Antenatal Steroids - Friends or Foes in Indian Scenario

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Executive Director, International Neonatology Association, Geneva
Respiratory Distress Syndrome

PREMATURITY
- Surfactant Deficiency
- Atelactasis
- Structurally Immature Lung
- V/Q Mismatch
- Hypoventilation

ACUTE
- Hypoxemia & Hypercarbia
- Respiratory & Metabolic Acidosis
- Pulmonary Vasoconstriction
- Impaired endothelial and epithelial integrity
- Proteinaceous exudate

CHRONIC
- High FiO₂ & Baro or Volutrauma
- Inflammatory Cell Influx
- Cytokine Release
- Antioxidant Reduction
- Free-radical reactions
- Lung Injury

RDS
Chronic Lung Disease / BPD

Graph showing birth weight distribution:
- Birth weight (g)
- Frequency distribution across different birth weight ranges.
Graham Liggins was investigating factors involved in the initiation of labor in a sheep model. His hypothesis was that the fetus produces substances that trigger labor, possibly steroid hormones. In postmortem analyses, Liggins incidentally found that preterm lambs exposed to corticosteroids had structurally more mature lungs than expected, and were also viable at an earlier gestational age and had less severe respiratory distress at birth.

1972

Landmark study
Lung Physiology

Surfactant function:
- Lower surface tension at air liquid surface
- Protect patency of small airways
- Prevent movement of fluid into the alveolus
- Stimulates lung host defence system
**Cortico-steroid**

**Mechanism of Action**

1. **Inducing fetal lung antioxidant system**
2. **Regulate gene function in maturation lung**
3. **Inducing pulmonary beta receptor**
4. **Increase surfactant production**
5. **Upregulate gene expression of epithelial Na channel**
6. **Improve lung mechanics and gas exchange**
7. **Accelerate development of type 1 & 2 pneumocytes**
8. **Inducing production of surfactant proteins and enzyme phospholipid synthetase**

**Regulate gene function in maturation lung**
- Single course of injection of Dexamethasone to be administered to women with pre term labour (between 24 & 36 weeks of gestation) at all levels of health facilities in the public as well as the private sector.

- Oral preparations of steroids are not to be used

- Repeated courses of steroids or more frequent doses are not useful, multiple courses in fact could have harmful neuro-developmental effects
Contraindications?

- Frank Chorioamnionitis is an absolute contraindication for using antenatal steroids.
- Maternal Diabetes, Pre-eclampsia & Hyper-tension are not contraindications for using steroids, careful monitoring of sugar & BP.
NICU at J K Lon Hospital
Baby with RDS
## Antenatal Steroids - in Out born Babies

From a Tertiary Care Hospital (J K Lon) – 200 Beded NICU

<table>
<thead>
<tr>
<th>Month/Year</th>
<th>&lt; 34 week</th>
<th>Antenatal Steroids Given</th>
<th>Received Full Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>September</td>
<td>111</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>October</td>
<td>81</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>November</td>
<td>84</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2019</td>
<td>1253</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>
Weight & Gestational Maturity of Babies admitted at J K Lon Hospital (Six Months)

Tertiary Care Pediatric Hospital with 1000 Beds

<table>
<thead>
<tr>
<th>Birth Weight</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;= 2500 gms</td>
<td>182</td>
</tr>
<tr>
<td>1500 – 2499 gms</td>
<td>182</td>
</tr>
<tr>
<td>1000 – 1499 gms</td>
<td>78</td>
</tr>
<tr>
<td>&lt;1000 gms</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gestataion</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 37 weeks</td>
<td>248</td>
</tr>
<tr>
<td>34 - 37 weeks</td>
<td>104</td>
</tr>
<tr>
<td>&lt; 34 weeks</td>
<td>94</td>
</tr>
</tbody>
</table>
## AUGUST 2019

