# Antenatal corticosteroid therapy for reduction of neonatal respiratory morbidity and mortality from preterm delivery

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**INTRODUCTION** — In a landmark paper, Liggins and Howie showed that a single course of antenatal corticosteroid therapy administered to women at risk for preterm delivery (PTD) reduced the incidence and severity of respiratory distress syndrome (RDS) and mortality in offspring [1]. Over two dozen randomized trials have confirmed these findings [2]. Subsequent trials have also shown that antenatal corticosteroid therapy improves circulatory stability in preterm neonates, resulting in lower rates of intraventricular hemorrhage (IVH) and necrotizing enterocolitis compared with unexposed preterm neonates.

This topic will review evidence supporting the use of antenatal corticosteroids to improve neonatal outcomes in women at risk for preterm delivery, pharmacological issues, and clinical concerns about administration of this therapy. Postnatal interventions to prevent and treat RDS and its sequelae are reviewed separately. (See "Prevention and treatment of respiratory distress syndrome in preterm infants".)

## BACKGROUND

**Mechanism of action** — Antenatal administration of corticosteroids accelerate development of type 1 and type 2 pneumocytes, leading to structural and biochemical changes that improve both lung mechanics (maximal lung volume, compliance) and gas exchange [3-8]. Induction of type 2 pneumocytes increases surfactant production by inducing production of surfactant proteins and enzymes necessary for phospholipid synthesis. Other effects of antenatal corticosteroids include induction of pulmonary beta-receptors, which play a role in surfactant release and absorption of alveolar fluid when stimulated [5]; induction of fetal lung antioxidant enzymes [9]; and upregulation of gene expression for the epithelial Na+ channel, which is important for absorption of lung fluid after birth [10]. For these changes to occur, however, the lungs need to have reached a stage of development that is biologically responsive to corticosteroids. (See 'Gestational age at administration' below.)

The biologic rationale for repeating antenatal corticosteroid therapy is based upon the observation that biochemical stimulation of surfactant production appears to be reversible in cell culture models (eg, surfactant protein mRNA levels decline to control levels after cortisol is removed) [5,11]. However, other beneficial effects, such as cytostructural maturation, persist (in rhesus monkeys) after steroid exposure is withdrawn [12]. (See 'Use of repeated courses of therapy' below.)

Tests for fetal lung maturation following antenatal corticosteroid therapy may not be sufficiently sensitive to detect subtle changes in the surfactant concentration of amniotic fluid. In addition, they cannot assess the effects of steroid-induced architectural changes of the fetal lung. Although some studies have reported an increased lecithin-sphingomyelin ratio or TDx-FLM II five days to two weeks after corticosteroid therapy [13-15], several other series found no change in this ratio [1,16,17].

**Evidence of short-term clinical efficacy**

**Reduction of RDS** — Randomized trials performed worldwide have consistently reported a significant reduction in the incidence of RDS among infants exposed to antenatal corticosteroid therapy. In a 2017 systematic review of randomized trials comparing antenatal corticosteroid therapy versus placebo/no treatment in women at risk for preterm birth, antenatal corticosteroid therapy resulted in a [2]:

- Reduction in RDS (relative risk [RR] 0.66, 95% CI 0.56-0.77; 28 trials, 7764 infants)
- Reduction in moderate to severe RDS (RR 0.59, 95% CI 0.38-0.91; 6 trials, 1686 infants)
- Reduction in need for mechanical ventilation (RR 0.68, 95% CI 0.56-0.84; 9 trials, 1368 infants)

A previous meta-analysis reported a statistical benefit among infants born between one and seven days after the first treatment dose (RR 0.46, 95% CI 0.35-0.60; 9 trials, 1110 infants), but not for those born less than 24 hours or more than seven days after the first dose [18]. This outcome was not evaluated in the 2017 analysis.

The benefits of corticosteroids do not appear to be affected by fetal sex [2] or race [19]; however, these conclusions are based on analysis of subgroups defined after randomization and intervention, which may have biased the results.

Despite the reduction in RDS, no significant reduction in chronic lung disease was noted (RR 0.86, 95% CI 0.42-1.79; 6 trials, 818 infants) [2].

**Reduction of IVH, NEC, NNM, infection** — Other benefits of antenatal corticosteroid therapy demonstrated by the 2017 systematic review of randomized trials include reductions in the risk of [2]:

- Intraventricular hemorrhage (IVH) (RR 0.55, 95% CI 0.40-0.76; 16 trials, 6083 infants)
- Necrotizing enterocolitis (NEC) (RR 0.50, 95% CI 0.32-0.78; 10 trials, 4602 infants)
- Neonatal mortality (NNM) (RR 0.69, 95% CI 0.59-0.81; 22 trials, 7188 infants)
- Systemic infection in the first 48 hours of life (RR 0.60, 95% CI 0.41-0.88; 8 trials, 1753 infants)

Some of these benefits derive from the beneficial effect on respiratory morbidity; however, maturational effects in numerous tissues due to corticosteroid stimulation of developmentally regulated genes and physiological functions suggest an independent effect as well [20-27]. The composite of multiple maturational effects is likely to have a salutary effect on the fetus's transition to extrauterine life.

**GESTATIONAL AGE AT ADMINISTRATION**

**22+0 to 33+6 weeks** — We recommend administration of antenatal corticosteroids for all pregnant women at 23+0 to 33+6 weeks of gestation who are at increased risk of preterm delivery within the next one to seven days [2]. Selection of such pregnancies is a clinical judgment based on high probability of induction/cesarean

for obstetrical or medical indications (eg, preeclampsia) or high probability of spontaneous preterm labor and delivery (eg, preterm premature rupture of membranes, tocolysis for active preterm labor).

The administration of antenatal steroids at 22+0 to 22+6 weeks of gestation can be offered at some institutions if delivery in the next one to seven days is anticipated and the family is requesting aggressive neonatal intervention after thorough consultation with maternal-fetal medicine and neonatology specialists [28]. Parents should be informed that antenatal corticosteroids may provide a survival benefit while increasing the risk for survival with severe impairment. Also, if the pregnancy is not delivered, then a single repeat course of antenatal corticosteroids may be needed later in gestation when the treatment is thought to be more effective. (See "Periviable birth (Limit of viability)" and 'Use of repeated courses of therapy' below.)

