Antenatal Steroids & Late Preterm Delivery: What should we be doing?

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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
Landmark article demonstrating antenatal corticosteroids significantly reduced respiratory distress syndrome and neonatal mortality

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- Two injections of betamethasone 12 mg, 24 hours apart

Several studies followed which corroborated these findings. Concerns persisted regarding the quality of evidence and potential side effects. Physicians were hesitant to adopt this treatment into routine practice.

NIH Consensus Conference, 1994

- 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*)
A single course of antenatal steroids became standard of care for pregnant women at risk for preterm birth.
Review of 21 studies and >4200 infants

- Reduced risk of neonatal death, RDS, IVH, and necrotizing enterocolitis
- Helpful even if delivery occurs <24 hours after initiation of treatment

Review of 21 studies and >4200 infants

- Not associated with long-term intellectual impairment or learning/behavioral difficulties
- Treatment may result in a LOWER incidence of childhood neurodevelopmental delay and possibly cerebral palsy

We have clear and compelling evidence regarding the benefits, and safety, of a single course of antenatal corticosteroids for patients up to 33 6/7 weeks who are at risk for preterm delivery.
Success Stories in Obstetrics

- Antenatal Corticosteroids
- Rh D Immunoglobulin
- Sliced Bread (benefitting mothers everywhere)
Although the risk of RDS is greater before 34 weeks gestation...

- Majority of preterm births are late preterm
- Absolute number of infants with RDS is much greater in the late preterm period
- 17,000 infants >34 weeks admitted to NICU/yr.

Would corticosteroids help?
Objectives

- Review NEJM article addressing late preterm antenatal corticosteroids
  - Objective, clinical intervention, outcomes

- Discuss optimal clinical management
  - Development & implementation of clinical algorithms
3 KEY COMPONENTS

1. Maintenance of inflation during inhalation and expiration for adequate gas exchange

Facilitated by the surface tension lowering effect of phospholipids (surfactant) secreted in-utero by type II alveolar cells
3 KEY COMPONENTS

2. Fetal lung fluid must be sufficiently cleared from the alveolar spaces, a process initiated in late gestation.

- In the fetal lung, active chloride secretion leads to water secretion.
2. Fetal lung fluid must be sufficiently cleared from the alveolar spaces, a process initiated in late gestation.

- During late gestation, chloride secretion switches to active sodium resorption.
3. Pulmonary vascular resistance must fall sufficiently to allow the entire cardiac output to flow through the pulmonary circulation.
Effective Lung Function

- When these adaptations do not occur:
  - Respiratory distress syndrome (RDS)
  - Transient tachypnea of the newborn (TTN)
  - Persistent pulmonary hypertension (PPH)
Effect of Antenatal Corticosteroid Treatment

- Endogenous steroids = critical to lung development
- Exogenous steroids ACCELERATE these effects
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  - Induction of type II alveolar cells → surfactant
  - Stimulation of lung structural development
    - Improved gas exchange
    - Improved response to postnatal surfactant
Endogenous steroids = critical to lung development
Exogenous steroids ACCELERATE these effects

- Induction of type II alveolar cells $\rightarrow$ surfactant
- Stimulation of lung structural development
  - Improved gas exchange
  - Improved response to postnatal surfactant
- Increased sodium channel expression
  - Facilitates lung liquid clearance
2 of the 3 components necessary for effective lung function - maintenance of inflation and clearance of lung fluid - are affected by steroid administration.
Antenatal Betamethasone for Women at Risk for Late Preterm Delivery


Presented at the SMFM Annual Meeting, February 2016
Antenatal Late Preterm Steroids: ALPS Trial

- Conducted through the MFMU Network
  - Double-blind, placebo-controlled RCT
  - 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 (at least 3 cm, or 75% effaced)
  - PPROM
  - Other indication for delivery, 24 hrs – 7 days
    - Pragmatic- left to discretion of provider
Exclusion Criteria

- Antenatal steroids during pregnancy
- Major fetal anomalies
- Multiple gestation
- Pre-gestational diabetes
- Chorioamnionitis
- Non-reassuring fetal status
- Expected delivery <12 hours
Some Trial Nuances...

- Inclusion and exclusion factors selected with an eye toward maximizing exposure to steroids and avoiding overtreatment
- Tocolysis was not allowed
- Delivery for obstetric or medical indications was not delayed
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 ≥30% for at least 4 hrs
  - Mechanical ventilation
  - ECMO
  - Stillbirth/neonatal death (competing outcomes)
Results

- 2831 women were randomized
  - 1427 women who received betamethasone
  - 1400 women who received placebo
- > 80% delivered < 37 weeks
Composite Respiratory Outcome

- Treatment: 11.6%
- Placebo: 14.4%
Composite Respiratory Outcome

- RR 0.8 [95% CI 0.66-0.97], NNT= 35
Secondary Outcome: Composite SEVERE Respiratory Complications

- Composite end point of severe respiratory complications within 72 hours after birth:
  - CPAP or high-flow nasal cannula for at least 12 hrs
  - Supplemental O₂ ≥30% for at least 24 hrs
  - Mechanical ventilation
  - ECMO
  - Stillbirth/neonatal death
Composite Severe Respiratory Outcome

