Antenatal corticosteroid therapy

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Evidence of short-term clinical efficacy

1) Reduction of RDS
2) Reduction in moderate to severe RDS
3) Reduction in need for mechanical ventilation
4) Reduction of IVH, NEC, NNM, infection

Intraventricular hemorrhage (IVH)

Necrotizing enterocolitis

Neonatal mortality

Systemic infection in the first 48 hours of life

GESTATIONAL AGE AT ADMINISTRATION

A. **22+0 to 33+6 weeks** ; 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.antenatal steroids at 22+0 to 22+6 weeks of gestation can be offered if delivery in the next one to seven days is anticipated and the family is requesting aggressive neonatal intervention.

B. **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.*

Recommendations published by ACOG, SMFM, and RCOG

a) For women scheduled for cesarean delivery at ≥37+0 to 38+6 weeks, a course of steroids can be discussed but not necessarily encouraged.

b) 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.
- ●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 :
- 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.

- ACOG 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 ;
- 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.

- **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 ,
- respiratory distress syndrome,
- and admission to the NICU for respiratory morbidity .
- A trend toward reduction in need for mechanical ventilation was also noted.

- **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 and transient tachypnea of the newborn, but not RDS overall or mechanical ventilation .
- Steroid treatment increased the risk for neonatal hypoglycemia

Possible harms of steroid exposure after 34 weeks

—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.

We are concerned about the potential risks of administering antenatal corticosteroids to late preterm and term gestations, based on the following lines of evidence:

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 , 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

TIMING BEFORE DELIVERY

- 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 .

* Therapy should not be withheld if delivery is anticipated prior to completion of the second dose of the first course of medication.
* 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

CHOICE OF DRUG AND INITIAL DOSE

- Betamethasone and dexamethasone ;
- Both betamethasone and dexamethasone are effective for accelerating fetal lung maturity;
- 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

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.

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 .
* 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.

Potential fetal side effects

- **Fetal heart rate and biophysical parameters ;**

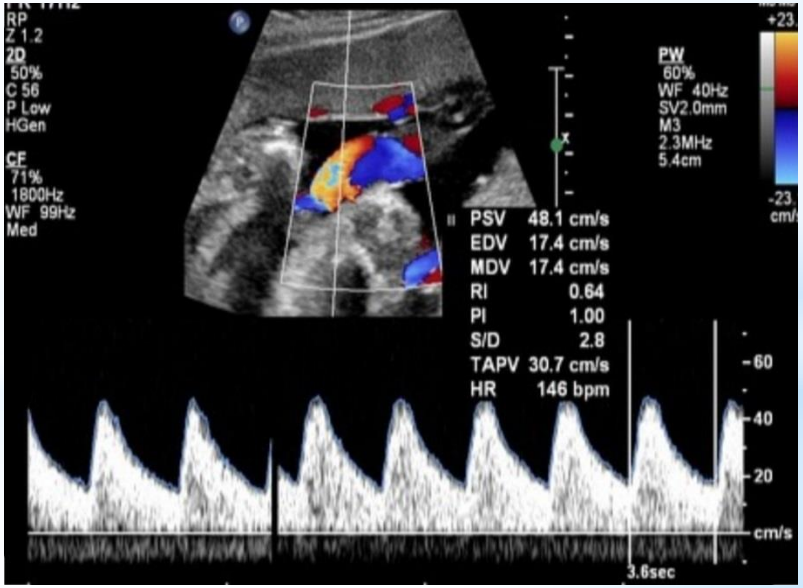
Administration of antenatal corticosteroids may be associated with transient fetal heart rate (FHR) and behavioral changes that typically return to baseline by four to seven days after treatment. When a nonreassuring fetal evaluation [NR-NST] or low biophysical profile [BPP] score) occurs within two or three days of corticosteroid administration, the possibility of transient drug-related changes should be considered.

The most consistent FHR finding is a decrease in variability on days two and three after administration. Reduced fetal breathing and body movements can result in a lower BPP score or NR-NST. However, this is not a consistent finding.

●Doppler flow studies ;

-A transient improvement in umbilical artery end-diastolic flow (EDF) after antenatal corticosteroid .

-The improvement began approximately eight hours after the first dose of betamethasone and lasted a median of three days (range 1 to 10 days).



- **-Potential long-term effects in children and adults** ;

- 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

-Maternal side effects ;

- ✓ — Most pregnant women tolerate a single course of antenatal corticosteroids.
- ✓ -Betamethasone has low mineralocorticoid activity compared with other corticosteroids; therefore, hypertension is not a contraindication to therapy .
- ✓ 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 .
- ✓ In women with diabetes, hyperglycemia can be severe if not closely monitored and treated

- ✓The total leukocyte count increases by approximately 30 percent within 24 hours after betamethasone injection,
- ✓and the lymphocyte count significantly decreases .
- ✓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;

- 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

The American College of Obstetricians and Gynecologists (ACOG) opine that "a single repeat course of antenatal corticosteroids should be considered in women

1. who are less than 34+0 weeks of gestation
2. who have an imminent risk of preterm delivery within the next 7 days,
3. 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".
- 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.

➢ This could result in a reduction in respiratory distress syndrome (RDS) without increasing the risk of potentially adverse outcomes.

❖ Evidence of effects from repeated courses of therapy;

❖ •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

❖ 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.

❖ Although statistically nonsignificant, repeat courses were associated with an increased incidence of cerebral palsy.

NONSTANDARD DOSING REGIMENS ;

a) •**Higher dose;** In a clinical study, doubling the dose of betamethasone to 24 mg per day was not associated with increased efficacy .

b) •**Shorter dosing interval ;** The safety and effectiveness of this approach are unclear as it is supported by limited low-quality evidence, and one of these studies reported a possible increased risk of necrotizing enterocolitis with a shorter dosing interval.

c) •**Intravenous administration ;** 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.

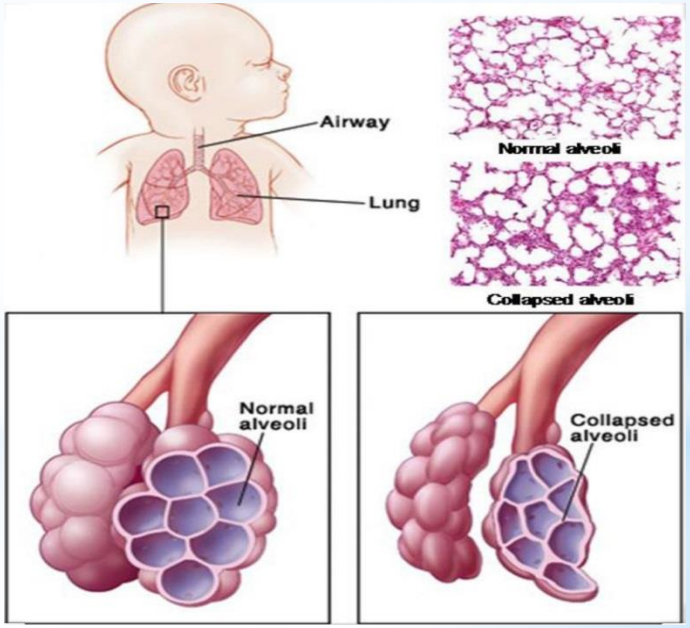
d) •**Oral administration of dexamethasone -;**In the absence of adequate data establishing the safety and efficacy of oral dexamethasone therapy for fetal maturation, we recommend using only intramuscular therapy.

SPECIAL POPULATIONS;

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

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 .



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