These gestational age recommendations are based on the meta-analysis described above, which provided evidence of efficacy before 34+0 or 35+0 weeks of gestation but was unable to assess very early gestational ages [2]. These data were provided by a 2018 meta-analysis of randomized trials of antenatal steroid administration before 25 weeks that established efficacy at 22, 23, and 24 weeks of gestation: reduction in mortality at 24 weeks of gestation (OR 0.46, 95% CI 0.34-0.62), 23 weeks (OR 0.49, 95% CI 0.43-0.56), and 22 weeks (OR 0.58, 95% CI 0.38-0.89) [29]. Intraventricular hemorrhage (IVH; stage III and IV) or periventricular leukomalacia was reduced at 23 and 24 weeks, but no reduction was observed at 22 weeks. No statistical reductions were observed for necrotizing enterocolitis >stage II or chronic lung disease.

Administration of antenatal corticosteroids before 22+0 weeks of gestation is unlikely to significantly improve lung function, as there are only a few primitive alveoli at this gestational age on which the drug can exert an effect (see 'Mechanism of action' above) [30]; however, it may improve survival [31].

**34+0 or more weeks** — The use of antenatal corticosteroids at ≥34+0 weeks of gestation is controversial because of inconsistent data about its efficacy and virtually no data about long-term safety. Limitations of available data are largely related to the low risk for severe respiratory morbidity after 34 weeks of gestation and lack of information on long-term developmental outcomes after exposure to corticosteroids in late gestation [32-36]. (See 'Potential adverse effects on infants' below and 'Potential long-term effects in children and adults' below.)

**Our approach** — Based on the data described below, the authors take the following approach, which limits late preterm in utero steroid exposure to pregnancies certain to deliver preterm and with neonates at most risk for experiencing serious respiratory problems from transient tachypnea of the newborn. This is a controversial area and our approach differs somewhat from recommendations published by ACOG, SMFM, and RCOG, which are described below. (See 'Other approaches' below.)

- For women scheduled for cesarean delivery at ≥37+0 to 38+6 weeks, a course of steroids can be discussed but not necessarily encouraged. We inform women who have not received a prior course of steroids that the overall risk of neonatal respiratory illness at this gestational age is low and rarely serious; however, steroid administration at least 48 hours prior to delivery may reduce neonatal respiratory morbidity and length of stay. We also discuss our concerns about possible long-term risks of steroid administration at term. After this discussion, some women may choose to receive a course of steroids before their scheduled cesarean delivery.

- For women scheduled for cesarean delivery at 34+0 to 36+6 weeks, we believe offering a first course of antenatal corticosteroids to reduce neonatal respiratory morbidity is reasonable. While there may be short-term advantages to receiving steroids prior to cesarean at this gestational age, the long-term risk-

to-benefit ratio is unknown. Families should be informed and participate in the decision-making.

We would not administer a second course of steroids at this gestational age to women who received steroids before 34+0 weeks as the benefits and risks have not been studied in this population.

- For women in whom vaginal delivery at ≥34+0 weeks is expected, we would not administer a first course of steroids as respiratory problems are less common after labor and vaginal birth [37-39], and we are concerned about the potential long-term risk to short-term benefit ratio.
- For women in whom delivery at 34+0 to 36+6 weeks is uncertain (eg, threatened preterm labor), we would not administer a course of steroids because there is potential for long-term harm with no benefit if the patient does not deliver preterm.

**Other approaches**

- The Society for Maternal-Fetal Medicine Specialists recommends a two-dose course of antenatal betamethasone for women at 34+0 to 36+6 weeks of gestation at high risk for preterm birth within seven days, with the following caveats [40]:
  - For women with symptoms of preterm labor, cervical dilation should be ≥3 cm or effacement ≥75 percent before treatment and tocolysis should not be used to delay delivery for completion of the course of steroids.
  - For women with potential medical/obstetric indications for early delivery, steroids should not be administered until a definite plan for delivery has been made.
- The American College of Obstetricians and Gynecologists states administration of betamethasone is recommended for women with a singleton pregnancy at 34+0 to 36+6 weeks of gestation at imminent risk of preterm birth within 7 days, with the following caveats [41,42]:
  - Antenatal corticosteroid administration should not be administered to women with chorioamnionitis.
  - Tocolysis should not be used to delay delivery in women with symptoms of preterm labor to allow administration of antenatal corticosteroids. Medically/obstetrically indicated preterm delivery should not be postponed for steroid administration.
  - Antenatal corticosteroids should not be administered if the patient has already received a course antenatal corticosteroids.
  - Newborns should be monitored for hypoglycemia.
- The NICE guideline (NG25) on preterm labor and birth recommends considering maternal corticosteroids for women between 34+0 and 35+6 weeks of gestation who are in suspected, diagnosed, or established preterm labor, are having a planned preterm birth, or have preterm prelabor rupture of membranes [43].
- However, others have cautioned against universal adoption of antenatal corticosteroids for pregnancies at risk of preterm birth at 34+0 to 36+6 weeks of gestation because it is unclear whether the short-term benefits (reduction in transient tachypnea of the newborn) clearly outweigh the risks (neonatal hypoglycemia, unknowns about long-term neurodevelopmental outcome and metabolic risks) [44].

**Evidence**

**Efficacy at 37+0 to 39+6 weeks of gestation** — A 2018 meta-analysis of four randomized trials of antenatal corticosteroids (betamethasone or dexamethasone) administered 48 hours before planned cesarean delivery at ≥37 weeks of gestation found reductions in neonatal respiratory morbidity compared with placebo or no treatment: transient tachypnea of the newborn (2.3 versus 5.4 percent; RR 0.43, 95% CI 0.29-0.65), RDS (2.6 versus 5.4 percent; RR 0.48, 95% CI 0.27-0.87), and admission to the NICU for respiratory morbidity (2.3 versus 5.1 percent; RR 0.45, 95% CI 0.22-0.90) [45]. A trend toward reduction in need for mechanical ventilation also noted. Neonatal hypoglycemia and long-term outcomes in offspring were not reported. Of note, the upper gestational age at randomization in the three trials was not limited in two trials and 38+6 and 39+6 weeks of gestation in the other two trials.

