

**ANTENATAL CORTICOSTEROID ADMINISTRATION
EVIDENCE-BASED GUIDELINES**

Evidence Based Guidelines	Controversies & Comments
<p>“Recommendations for Use of Antenatal Corticosteroidsⁱ</p>	
<p>1. 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.</p>	
<p>2. All fetuses between 24 and 34 weeks gestation at risk of preterm delivery should be considered candidates for antenatal treatment with corticosteroids.”</p> <p>In selected situations beyond 34 weeks gestational age with an indicated delivery (e.g., placenta previa, prior uterine rupture) in the presence of an immature fetal lung profile, treatment with antenatal corticosteroids can be effective. The same medication regimens would be utilized.</p>	<p>Timing of Antenatal Corticosteroid Therapy</p> <p>While the NIH Consensus Statement regarding the effect of antenatal corticosteroids for fetal maturation on perinatal outcomes recommends that only fetuses between 24 and 34 weeks gestation at risk of preterm delivery should be considered candidates for antenatal treatment with corticosteroids, clinicians and researchers have considered the risks and benefits of early treatment (i.e., prior to 24 weeks gestation) and late treatment (i.e., after 34 weeks gestation).</p> <p>Early Administrations of Antenatal Corticosteroids (i.e., prior to 24 weeks gestation)</p> <p>One studyⁱⁱ examined whether or not the use of antenatal corticosteroids would improve neonatal outcome in extremely low birth weight infants, using a retrospective case-control chart review over a ten-year period of all infants whose mothers were admitted prior to 24 weeks gestation and delivered by 26 weeks. The authors concluded that fetuses exposed to antenatal corticosteroids prior to 24 weeks gestation had decreased mortality and higher Apgar scores compared to those infants not exposed, with no differences in any of the other neonatal outcome measured (i.e., sepsis, RDS, IVH, NEC, PVL, and ROP). No recommendations concerning routine early treatment with antenatal corticosteroids were made, and the group suggested further prospective randomized study. This non-randomized study is subject to significant bias as mothers who receive antenatal corticosteroids would be more likely to have additional aggressive obstetric and neonatal treatments that may increase neonatal survival and reduce morbidity.</p> <p>Late Administration of Antenatal Corticosteroids (i.e., after 34 weeks gestation)</p> <p>Several studies have examined the effects of antenatal corticosteroids administered later than currently recommended. Shanks, et alⁱⁱⁱ looked at the effect of antenatal corticosteroid administration on fetal lung maturity in pregnancies with known fetal lung immaturity between the 34th and 37th weeks of gestation. The authors concluded “a single course of IM glucocorticoids even after 34</p>

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	<p>weeks in pregnancies with documented lung immaturity can significantly increase the TDx-FLM-II in one week. Patients with negative fetal lung maturity parameters between the 34th and 37th weeks can benefit from a single course of steroids.” This concept was also supported by ACOG in its 2002 Committee Opinion on Antenatal Corticosteroid Therapy for Fetal Maturation.</p> <p>The frequency of respiratory distress syndrome diminishes markedly after 34 weeks gestation so many studies in the apst were under-powered to identify a difference. Stutchfield, et al^{iv} used a very large sample size (998 women) to examine whether administration of antenatal corticosteroids would reduce respiratory distress in infants born by elective cesarean section at near term. The reduction was significant from 5.1% to 2.1% (RR=0.46; 95% CI: 0.23 to 0.93). They concluded that “antenatal betamethasone is effective in reducing admission to the special care unit with respiratory distress after elective cesarean section at term” and that “the likely benefits of antenatal corticosteroids should be compared with those of delaying delivery until 39 weeks when possible.”</p>
<p>3. “The decision to use antenatal corticosteroids should not be altered by fetal race or gender or by the availability of surfactant replacement therapy.</p>	
<p>4. Patients eligible for therapy with tocolytics should also be considered for treatment with antenatal corticosteroids.</p>	
<p>5. Treatment consists 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.</p>	<p>Betamethasone vs. Dexamethasone</p> <p>While it is now well accepted that the administration of a single course of antenatal corticosteroids results in a decrease in neonatal morbidity and mortality, identification of the safest and most effective steroidal agent has some controversy. The preferred agents, betamethasone and dexamethasone are favored over other forms of steroids because they have both been studied extensively, seem to react in identical fashion and readily cross the placenta. The choice of which agent to use is currently based on ease of administration, cost effectiveness, drug availability and results from previous conflicting studies.</p> <p>Elimian, et al^v conducted a randomized controlled trial (i.e., Betacode Trail) to “compare betamethasone with dexamethasone in terms of effectiveness in reducing perinatal morbidities and mortality among preterm infants.” They found that both drugs were largely comparable in reducing most morbidity and mortality in preterm infants. However, contrary to the finding of a higher rate of periventricular leukomalacia (PVL) in infants exposed to dexamethasone noted in earlier studies^{vi}, this study found no such outcome, and in fact, found that PVL in the dexamethasone group was lower than in the betamethasone group. They concluded that both betamethasone and dexamethasone were</p>

