the risk of neonatal infection associated with antenatal corticosteroid use in the face of PPROM may be increased, the magnitude of the increase is small. Because of the effectiveness of antenatal corticosteroids in reducing mortality and IVH in fetuses of less than 30–32 weeks' gestation, antenatal corticosteroid use is appropriate in the absence of chorioamnionitis.

Other Conditions

Data are insufficient to assess the effectiveness of antenatal corticosteroid use in certain maternal high-risk conditions such as hypertension and diabetes. In the absence of evidence of adverse effects, it may be reasonable to treat these women as one would others with threatened premature delivery. Similarly, in the presence of high-risk fetal conditions, such as multiple gestation, intrauterine growth retardation, and hydrops, it is reasonable to treat these patients as one would others with threatened premature delivery.

Associated Therapies

Surfactant

Antenatal administration of corticosteroids acts additively with postnatal administration of surfactant to reduce mortality, RDS, and IVH. Furthermore, surfactant replacement appears to have little or no impact on the incidence

of IVH or PDA. For these reasons the decision to use antenatal corticosteroids should not be altered by availability of surfactant replacement therapy.

Thyrotropin-Releasing Hormone

Thyroid hormones accelerate fetal lung maturation in animal studies. However, T_3 and T_4 do not cross the placenta. This problem has been circumvented by maternal administration of thyrotropin-releasing hormone (TRH). The combination of TRH plus antenatal corticosteroids was more effective than corticosteroids alone in two randomized studies. Women who received both drugs had infants with fewer adverse outcomes, fewer days on the ventilator, and a lower incidence of BPD. The use of TRH to accelerate fetal pulmonary maturation currently is experimental, and randomized studies are in progress.

Beta-Mimetic Tocolytics

Beta-mimetic agents such as ritodrine and terbutaline are frequently administered in an attempt to arrest preterm labor. Women receiving tocolytic therapy are candidates for antenatal corticosteroids to accelerate fetal maturation in the face of threatened premature delivery. Several studies have examined the outcomes of infants born prematurely to mothers who received both ritodrine and dexamethasone or betamethasone. Although there are flaws in the design of each of these studies, they all showed a significant decrease in incidence of RDS. In addition, one study demonstrated a decrease in ventilator dependency and incidence of PDA. There is evidence that beta-mimetic agents may be associated with increased risk of IVH. However, the use of antenatal corticosteroids may reduce this risk.

What Are the Economic Consequences of This Treatment?

Neonatal intensive care is expensive but is more cost-effective in terms of years of life gained than many other accepted medical interventions. Because the costs of caring for infants with RDS are so high, interventions that may reduce its incidence, such as antenatal corticosteroids or prophylactic surfactant, have the potential of producing large cost savings, in addition to improving health.

The net economic consequences include the costs of initial treatment, changes in treatment made to allow the corticosteroids to work, the costs of any harmful side effects of treatment, the savings resulting from reduced length of stay and intensity of treatment, and the long-term costs of the burden of chronic diseases in surviving infants. Because the direct costs of corticosteroid treatment are so low and differential extra long-term burden has not been well quantified, net cost estimates were derived from the balance of costs of the health outcomes of initial treatment. Costs of infant care are relatively low for both uncomplicated preterm infants and early neonatal deaths. For any proposed clinical situation, costs are decreased to the extent that corticosteroids reduce illness in survivors and increased for infants that would have died quickly without them. Data on costs from randomized trials are scant, but length of stay was reduced by about one-third in corticosteroid-treated infants in the four trials for which these data were collected. To estimate costs or savings from increased use, data on efficacy from all corticosteroid trials can be applied to data on current costs of caring for infants with and without disease. The resulting calculated base-case cost savings were more than \$3,000 per treated neonate. Of the 4,100,000 babies born in the United States each year, 106,000 weigh less than 2,000 grams at birth. Currently, 15 percent of these babies are treated with corticosteroids. If this were increased to 60 percent, as observed in some hospitals, a conservative estimate of the annual savings in health care costs would be \$157 million from the initial hospitalization alone.

What Are the Recommendations for Use of Antenatal Corticosteroids?