**Efficacy at 34+0 to 36+6 weeks of gestation** — A 2016 meta-analysis of randomized trials of antenatal corticosteroids (betamethasone or dexamethasone) administered 48 hours before planned cesarean delivery evaluated the efficacy of steroid administration at 34+0 to 36+6 weeks of gestation, and found statistically significant reductions in severe RDS (1.4 versus 2.3 percent; RR 0.60, 95% CI 0.24-0.98) and transient tachypnea of the newborn (8.2 versus 10.9 percent; RR 0.72, 95% CI 0.50-0.98), but not RDS overall or mechanical ventilation [46]. Steroid treatment increased the risk for neonatal hypoglycemia (22.8 versus 14.2 percent; RR 1.61, 95% CI 1.16-2.12).

The analysis was dominated by the Antenatal Late Preterm Steroids Trial (ALPS), in which women at 34+0 to 36+5 weeks of gestation at high risk for late preterm birth were randomly assigned to receive a first course of antenatal corticosteroids (two injections of betamethasone 24 hours apart) or placebo [47]. No tocolytics were administered. The primary outcome was a composite of neonatal respiratory treatment in the first 72 hours (continuous positive airway pressure [CPAP] or high-flow nasal cannula for ≥2 hours, supplemental oxygen with $FIO_2$ ≥0.30 for ≥4 hours, extracorporeal membrane oxygenation, or mechanical ventilation), stillbirth, or neonatal death within 72 hours of delivery. Major findings were:

- The primary outcome occurred less often in the treatment group (11.6 versus 14.4 percent; relative risk [RR] 0.80; 95% CI 0.66-0.97), and was primarily driven by reductions in CPAP and high flow nasal cannula use.
- Severe respiratory complications (CPAP or high flow nasal cannula for ≥12 hours, $FIO_2$ ≥0.30 for at least 24 hours), transient tachypnea of the newborn, surfactant use, and bronchopulmonary dysplasia, while infrequent in absolute terms, also occurred significantly less frequently in the treatment group.
- Neonatal hypoglycemia occurred more frequently in the treatment group (24 versus 15 percent; RR 1.60; 95% CI 1.37-1.87).
- The rates of respiratory distress syndrome (RDS) and mechanical ventilation were similar in both groups (RDS: 5.5 versus 6.4 percent with placebo; mechanical ventilation: 2.4 versus 3.1 percent with placebo).

No data are available about the long-term neurodevelopmental outcomes of children exposed to corticosteroids between 34+0 and 36+5 weeks of gestation. This is a significant concern because exponential brain growth through cell division is occurring at this time and might be inhibited by administration of corticosteroids, which might affect neurodevelopment adversely (see 'Potential long-term effects in children and adults' below). In newborns, postnatal systemic glucocorticoid therapy contributes to neurodevelopmental impairment, especially cerebral palsy (see "Postnatal use of corticosteroids in bronchopulmonary dysplasia", section on 'Long-term outcome'). Other limitations of this study are that over 25 percent of participants were under 34+6 weeks at trial entry, 40 percent of women in the betamethasone group did not receive the

prespecified two doses of study medication, and more than half of the subjects delivered after 36 weeks and over 15 percent delivered at term.

**Possible harms of steroid exposure after 34 weeks** — We are concerned about the potential risks of administering antenatal corticosteroids to late preterm and term gestations, based on the following lines of evidence:

- The ASTECS trial compared administration of betamethasone 48 hours before planned cesarean delivery at ≥37 weeks with usual care [32]. When follow-up was performed at 8 to 15 years of age, schools were more likely to perceive steroid-exposed children to be in the lowest achievement group compared with the control group [36]. However, objective testing of academic ability was not performed as part of the trial and results from national standardized assessments did not show statistical differences between the scores for each group.

- A surge in endogenous cortisol occurs near term when the fetus is in a critical period of brain development in preparation for parturition and transition to life ex utero [48]. High levels of 11β-hydroxysteroid dehydrogenase-2 (11β-HSD-2) in the fetal brain help to protect it from the effects of the physiological rise in endogenous cortisol, but do not protect it from maternally administered betamethasone or dexamethasone due to the resistance of these drugs to metabolism by 11β-HSD-2 [49]. Thus, these steroids may cause supraphysiological activation of glucocorticoid receptors in the fetal brain near term.

  It has been proposed that exogenous steroids may have different effects at different gestational ages due to the multiple factors that change with advancing gestational age and the complex regulation of glucocorticoid receptor-mediated responses [49]. Because the human brain grows by 35 percent, cortical volume increases by 50 percent, and 25 percent of cerebellar development occurs between 34 weeks of gestation and term [50,51], exposure to exogenous betamethasone or dexamethasone during this time period is likely to have greater adverse consequences on brain development than at any other period of development. In particular, disruption of the normal fetal environment at this critical time may lead to changes in development of the neuroendocrine system, life-long effects on endocrine, behavioral, emotional, and cognitive function, and increased risks for development of a wide range or metabolic, cardiovascular, and brain disorders in later life [52-55].

- In a study of 54 preadolescent children (age 6 to 10 years) who received a single course of betamethasone at a mean gestational age of 29.3 weeks (+/- 3 weeks), delivered at term, and matched 1:2 to term infants not exposed to antenatal corticosteroids, antenatal corticosteroid exposure was associated with significant cortical thinning, particularly the rostral anterior cingulate cortex, which is strongly associated with development of affective disorders, as well as HPA axis dysregulation [56]. However, there with no overall differences in child affective problems or in total gray matter volume.

