Antenatal Steroids and Late Preterm Delivery: What Should We Be Doing?
Late 1960’s: Professor Graham Liggins was investigating initiation of labor in sheep model
Postmortem analysis:

- Structurally more mature lungs
- Less severe respiratory distress
- Viable at earlier gestational age
In 1972, Liggins and Howie published a landmark article demonstrating that antenatal corticosteroids significantly reduced the frequency of respiratory distress syndrome and neonatal mortality.

- Two 12 mg injections of betamethasone 24 hours apart

Several studies followed which corroborated these findings.

Concerns persisted regarding the quality of evidence and fears of potential side effects.

Physicians were hesitant to adopt this treatment into routine practice.

Meta-analysis of 15 RCTs (> 3000 infants)
- Reduces neonatal mortality
- Reduces respiratory distress syndrome (RDS)
- Reduces intraventricular hemorrhage (IVH)
- No proven short- or long-term risks to the infant

“Antenatal corticosteroids should be administered to ALL women at risk of preterm delivery between 24-34 weeks’ gestation”

Endorsed the NIH consensus statement on antenatal corticosteroids

Subsequently, the use of antenatal corticosteroids in the U.S. increased...slowly

Use After the NIH Consensus

Antenatal Corticosteroid Use Among Eligible Patients

- Before NIH Conference
- After NIH Conference
- After NIH Conference (TRYING HARD*)

Current Use

- After another decade of propaganda, administration of a single course of antenatal steroids became standard care for pregnant women at risk for preterm birth
Success Stories in Obstetrics

- Antenatal Corticosteroids
- Rh D Immunoglobulin
- Sliced Bread (benefitting mothers everywhere)
Objectives

- Review recent NEJM article addressing late preterm antenatal corticosteroids
- Discuss optimal clinical management
Corticosteroid Dosing

- **Betamethasone:**
  2 doses of 12 mg IM, 24 hours apart

- **Dexamethasone:**
  4 doses of 6 mg IM, 12 hours apart

The dose and regimen of antenatal corticosteroids were chosen arbitrarily, and the optimal dosing regimen is not known.
Review of 21 studies and >4200 infants

- Reduced risk of neonatal death, RDS, IVH, and necrotizing enterocolitis, and systemic infection in the first 48 hours of life
- Helpful even if delivery occurs <24 hours after initiation of treatment
- Safe and effective in the setting of PPROM

Evidence for a Single Course

- Review of 21 studies and >4200 infants
  - Not associated with long-term intellectual impairment or learning/behavioral difficulties
  - Suggested that treatment results in a LOWER incidence of childhood neurodevelopmental delay and possibly cerebral palsy

Evidence for a Single Course

We have clear and compelling evidence regarding the benefits, and safety, of a single course of antenatal corticosteroids for patients at 24-34 weeks who are at risk for preterm delivery.
Late Preterm Delivery

- 34 weeks 0 days to 36 weeks 6 days
- 70% of preterm births occur late preterm
- Associated with increased risk of neonatal and childhood complications
Late Preterm Delivery

- Although the risk of RDS is higher under 34 weeks, the absolute number of infants delivering in the late preterm period and requiring NICU admission for RDS is higher
  - 17,000 infants >34 weeks admitted to the NICU/yr.

Would corticosteroids help?
Antenatal Betamethasone for Women at Risk for Late Preterm Delivery

for the NICHD Maternal–Fetal Medicine Units Network*
Late Preterm Steroid Trial

- Conducted through the MFMU Network
  - 17 University-based clinical centers, including University of Utah and Intermountain Healthcare
  - October 2010 - February 2015
Enrollment

- Singleton pregnancies 34 0/7 to 36 5/7
- High probability of delivery in the late preterm period
  - Preterm labor
  - PPROM
  - Other indication for delivery within 24 hrs – 7 days
Exclusion Criteria

- Antenatal steroids during pregnancy
- Expected delivery <12 hours
- Chorioamnionitis
- Pre-gestational diabetes
- Non-reassuring fetal status
Treatment

- Randomized to two IM injections of betamethasone (12 mg) or placebo, 24 hours apart.
Primary Outcome

- Composite end point of need for respiratory support within 72 hours after birth:
  - CPAP or high-flow nasal cannula for at least 2 hrs
  - Supplemental O2 $\geq 30\%$ for at least 4 hrs
  - ECMO
  - Mechanical ventilation
  - Stillbirth/neonatal death (competing outcomes)
2831 women were randomized

Intent-to-treat analysis
- 1427 women who received betamethasone
- 1400 women who received placebo

>80% delivered <37 weeks
Results

- **Primary outcome**
  - Lower in the betamethasone vs. placebo group
    - 11.6% vs. 14.4%, RR 0.8, 95% CI 0.66-0.97
    - NNT = 35
Secondary outcomes

- Composite severe respiratory complications (CPAP or high-flow nasal cannula for at least 12 hrs, supplemental O2 ≥30% for at least 24 hours, ECMO, mechanical ventilation, stillbirth/neonatal death)
  - 8.1% vs. 12.1%, RR 0.67, 95% CI 0.53-0.84
  - NNT = 25
Results

Secondary outcomes

Lower rates of:
- TTN
- BPD
- Composite of RDS, TTN, or apnea
- Resuscitation at birth
- Surfactant use
- Prolonged stay in NICU or intermediate care nursery

No difference:
- Length of hospital stay
- Rates of sepsis, NEC, IVH, SGA
Results

- Secondary outcomes
  - Higher incidence of neonatal hypoglycemia
    24% vs. 15%, RR 1.6, 95% CI 1.37-1.87
  - Minor- no related adverse events or prolonged hospital stay
Antenatal betamethasone administered to women at risk for late preterm delivery decreases the need for significant respiratory support in the first 72 hours after birth.

Also decreased severe respiratory complications, TTN, BPD, surfactant use, resuscitation, and pronged nursery stay.
Benefits were seen although only 60% of participants randomized to betamethasone received 2 doses of study drug
So what should we do?

Implementation of the use of antenatal corticosteroids in the late preterm birth period in women at risk for preterm delivery

Society for Maternal-Fetal Medicine (SMFM) Publications Committee
In women with a singleton pregnancy between 34 0/7 and 36 6/7 who are at high risk for preterm birth within 7 days (but before 37 weeks), treat with betamethasone (1 dose of 12 mg IM 24 hours apart)
So what should we do?

- In women with preterm labor symptoms in the late preterm period, wait for evidence of preterm labor, such as cervical dilation of at least 3 cm or effacement of at least 75% before treatment.
So what should we do?

- Recommend against the use of tocolysis to attempt to delay delivery to complete the steroid course - unclear if steroid benefits outweigh risks of attempts to delay delivery.

- Recommend against expectant management for preeclampsia with severe features.
So what should we do?

- In women with a potential medical indication for delivery, recommend steroids not be given unless there is a definitive plan for late preterm delivery.
Recommend against use of this protocol for conditions not studied in the trial
- Multiple gestations
- Prior steroid course <34 weeks
- Pre-gestational diabetes

...unless performed as part of research or quality improvement...
So what should we do?

University of Utah Approach

- Liberal approach to administration
  - Reasonable expectation of getting at least 12 hrs
- Administering to pregnancies with multiple gestation, diabetes, chorioamnionitis
- No tocolysis
- No expectant management of severe preeclampsia
- No delay of induction/delivery if clear medical indication to proceed
Success Stories in Obstetrics

- Antenatal Corticosteroids
  - Viability up to 36 6/7