- The benefits of antenatal administration of corticosteroids to fetuses at risk of preterm delivery vastly outweigh the potential risks. These benefits include not only a reduction in the risk of RDS but also a substantial reduction in mortality and IVH.
- All fetuses between 24 and 34 weeks' gestation at risk of preterm delivery should be considered candidates for antenatal treatment with corticosteroids.
- The decision to use antenatal corticosteroids should not be altered by fetal race or gender or by the availability of surfactant replacement therapy.
- Patients eligible for therapy with tocolytics should also be eligible for treatment with antenatal corticosteroids.
- Treatment consists of two doses of 12 mg of beta-methasone given intramuscularly 24 hours apart or four doses of 6 mg of dexamethasone given intramuscularly 12 hours apart. Optimal benefit begins 24 hours after initiation of therapy and lasts 7 days.
- Because treatment with corticosteroids for less than 24 hours is still associated with significant reductions in neonatal mortality, RDS, and IVH, antenatal corticosteroids should be given unless immediate delivery is anticipated.
- In PPRM at less than 30–32 weeks' gestation in the absence of clinical chorioamnionitis, antenatal corticosteroid use is recommended because of the high risk of IVH at these early gestational ages.
- In complicated pregnancies where delivery prior to 34 weeks' gestation is likely, antenatal corticosteroid use is recommended unless there is evidence that corticosteroids will have an adverse effect on the mother or delivery is imminent.

What Research Is Needed to Guide Clinical Care?

Areas of animal and human research that need to be addressed include the following:

- The short-term and long-term benefits and risks of repeating administration of antenatal corticosteroids 7 days after the initial course.
- Long-term effect of antenatal corticosteroids on cognitive, behavioral, psychological, and physical development of the neonate.
- Effects of antenatal corticosteroids on organ maturation.
- Effects of antenatal corticosteroids on hypoxic–ischemic insults.
- Effects of antenatal corticosteroids on neonatal hemodynamic stability.
- Mechanism of antenatal corticosteroid induction of cell and organ maturation at the molecular level.
- The interaction of antenatal corticosteroids with other therapies administered during the perinatal period (e.g., the effect of corticosteroids and tocolytics on the incidence of IVH).
- Development of alternative therapies to antenatal corticosteroids for fetal maturation.
- Systematic study of the diffusion of these scientifically based recommendations into clinical practice.

Conclusion

Antenatal corticosteroid therapy for fetal maturation reduces mortality, respiratory distress syndrome, and intraventricular hemorrhage in preterm infants. These benefits extend to a broad range of gestational ages (24–34 weeks) and are not limited by gender or race. Although the beneficial effects of corticosteroids are greatest more than 24 hours after beginning treatment, treatment less than 24 hours in duration also improves outcomes. The benefits of antenatal corticosteroids are additive to those derived from surfactant therapy.

In the presence of preterm premature rupture of the membranes, antenatal corticosteroid therapy reduces the frequency of respiratory distress syndrome, intraventricular hemorrhage, and neonatal death, although to a lesser extent than with intact membranes. Whether this therapy increases either neonatal or maternal infection is unclear. However, the risk of death from prematurity is greater than the risk from infection.

Data from trials with followup of children up to 12 years indicate that antenatal corticosteroid therapy does not adversely affect physical growth or psychomotor development.

Antenatal corticosteroid therapy is indicated for women at risk of premature delivery with few exceptions and will result in a substantial decrease in neonatal morbidity and mortality, as well as substantial savings in health care costs. The use of antenatal corticosteroids for fetal maturation is a rare example of a technology that yields substantial cost savings in addition to improving health.

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"Historic Overview of Antenatal
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"Hormone Levels Achieved
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"Update of the Antenatal
Steroid Meta-Analysis:
Current Knowledge and
Future Research Needs"

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"Evidence for Adverse and
Beneficial Effects of Antenatal
Steroid Use for Fetal Matura-
tion on Perinatal Outcome:
Introduction and Definition
of the Problem"

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"The Use of Corticosteroids
for Acceleration of Fetal
Pulmonary Maturity in
Special Clinical Situations"

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Robert L. Goldenberg, M.D.

"Use of Antenatal Steroids in
Special Circumstances and
Populations: Introduction and
Definition of the Problem"

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“The Effect of Corticosteroid
Therapy in the Very
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“Antenatal Steroids To Reduce
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