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity</td>
<td>8.1%</td>
<td>12.1%</td>
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</tbody>
</table>

Composite Severe Respiratory Outcome
Composite Severe Respiratory Outcome

- RR 0.67 [95% CI 0.53-0.84], NNT= 25
<table>
<thead>
<tr>
<th>Treatment</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-hypertensives to prevent death</td>
<td>125</td>
</tr>
<tr>
<td>Statins to prevent heart attack</td>
<td>104</td>
</tr>
<tr>
<td>Aspirin for acute MI to prevent death</td>
<td>42</td>
</tr>
<tr>
<td>MgSO4 to prevent eclampsia</td>
<td>90</td>
</tr>
<tr>
<td>Composite respiratory outcome</td>
<td>35</td>
</tr>
<tr>
<td>Severe composite respiratory outcome</td>
<td>25</td>
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</tbody>
</table>
Assorted Secondary Outcomes

- Lower risk of:
  - TTN
  - BPD
  - Resuscitation at birth
  - Surfactant use
  - Prolonged stay in NICU (3 or more days)
No difference:
- Neonatal sepsis
- Birth weight, SGA
- Admission to NICU
- Median length of neonatal hospital stay
Increased risk:

24% vs. 15%, RR 1.6 [95% CI 1.37-1.87]

- Minor- no related adverse events or prolonged hospital stay
- Rates in betamethasone group are similar to reported rates in late preterm babies
Antenatal betamethasone administered to women at risk for late preterm delivery

- Decreases the need for ‘respiratory support’ in the first 72 hours after birth by 20%
- Decreases the risk of ‘severe respiratory complications’ by 33%
- Decreases the risk of other secondary outcomes (TTN, BPD, resuscitation, surfactant, NICU stay >3 days)
So what should we be doing?

- When translating a clinical trial into clinical practice:
  1. Think critically about exclusion groups
  2. Carefully consider biologic mechanisms
  3. Ponder possible risks and benefits when there is equipoise
  4. Where there is uncertainty, try to reach consensus in your group
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
Antenatal Corticosteroid Therapy for Fetal Maturation
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 (and before 37 weeks) treat with betamethasone
Benefits were seen although only 60% of participants randomized to betamethasone received 2 doses of study drug
So what should we do?

- Benefits were seen although only 60% of participants randomized to betamethasone received 2 doses of study drug
  - If reasonable chance of being pregnant at least 12 hours, give the drug
Preterm Labor

In women with preterm labor symptoms in the late preterm period, wait for objective evidence of preterm labor

- Such as cervical dilation of at least 3 cm or effacement of at least 75%
- [The trial was more dogmatic than we should be...there is room for clinical intuition...]
Chorioamnionitis

“Late preterm administration of antenatal corticosteroids is not indicated in women diagnosed with clinical chorioamnionitis.”

-ACOG Committee Opinion

- Derived from trial methodology
  - Not candidates for expectant management, unlikely to be pregnant in 12 hours

- Not a contraindication to betamethasone treatment <34 weeks
Don’t use tocolytics to attempt to delay delivery to complete the steroid course

- Unclear if steroid benefits outweigh risks of attempts to delay delivery
No: Preeclampsia with severe features
  - Perceived risks outweigh estimated benefit
Expectant Management

- No: Preeclampsia with severe features
  - Perceived risks outweigh estimated benefit

- No (?): PPROM
  - Neonatal data for expectant management past 34 weeks is favorable (< RDS, mechanical ventilation, ICU days without increase in rate of sepsis), but this remains controversial
  - Risk/benefit may favor treatment

In women with a potential medical indication for late preterm delivery, recommend steroids not be given unless there is a definitive plan.
Fetal programming
Long-term neurodevelopment

Demonstrated neonatal short-term benefit

Risks vs. Benefits of Treatment
ACOG/SMFM recommend against use for conditions not studied in the trial

- Multiple gestation
- Prior steroid course <34 weeks
- Pre-gestational diabetes

...unless performed as part of research or quality improvement...
Neonatal Hypoglycemia

- Don’t sweat it.
- Utilize standard guidelines for assessment and management of neonatal hypoglycemia in late preterm infants per AAP guidelines.
We now have clear and compelling evidence regarding the short-term benefits, and safety, of a single course of antenatal corticosteroids for patients who are at risk for late preterm delivery.
University of Utah Approach

- Thoughtfully liberal approach to administration...
  - Reasonable expectation of getting at least 12 hours of exposure
University of Utah Approach

- *Thoughtfully liberal approach to administration…*
  - Reasonable expectation of getting at least 12 hours of exposure
  - Following SMFM and ACOG Guidelines
    - Diverge with expectant management of PPROM
University of Utah Approach

- Thoughtfully liberal approach to administration...
  - Reasonable expectation of getting at least 12 hours of exposure
  - Following SMFM and ACOG Guidelines
    - Diverge with expectant management of PPROM
  - Where there is equipoise...
    - Research and QI opportunities