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	<p>appropriate for use in treating women at risk for preterm delivery, and found that dexamethasone was superior to betamethasone in reducing the rate of intraventricular hemorrhage.</p> <p>A Cochrane review^{vii} completed in 2008 found that while the use of antenatal corticosteroid therapy in preventing neonatal morbidity is not in dispute, it is not yet clear which corticosteroid and which regimen performs best. The only definite finding reported was that intramuscular dexamethasone was noted to be superior to its oral form. Future controlled trials were recommended.</p> <p>Current standard of care includes the use of either betamethasone or dexamethasone, but since the large majority of data is with betamethasone and it involves only two injections, betamethasone generally remains the first choice.</p>
<p>6. Because treatment with corticosteroids for less than 24 hours can be associated with significant reductions in neonatal mortality, RDS and IVH, antenatal corticosteroids should be given unless immediate delivery is anticipated.</p>	
<p>7. In preterm premature rupture of membranes at less than 30 to 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.</p>	<p>Antenatal Corticosteroids and PROM</p> <p>Antenatal steroids are equally effective in the setting of preterm rupture of membranes. The upper limit of gestational age for use of antenatal steroids in this population has some controversy. Some centers with higher rates of chorioamnionitis limit use to under 32 weeks of gestation while others use antenatal steroids up to the standard 34-week limit.</p> <p>In their <i>Guideline for the use of antenatal corticosteroids for fetal maturation</i>, Miracle et al^{viii} concluded that antenatal corticosteroid therapy is indicated in women with PROM from 24-32 weeks' gestation not presenting clinical signs of chorioamnionitis. While administration of antenatal corticosteroids in this population involves some risk of infection for both mother and infant, the authors justified their recommendation based on 2 major meta-analyses:</p> <ul style="list-style-type: none"> • The 2006 Cochrane Review^{ix} in which “ANS are shown to be beneficial in the subgroup of infants whose mothers have PROM. Neonatal death, RDS, IVH, NEC and duration of respiratory support are all reduced, without an increase in either maternal or neonatal infection”. • Harding et al.’s^x 2001 meta-analysis which reported that “administration of corticosteroids to women with rupture of membranes substantially reduces the risks to their babies of respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis...may also reduce the risk of neonatal death...benefits do not appear to be accompanied by an increased risk of maternal or neonatal infection.” They further stated that, in their opinion, further trials to address the use of antenatal corticosteroids in PROM cannot be justified.

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<p>8. 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.”</p>	
<p>9. Weekly repetitive courses of antenatal steroids are no longer recommended because of concerns for fetal head and somatic growth. However, in mothers likely to deliver beyond 2 weeks from the primary course and before 34 weeks gestation, a single “rescue” course of antenatal corticosteroids appears to provide additional benefit. The same medication regimens would be utilized.</p>	<p>Repeat Courses^{xi}</p> <p>The NIH Consensus Statement regarding the effect of antenatal corticosteroids for fetal maturation on perinatal outcomes states that the “optimal benefit begins 24 hours after initiation of therapy and last 7 days”, which prompted clinicians and researchers to question whether or not repeat courses of antenatal corticosteroid therapy should be administered.</p> <p>The NIH organized a consensus conference August 17-18, 2000 to review the current research and address whether or not there was sufficient evidence on benefits and risks of repeated courses of antenatal corticosteroids to permit consensus recommendations. They determined that data assessing benefits and risks from the studies available at the time were inadequate to argue for or against the use of repeat or rescue courses of antenatal corticosteroids for fetal maturation. They reaffirmed the 1994 Consensus recommendations and further stated that repeat courses of corticosteroids should not be used routinely, but should be reserved for patients enrolled in randomized controlled trials. ACOG endorsed these recommendations in its 2002 Committee Opinion on Antenatal Corticosteroid Therapy for Fetal Maturation^{xii}</p> <p>In 2000, Wapner, et al^{xiii} initiated a randomized, double-masked, placebo-controlled, multicenter clinical trial performed by 18 centers of the NICHD MFMU Network to determine if weekly corticosteroids improved neonatal outcome without undue harm. The study was halted in April 2003 because of a concerns regarding decreased birth weight in the treatment group. The authors concluded that “repeat antenatal corticosteroids significantly reduce specific neonatal morbidities but do not improve composite neonatal outcome...accompanied by reduction in birth weight and increase in small for gestational age infants.”</p> <p>A Cochrane review completed in 2007 found that “repeat dose(s) of prenatal corticosteroids reduce the occurrence and severity of neonatal lung disease and the risk of serious health problems in the first few weeks of life. These short-term benefits for babies support the use of repeat dose(s) of prenatal corticosteroids for women at risk of preterm birth. However, these benefits are associated with a reduction in some measures of weight, and head circumference at birth, and there is still insufficient evidence on the longer-term benefits and risks.^{xiv}</p> <p>Rescue Course</p>