  On the other hand, a study that attempted to distinguish the direct effects of antenatal steroid treatment on general cognitive functioning from confounding influences of preterm delivery found that children born at term of women without pregnancy complications scored on average 6 to 7 IQ points higher than children born at term of women hospitalized for threatened preterm delivery, whether or not they were exposed to corticosteroids in utero [57]. This suggests that factors related to risk for preterm birth may have adverse effects and imply that a single course of antenatal steroids does not contribute to long-term cognitive deficits.

- In a multifaceted intervention trial (ACT) designed to increase the use of antenatal corticosteroids in low-income and middle-income countries, increased use of steroids increased neonatal and perinatal mortality in the overall population, particularly in the late preterm and early term births. This was an unexpected and unexplained finding that may have been related, in part, to increased infectious morbidities in steroid-exposed mothers and infants [34].

- Animal models of antenatal corticosteroid exposure consistently report adverse effects [48,58-64]. As an example, various dexamethasone dosing regimens administered to preterm macaques resulted in severe adverse effects on the brain, including significant changes in the hippocampus, neural damage in the cerebral cortical neurons, and severely retarded cerebellar growth [59,61].

We are also concerned because postnatal systemic corticosteroid therapy contributes to neurodevelopmental impairment, especially cerebral palsy. (See "Postnatal use of corticosteroids in bronchopulmonary dysplasia", section on 'Long-term outcome'.)

**TIMING BEFORE DELIVERY** — Maximum efficacy appears to occur when delivery occurs two to seven days after administration of the first dose of antenatal corticosteroids [18,65]. Efficacy is incomplete <24 hours from administration and appears to decline after 7 days [66-68].

Antenatal corticosteroid therapy should be administered when indicated unless imminent delivery is anticipated [20]. Therapy should not be withheld if delivery is anticipated prior to completion of the second dose of the first course of medication. We suggest this liberal approach to treatment because the minimal interval between drug administration and delivery required to achieve neonatal benefits has not been clearly defined and the hour of delivery cannot be predicted accurately. In one study, only one-quarter of women delivered within the optimal window after steroid administration [1,69].

Observational data suggest neonatal benefits begin to accrue within a few hours of corticosteroid administration [70,71]. Infants who received one dose of betamethasone in utero, but delivered before the second dose was given, had better outcomes than infants who did not receive any antenatal corticosteroids [70,71]. Laboratory data also support an early physiologic effect as early as 6 hours following the first injection [72,73]. One study, however, observed that a betamethasone booster appeared to increase the risk of respiratory distress syndrome and decrease intact survival rates among infants who were delivered within 1 to 24 hours [74]; this finding warrants further study.

**CHOICE OF DRUG AND INITIAL DOSE**

**Betamethasone and dexamethasone** — Both betamethasone and dexamethasone are effective for accelerating fetal lung maturity; either drug is acceptable for antenatal corticosteroid therapy. We prefer betamethasone because long-term follow-up data of fetuses exposed only to dexamethasone are limited and do not clearly demonstrate equivalence or superiority of dexamethasone over betamethasone for both short- and long-term outcomes. Use of betamethasone also requires fewer injections than use of dexamethasone.

In meta-analyses of randomized trials comparing use of different corticosteroids in women at risk of preterm birth, no statistical differences between dexamethasone and betamethasone were observed [2,75].

A course of therapy consists of:

- Betamethasone two doses of 12 mg given intramuscularly 24 hours apart **OR**

- Dexamethasone four doses of 6 mg given intramuscularly 12 hours apart. A nonsulfite-containing preparation should be used as the sulfite preservative (NNF60211) commonly used in dexamethasone preparations may be directly neurotoxic in newborns [76-79].

These steroids are preferred over other steroids because they are less extensively metabolized by the placental enzyme 11 beta-hydroxysteroid dehydrogenase type 2. At the above doses, 75 to 80 percent of available corticosteroid receptors are occupied, which should provide near-maximal induction of corticosteroid receptor-mediated response in fetal target tissues [80]. These doses result in cord blood glucocorticoid levels in the range seen with physiologic stress in the preterm neonate.

There is no convincing evidence that the beneficial fetal effects of standard doses of antenatal corticosteroids are significantly reduced in overweight or obese women (body mass index [BMI] ≥25 kg/m$^2$), but further study is needed [81]. In a randomized trial, maternal and cord blood betamethasone levels were similar for obese (BMI ≥30 kg/m$^2$) and nonobese women; however, this trial did not evaluate clinical outcomes [82].

The efficacy of alternative dosing regimens is unproven and discussed below. (See 'Nonstandard dosing regimens' below.)

**Pharmacology**

- Betamethasone – One milliliter of the betamethasone suspension commonly used in clinical practice is a combination of 3 mg of betamethasone sodium phosphate and 3 mg of betamethasone acetate. Betamethasone sodium phosphate is soluble so it is rapidly absorbed, while betamethasone acetate is only slightly soluble and, therefore, provides sustained activity. It is only available for intramuscular injection.

  The biological half-life is 35 to 54 hours [20]. The onset and duration of action is affected by the vascularity at the injection site. Drug concentrations in cord blood are approximately 20 percent of maternal levels one hour following maternal injection [80].

- Dexamethasone – Dexamethasone is available as dexamethasone sodium phosphate, which has a rapid onset and short duration of action. Therefore, the dosing frequency for dexamethasone is shorter than that for betamethasone. It is less costly and more widely available than betamethasone; only sulfite-free dexamethasone preparations should be used.

  Although dexamethasone is well absorbed from the gastrointestinal tract, safety and efficacy of the oral route for fetal maturation has not been established. (See 'Nonstandard dosing regimens' below.)

**Other drugs for prevention of respiratory and related morbidity**

**Hydrocortisone** — Hydrocortisone is extensively metabolized by placental enzymes so relatively little active drug crosses into the fetal compartment; therefore, beneficial fetal effects may not occur. However, if both betamethasone and dexamethasone are unavailable due to drug shortages, hydrocortisone 500 mg intravenously every 12 hours for four doses has been proposed as a last resort [83,84].

In women incidentally receiving high-dose hydrocortisone for treatment of a medical disorder, a standard course of betamethasone or dexamethasone, when indicated for fetal lung maturation, is recommended.

**Ineffective and unproven drugs** — In systematic reviews, prophylactic antenatal maternal administration of thyrotropin-releasing hormone (TRH) [85] or ambroxol [86] did not clearly reduce respiratory morbidity, and

prophylactic antenatal maternal administration of phenobarbital [87] or vitamin K [88] did not clearly reduce periventricular hemorrhage in preterm infants.

**SAFETY AND SIDE EFFECTS OF A SINGLE COURSE THERAPY** — Administration of a single course of antenatal corticosteroid therapy (ie, two doses of betamethasone or four doses of dexamethasone) before 34+0 weeks of gestation appears to be safe for the fetus/infant and mother, but has some side effects. The safety of administration later in pregnancy is less clear. (See '34+0 or more weeks' above and 'Potential long-term effects in children and adults' below.)

**Potential fetal side effects**

- **Fetal heart rate and biophysical parameters** – Administration of antenatal corticosteroids may be associated with transient fetal heart rate (FHR) and behavioral changes that typically return to baseline by four to seven days after treatment [89,90]. When a nonreassuring fetal evaluation (eg, nonreactive nonstress test [NR-NST] or low biophysical profile [BPP] score) occurs within two or three days of corticosteroid administration, the possibility of transient drug-related changes should be considered. Whether continued close fetal monitoring or delivery is preferable in this setting depends on assessment of the total clinical scenario and clinical judgment. (See "Nonstress test and contraction stress test" and "The fetal biophysical profile".)

  The most consistent FHR finding is a decrease in variability on days two and three after administration [91-95]. Reduced fetal breathing and body movements can result in a lower BPP score or NR-NST [95-98]. However, this is not a consistent finding; a placebo-controlled randomized trial in humans did not report a decrease in maternal perception of fetal movements in patients who received antenatal corticosteroids [99].

  FHR and behavioral changes may reflect a direct physiologic response of the brain to corticosteroids or they may be an indirect result of a transient increase in fetal vascular resistance and blood pressure, which has been demonstrated in some animal studies [100-104].

- **Doppler flow studies** – A transient improvement in umbilical artery end-diastolic flow (EDF) after antenatal corticosteroid administration has been described in 63 to 71 percent of patients participating in three studies [105-107]. The improvement began about eight hours after the first dose of betamethasone and lasted a median of three days (range 1 to 10 days). However, other studies have not observed effects on fetal blood flow velocity waveform patterns in the umbilical artery, middle cerebral artery, or ductus venosus [97,108].

  However, preterm fetuses with severe early-onset growth restriction and absent or reversed EDF do not have a consistent cardiovascular response to maternal betamethasone administration. Some exhibit transient improvement of EDF, while others do not. The latter group appears to be at higher risk of severe intrauterine acidosis or death. However, these observations are based on a small number of events in two studies and need to be confirmed before a change in management of this subgroup of fetuses is considered [107,109]. (See "Doppler ultrasound of the umbilical artery for fetal surveillance".)

**Potential adverse effects on infants** — In a 2017 systematic review of randomized trials, a single course of antenatal corticosteroids did not increase the risk of any adverse infant outcome, including neonatal infection, small for gestational age infant, hypothalamic-pituitary-adrenal (HPA) function, or air leak syndrome [2]. However, further research is needed, as several studies of infants exposed to antenatal corticosteroids have

observed reduced basal and stress-induced cortisol secretion in these infants [110-114].

The safety of steroid administration at ≥34+0 weeks is less clear. (See 'Possible harms of steroid exposure after 34 weeks' above.)

**Potential long-term effects in children and adults** — More data are needed on the long-term effects of antenatal corticosteroids [2]. Most studies of children/adults exposed to a single course of antenatal corticosteroids before 34 weeks of gestation have not reported adverse effects on growth; lung function; or psychosexual, motor, cognitive, neurologic, and ophthalmologic outcomes compared with unexposed controls [4,115,116]. However, fetal programming and its consequences remain a concern. Exposure to excess corticosteroids before birth has been postulated to contribute to development of some adult diseases [117]. Some potentially adverse cardiovascular, renal, and metabolic effects have been reported and require further study (eg, increased cortisol reactivity to psychological stress, increased aortic arch stiffness, increased insulin resistance, increased risk of adult hypertension) [116,118-124].

Concerns also remain regarding potential adverse effects on neurodevelopmental outcome, particularly with in utero exposure late in gestation. (See 'Possible harms of steroid exposure after 34 weeks' above.)

Multiple courses of steroids could accentuate potential adverse effects. (See 'Use of repeated courses of therapy' below.)

**Maternal side effects** — Most pregnant women tolerate a single course of antenatal corticosteroids without difficulty. In a 2017 systematic review of randomized trials, treatment did not increase the risk of maternal death, chorioamnionitis, or endometritis [2]. Case reports have described pulmonary edema, primarily associated with combination treatment with tocolytics, especially in the setting of chorioamnionitis, fluid overload, or multiple gestation [125-127]. Betamethasone itself has low mineralocorticoid activity compared with other corticosteroids; therefore, hypertension is not a contraindication to therapy [128].

Transient hyperglycemia occurs in many women; the steroid effect begins approximately 12 hours after the first dose and may last for five days. Screening for gestational diabetes, if indicated, should be performed either before corticosteroid administration or at least five days after the first dose [129,130]. In women with diabetes, hyperglycemia can be severe if not closely monitored and treated. (See "Pregestational diabetes mellitus: Obstetrical issues and management", section on 'Antenatal glucocorticoids'.)

The total leukocyte count increases by approximately 30 percent within 24 hours after betamethasone injection, and the lymphocyte count significantly decreases [131,132]. These changes return to baseline within three days, but may complicate the diagnosis of infection.