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	<p>Previous studies using repetitive courses of antenatal corticosteroids have shown improved neonatal outcome with no apparent increase in short term risk, but unclear long-term risk. Ring, et al^{xv} looked at whether the neonatal benefit of a single complete course of antenatal corticosteroids diminishes when delivery is remote from administration (>14 days). They concluded that “a time interval of >14 days is associated with an increased risk for ventilatory support and surfactant use in neonates who deliver at >28 weeks gestation”, and recommended further investigation to assess the risk vs. benefit of a rescue course of corticosteroids for those fetuses remaining undelivered >14 days after the initial course of treatment.</p> <p>Current research has focused on the impact of a single “rescue” course of antenatal corticosteroids. A recent, randomized multicenter trial^{xvi} looked at whether the use of rescue steroids reduces morbidity and/or mortality in patients who have been previously treated with antenatal corticosteroids, but who again threaten to deliver before 34 weeks. They demonstrated a benefit in composite morbidity and a decrease in the presence and severity of RDS, but not mortality or other morbidities at <34 weeks. They also looked at the difference between methods of rescue therapy (i.e., discretionary antenatal corticosteroid administration based on the clinician’s judgment of impending risk vs. giving repeated doses to all patients at risk). They found that with the discretionary method, as opposed to routine repetitive dosing, they appeared better able to correctly identify patients who would truly benefit by this treatment and avoid unnecessarily treating those who would not. They finally concluded that “choosing to administer a rescue course of antenatal corticosteroids in pregnant women treated initially >2 weeks prior, and who are judged by the clinician to be likely to deliver within the next week and before 34 weeks gestation, is a beneficial approach that significantly decreases respiratory complications of prematurity and is without apparent immediate or short-term adverse effects to the mother or infant.”</p> <p>A second study^{xvii} compared pulmonary function in preterm infants randomized to a single rescue course of antenatal corticosteroids, as compared to placebo. The authors concluded that infants randomized to one rescue course of antenatal corticosteroids, delivering at ≤34 weeks, have a significantly increased respiratory compliance vs. those randomized to placebo, suggesting improved clinical respiratory outcome.</p>
	<p>Potential for Adverse Maternal Outcomes</p> <p>Currently, the benefit of a single course of antenatal corticosteroid therapy in the setting of anticipated preterm delivery is undisputed with 20-year follow-up studies demonstrating long-term safety, although concern over the possibility of fetal and maternal adverse effects persists in the case of repeated doses. Potential detrimental fetal effects include neurodevelopmental delay, growth delay and adrenal suppression, while studies of adverse maternal effects have focused on the</p>

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	<p>potential for infection.</p> <p>Early research focused on the potential for an increase in maternal osteoporosis related to a single course of antenatal corticosteroid and found no evidence to support this.^{xviii}^{xix} Carroll MA et al.^{xx} compared markers of maternal bone metabolism between women who received single vs. multiple courses of antenatal corticosteroids. The authors concluded that “multiple courses of corticosteroids for fetal maturation are not associated with persistent or cumulative effects on bone metabolism as measured by PICP and ICTP.”</p>
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^{xii} Antenatal corticosteroid therapy for fetal maturation. ACOG Committee Opinion No. 273. American College of Obstetricians and Gynecologists. Obstet Gynecol 2002; 99: 871-873.

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