## USE OF REPEATED COURSES OF THERAPY

**Our approach** — We administer a single repeat dose of betamethasone 12 mg to pregnancies up to 34 weeks of gestation with all of the following characteristics, as we feel the benefit-to-risk ratio is most favorable in this setting (see 'Evidence for salvage, rescue, booster therapy' below):

- Clinically estimated to be at high risk of delivery within the next one to seven days
- Prior exposure to antenatal corticosteroids at least 14 days earlier
- Initial course of antenatal corticosteroids administered at ≤28 weeks of gestation [133]

We use a single dose rather than a two-dose course of betamethasone for repeat therapy based on indirect evidence from the Australasian Collaborative Trial of Repeat Doses of Steroids (ACTORDS), which demonstrated that weekly repeat dosing with a single injection of betamethasone was effective after initial standard therapy [134]. We also have concerns about potential adverse effects of repeat corticosteroid injections (see 'Evidence of effects from repeated courses of therapy' below). However, a single repeat course of therapy using the two-dose betamethasone or four-dose dexamethasone regimen is also reasonable [135] and commonly used [136,137].

The American College of Obstetricians and Gynecologists (ACOG) opine that "a single repeat course of antenatal corticosteroids should be considered in women who are less than 34+0 weeks of gestation who have an imminent risk of preterm delivery within the next 7 days, and whose prior course of antenatal corticosteroids was administered more than 14 days previously. Rescue course corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario" [42]. In contrast to our approach, ACOG does not limit rescue steroids to women whose initial course of antenatal corticosteroids was administered at ≤28 weeks of gestation.

**Evidence for salvage, rescue, booster therapy** — Use of a single repeat course of antenatal corticosteroids has been termed salvage, rescue, or booster therapy. Salvage (rescue, booster) therapy is an attractive alternative to routinely repeating weekly courses of antenatal corticosteroids once an initial course has been given. Salvage (rescue, booster) therapy is limited to pregnancies estimated to be at high risk of delivering within seven days. In theory, this would allow a single booster or rescue course of therapy to those pregnancies most likely to benefit. This could result in a reduction in RDS without increasing the risk of potentially adverse outcomes.

Three placebo-controlled randomized trials of salvage (rescue, booster) therapy have been published. One trial (n = 249 pregnancies) did not show a reduction in the incidence of RDS with salvage therapy (52 percent with betamethasone versus 48 percent with placebo) [74], while the other (n = 437 pregnancies) reported a significant reduction in RDS (41.4 percent [67/162] with betamethasone versus 61.6 percent [101/164] with placebo; OR 0.45, 95% CI 0.27-0.75) [136]. A higher proportion of subjects that actually received the intervention in the second trial compared with the first trial likely accounted for the significant reduction in RDS. A third placebo-controlled randomized trial (n = 85 pregnancies) also suggested a benefit: a rescue course of betamethasone significantly increased respiratory compliance (primary outcome) and, in deliveries less than 34 weeks, significantly decreased the incidence of RDS (15/44 [34 percent] versus 22/39 [56 percent] in the placebo group) [137]. When deliveries at all gestational ages were included, the reduction in RDS remained but was not statistically significant (15/56 [27 percent] versus 23/56 [41 percent]).

Although none of these trials reported a statistical increased risk of adverse effects, no firm conclusions can be made since the number of subjects and events was small and the infants were followed for only a short time after birth.

**Evidence of effects from repeated courses of therapy** — Evidence for repeating steroid therapy was provided by a 2015 systematic review of randomized trials that assessed the effectiveness and safety of repeated doses of antenatal betamethasone versus no repeat courses for women who remain at risk of preterm birth ≥7 days after an initial course of therapy [138]. Compared with a single course of therapy, repeated courses of betamethasone resulted in:

For the neonate:

- Reduced risk of respiratory distress syndrome (RDS) (relative risk [RR] 0.83, 95% CI 0.75-0.91, 8 trials, 3206 infants, numbers needed to treat [NNT] 17, 95% CI 11-32).

- Reduced risk of composite serious infant outcomes (RR 0.84, 95% CI 0.75-0.94, 7 trials, 5094 infants, NNT 30, 95% CI 19-79). Serious infant outcomes were variably defined in each trial and included perinatal death, bronchopulmonary dysplasia, severe intraventricular hemorrhage, necrotizing enterocolitis, sepsis, periventricular leukomalacia, and/or retinopathy of prematurity.

  However, repeated dosing did not result in statistically significant reductions in risk for individual outcomes of severe lung disease (RR 0.80, 95% CI 0.56-1.14, 6 trials, 4826), perinatal mortality (RR 0.94, 95% CI 0.71-1.23, 9 trials, 5554 infants), chronic lung disease (RR 1.06, 95% CI 0.87-1.30, 8 trials, 5393 infants), or intraventricular hemorrhage (RR 0.94, 95% CI 0.75-1.18, 6 trials, 3065 infants).

- Reduction in mean birth weight (mean difference -75.79 g, 95% CI -117.63 to -33.96, 9 trials, 5626 infants), which was not statistically significant when birth weight was adjusted for gestational age.

For the mother:

- No significant increase in chorioamnionitis (RR 1.16, 95% CI 0.92-1.46, 6 trials, 4261 women)

- No significant increase in puerperal sepsis (RR 1.15, 95% CI 0.83-1.60, 5 trials, 3091 women)

For the young child:

- No significant harm or benefit. At follow-up in early childhood (18 months to two years corrected age), there were no statistically significant differences in total deaths; survival free of any disability or major disability; major disability; composite serious outcome; growth assessment (weight, height); developmental delay; blindness; deafness; or cerebral palsy. The ACTORDS follow-up group confirmed these findings and lack of effect on bone mass at six to eight years of age [139,140].

However, we and others [114] remain concerned about administering multiple repeat courses of steroid therapy because the systematic review did not evaluate whether there was an increased risk of harm as the number of repeat courses of betamethasone increased. Individual trials suggest increasing exposure to steroids is associated with increasing risk of adverse effect:

- In the Maternal Fetal Medicine Units network (MFMU) trial, 63 percent of patients received ≥4 courses of therapy. The percentage of small for gestational age (SGA) fetuses below the 10th percentile and below the 5th percentile was significantly higher in the repeated steroid course group compared with the single course group (for the 10th percentile: 19.3 versus 8.4 percent; for the 5th percentile 10.4 versus 4.7 percent) [141]. After 32 weeks of gestation, placental weight was significantly less in the repeat corticosteroid group and was related inversely to the number of steroid courses [142]. Although statistically nonsignificant, repeat courses were associated with an increased incidence of cerebral palsy (one case of cerebral palsy in the control group and five in the weekly steroid group; RR 5.68, 95% CI 0.69-46.7); five of the six children with cerebral palsy were delivered near term or term and five of the six were exposed to ≥4 courses of antenatal corticosteroids [141].

- A secondary analysis of data from the Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study, a randomized trial of single versus multiple course steroid therapy, reported a dose-response relationship between the number of corticosteroid courses and a decrease in fetal growth [143]. Multiple

courses of therapy were not associated with an increased risk of maternal side effects [144] or the composite outcome of death/survival with a neurodevelopmental disability at five years of age [145].

- In a small prospective cohort study, exposure to repeat courses of antenatal corticosteroids appeared to impact some aspects of executive functioning, but was not associated with general deficits in higher cognitive functions, self-reported attention, adaptability, or overall psychological function [146].

Other experimental evidence from human and animal studies also supports a link between prenatal exposure to synthetic glucocorticoids and alterations in fetal development that may be permanent [48,147-150].

**NONSTANDARD DOSING REGIMENS** — There is no convincing evidence of the safety and efficacy of increasing the steroid dose, accelerating the dosing interval, or using an intravenous or oral route of administration.

- **Higher dose** – In a clinical study, doubling the dose of betamethasone to 24 mg per day was not associated with increased efficacy [151].

  Pharmacokinetic studies demonstrated that the standard dosing intervals of two 12 mg doses of betamethasone administered 24 hours apart provide maximum glucocorticoid receptor occupancy and near-maximal stimulation of glucocorticoid receptor target genes in fetal tissues [5,152,153]. If receptors are not available for activation, then a higher daily dose of glucocorticoid would not be expected to increase efficacy and the excess drug would likely be excreted. In addition, supraphysiological doses of glucocorticoids suppress glucocorticoid receptor levels by "homologous down-regulation" [154]. Thus, administration of a higher dose of steroid would probably result in no more than a negligible increase in fetal lung maturation.

- **Shorter dosing interval** – Shortening the dosing interval has been proposed to increase the probability of completing the steroid course before delivery. The safety and effectiveness of this approach are unclear as it is supported by limited low-quality evidence [155,156], and one of these studies reported a possible increased risk of necrotizing enterocolitis with a shorter dosing interval, which is concerning [155]. Therefore, a shortened dosing interval should be avoided until data from appropriately powered randomized trials demonstrate efficacy and safety.

- **Intravenous administration** – The clinical efficacy of intravenous antenatal corticosteroids has not been studied in human pregnancy. Intravenous administration results in rapid peaks and troughs in maternal and fetal steroid concentrations. This produces less sustained fetal exposure to corticosteroid stimulation and thus may not be as effective as intramuscular administration.

- **Oral administration of** dexamethasone – In the absence of adequate data establishing the safety and efficacy of oral dexamethasone therapy for fetal maturation, we recommend using only intramuscular therapy.

  Outpatient oral administration of dexamethasone has been used to facilitate completion of full courses of corticosteroids in ambulatory women at increased risk of preterm delivery. In the only randomized trial of this approach, 170 women between 24 and 33 weeks of gestation at high risk of preterm delivery were randomly assigned to receive either 6 mg intramuscular dexamethasone or 8 mg oral dexamethasone every 12 hours for 4 doses, repeated weekly until 34 weeks [157]. There was no statistical difference between groups in the frequency of RDS, but the oral dexamethasone group had significantly higher rates of intraventricular hemorrhage (IVH) and neonatal sepsis, leading to premature discontinuation of

the trial after 39 percent enrollment.

**SPECIAL POPULATIONS**

**Multiple gestation** — We use a standard dosing schedule for both singleton and multiple gestations.

In a 2017 systematic review, the small number of multiple gestations included in the antenatal corticosteroid trials precluded a definite conclusion about the effectiveness of the therapy or the optimum dose (respiratory distress syndrome [RDS] in multiple gestations exposed to antenatal steroids: relative risk [RR] 0.90, 95% CI 0.67-1.22; 4 trials, 320 infants) [2]. In theory, multiple gestations may require higher doses of antenatal corticosteroids to maximize fetal exposure. However, maternal and cord blood betamethasone levels were similar in singleton and multiple gestations in a randomized trial [82]. This trial did not compare clinical outcomes. A prospective pharmacokinetic study also reported pharmacokinetics were the same for singleton and multiple gestations [158].

Observational data suggest benefits in multiple gestations exposed to antenatal corticosteroids, although these studies have not consistently reported a statistical benefit or the benefits achieved in singletons [159-164].

ACOG recommends consideration of a single repeat course of antenatal corticosteroids in pregnancies <34 weeks that have an imminent risk of preterm delivery within the next seven days and had a prior course of antenatal corticosteroids >14 days previously [165]. They also state that rescue-course corticosteroids could be provided as early as seven days from the prior dose, if indicated by the clinical scenario.

**Hypertension** — Betamethasone has low mineralocorticoid activity compared with other corticosteroids and does not aggravate hypertension. A meta-analysis of five small randomized trials supported both the safety and efficacy (reduction in RDS) of antenatal corticosteroid therapy in pregnancies complicated by hypertension [2].

**Diabetes** — Antenatal corticosteroid therapy should be administered to women with diabetes when indicated; however, hyperglycemia related to corticosteroid administration can be severe in this population if not closely monitored and treated. The steroid effect on glucose levels begins approximately 12 hours after the first dose and may last for five days. Women with diabetes generally have been excluded from randomized trials of antenatal corticosteroid therapy because of the adverse effects of steroids on glycemic control, thus efficacy in this population is inferred [166]. (See "Pregestational diabetes mellitus: Obstetrical issues and management", section on 'Antenatal glucocorticoids'.)

**Preterm premature rupture of membranes** — Antenatal corticosteroid administration improves neonatal outcome in pregnancies complicated by preterm premature rupture of membranes and does not increase the risk of neonatal or maternal infection. (See "Preterm prelabor rupture of membranes", section on 'Administration of antenatal corticosteroids'.)

**POSTNATAL SURFACTANT THERAPY** — Postnatal surfactant administration is not a substitute for antenatal corticosteroid therapy. The combination of antenatal corticosteroid therapy and postnatal exogenous surfactant reduces neonatal morbidity and mortality more than use of exogenous surfactant alone [167]. A 2017 meta-analysis that evaluated data from trials before and after the widespread use of surfactant concluded that antenatal corticosteroids appeared to be beneficial in the era of advanced neonatal practice [2].

## SUMMARY AND RECOMMENDATIONS

- Antenatal corticosteroid therapy leads to improvement in neonatal lung function by enhancing maturational changes in lung architecture and by inducing lung enzymes involved in respiratory function. (See 'Mechanism of action' above.)

- Antenatal corticosteroid therapy reduces the incidence of respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, sepsis, and neonatal mortality by approximately 50 percent. These effects are not limited by gender or race; efficacy in multiple gestations is unclear, as high-quality data are sparse. (See 'Evidence of short-term clinical efficacy' above and 'Multiple gestation' above.)

- Given these benefits, we recommend administration of antenatal corticosteroids to pregnant woman who are at 23+0 to 33+6 weeks of gestation and at increased risk of preterm delivery within the next one to seven days (**Grade 1A**). In our practice, we restrict administration of the first course of antenatal corticosteroids to women who rupture membranes or are receiving tocolysis for active preterm labor, or in whom delivery for maternal or fetal indications is anticipated within the next seven days. Antenatal hospitalization does not necessarily mandate a course of antenatal steroids. This approach minimizes the need for salvage (rescue, booster) therapy while allowing most patients to receive a course of antenatal corticosteroids prior to preterm delivery.

  A course of antenatal corticosteroids consists of betamethasone suspension 12 mg intramuscularly every 24 hours for two doses **or** four doses of 6 mg dexamethasone intramuscularly 12 hours apart. We prefer betamethasone over dexamethasone. (See 'Choice of drug and initial dose' above.)

- Observational data suggest neonatal benefits begin to accrue within a few hours of corticosteroid administration. Maximum efficacy appears to occur when delivery occurs two to seven days after administration of the first dose of antenatal corticosteroids. Efficacy is incomplete <24 hours from administration and appears to decline after 7 days. (See 'Timing before delivery' above.)

- We consider approximately 23+0 weeks of gestation the lower limit for administration of antenatal corticosteroids since only a few primitive alveoli are present below this gestational age. Earlier administration in the 22$^{nd}$ week is reasonable if aggressive neonatal intervention is planned after thorough counseling about the limit of viability. (See '22+0 to 33+6 weeks' above.)

- In contemporary obstetric practice in the United States, women delivered at 34+0 to 38+6 weeks of gestation for an obstetric indication are increasingly delivered without amniocentesis to test for fetal lung maturity. The following approach reflects our concern that widespread use of antenatal steroids at ≥34+0 weeks will result in treatment of many pregnancies that will not benefit or will derive only a modest clinical benefit, while exposing them to the theoretical long-term hazards of steroid administration, particularly adverse neurodevelopment outcome in offspring. (See '34+0 or more weeks' above and 'Potential long-term effects in children and adults' above.)

  - For women scheduled for cesarean delivery at 34+0 to 36+6 weeks, we suggest a first course of antenatal corticosteroids (**Grade 2C**). Some clinicians and patients may choose not to use steroids after 34+0 weeks of gestation, given uncertainly in the balance between benefits and risks at ≥34+0 weeks. Families should be informed regarding potential benefits and risks.

  - For women at 34+0 to 36+6 weeks who have already received a course of antenatal corticosteroids, or who are expected to deliver vaginally, or whose likelihood of delivery within the next one to seven

days is uncertain, we suggest not administering a course of antenatal corticosteroids (**Grade 2C**). Repeat courses of steroids have not been recommended at ≥34+0 weeks since transient tachypnea of the newborn is less common after labor and vaginal birth, and most women with threatened preterm labor do not deliver preterm. This is a controversial area, and some national obstetrical organizations have taken a more liberal approach to steroid administration at this gestational age. (See 'Other approaches' above.)

- We also suggest not administering steroids to women undergoing scheduled cesarean delivery at ≥37+0 weeks (**Grade 2C**). The overall risk of neonatal respiratory problems at this gestational age is low and illness is rarely serious. Families should be informed regarding potential benefits and risks.

- The absence of consistent and long-term data precludes making a strong recommendation for the number of courses that are safe for the fetus, the appropriate time interval between courses, the optimal dose for repeated courses of therapy, or the full ramifications of the single course approach to therapy. Given the potential for harm from repeated courses of antenatal corticosteroid therapy:

  - We suggest a single course of salvage (rescue, booster) therapy only if the patient is clinically estimated to be at high risk of delivery within the next seven days, more than two weeks have elapsed since the initial course of antenatal corticosteroid therapy, and the gestational age at administration of the initial course was ≤28 weeks of gestation (**Grade 2C**).

  - We also suggest that providers who elect to give salvage (rescue, booster) therapy use one dose of 12 mg betamethasone and limit treatment to this one additional dose (**Grade 2C**). One dose appears to be effective and may minimize complications related to steroid use; however, a two dose course is also reasonable. No more than one salvage dose or course is recommended over a single pregnancy. Patients should be informed of potential adverse effects. (See 'Use of repeated courses of therapy' above.)



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## Contributor Disclosures

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