<table>
<thead>
<tr>
<th>PARTICULARS</th>
<th>NICU-A</th>
<th>NICU-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO. OF BEDS</td>
<td>35</td>
<td>88</td>
</tr>
<tr>
<td>ADMISSION</td>
<td>125</td>
<td>231</td>
</tr>
<tr>
<td>MALE</td>
<td>79 (63.2%)</td>
<td>159 (68.8%)</td>
</tr>
<tr>
<td><strong>BIRTH WEIGHT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=2500 gm</td>
<td>45 (36%)</td>
<td>93 (40%)</td>
</tr>
<tr>
<td>1500-2499 gm</td>
<td>48 (38.4%)</td>
<td>86 (37.2%)</td>
</tr>
<tr>
<td>1000-1499 gm</td>
<td>20 (16%)</td>
<td>35 (15.2%)</td>
</tr>
<tr>
<td>&lt;1000 gm</td>
<td>12 (9.6%)</td>
<td>17 (7.5%)</td>
</tr>
<tr>
<td><strong>GESTATION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;37 weeks</td>
<td>50 (40%)</td>
<td>118 (51%)</td>
</tr>
<tr>
<td>34-37 weeks</td>
<td>45 (36%)</td>
<td>51 (22%)</td>
</tr>
<tr>
<td>&lt;34 weeks</td>
<td>30 (24%)</td>
<td>62 (26.8%)</td>
</tr>
<tr>
<td><strong>Morbidity Profile</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Distress syndrome</td>
<td>51 (40.8%)</td>
<td>42 (18%)</td>
</tr>
<tr>
<td>Meconium aspiration syndrome</td>
<td>6 (4.8%)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Other causes of respiratory distress (Congenital Pneumonia)</td>
<td>5 (4%)</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>HIE/Moderate severe birth asphyxia</td>
<td>36 (28.8%)</td>
<td>58 (25%)</td>
</tr>
<tr>
<td>Sepsis/Pneumonia/Meningitis</td>
<td>13 (10.4%)</td>
<td>42 (18%)</td>
</tr>
<tr>
<td>Major Congenital Malformation</td>
<td>5 (4%)</td>
<td>8 (3.5%)</td>
</tr>
<tr>
<td>Jaundice requiring phototherapy</td>
<td>2 (1.6%)</td>
<td>51 (22%)</td>
</tr>
<tr>
<td>Hypo/hypothermia</td>
<td>1 (0.8%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>4 (3.2%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Others (Extreme Prematurity+For Observation)</td>
<td>2 (1.6%)</td>
<td>16 (6.8%)</td>
</tr>
</tbody>
</table>
## AUGUST 2019

<table>
<thead>
<tr>
<th>PARTICULARS</th>
<th>NICU-A (54)</th>
<th>NICU-B (84)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality profile (Cause of death)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Distress syndrome</td>
<td>27 (50%)</td>
<td>8 (9.5%)</td>
</tr>
<tr>
<td>Meconium aspiration syndrome</td>
<td>5 (9.2%)</td>
<td>4 (4.7%)</td>
</tr>
<tr>
<td>HIE/Moderate-severe birth asphyxia</td>
<td>9 (16.7%)</td>
<td>25 (29.8%)</td>
</tr>
<tr>
<td>Sepsis/Pneumonia/Meningitis</td>
<td>7 (13%)</td>
<td>32 (38.1%)</td>
</tr>
<tr>
<td>Major congenital malformation</td>
<td>4 (7.4%)</td>
<td>3 (3.6%)</td>
</tr>
<tr>
<td>Prematurity</td>
<td>2 (3.6%)</td>
<td>10 (11.9%)</td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>2 (2.4%)</td>
</tr>
<tr>
<td><strong>Duration between the time of admission &amp; death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 day</td>
<td>9 (16.7%)</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>1-3 days</td>
<td>18 (33.3%)</td>
<td>28 (33.3%)</td>
</tr>
<tr>
<td>4-7 days</td>
<td>15 (27.8%)</td>
<td>23 (27.4%)</td>
</tr>
<tr>
<td>&gt;7 days</td>
<td>12 (22.2%)</td>
<td>32 (38.1%)</td>
</tr>
</tbody>
</table>
Evidence of Short Term Clinical Benefit of Corticosteroid

Reduction of RDS

2006 systematic review of RCT comparing antenatal corticosteroid vs placebo:
- Reduction of RDS (RR 0.66, 95% CI 0.59-0.73)
- Reduction in moderate to severe RDS (RR 0.55 95% CI 0.43-0.71)

Reduction of IVH, NEC, NNM, infection

2006 systematic review of RCT comparing antenatal corticosteroid vs placebo:
- Intraventricular hemorrhage (IVH) (RR 0.54, 95% CI 0.43-0.69)
- Necrotizing enterocolitis (NEC) (RR 0.46 95% CI 0.29-0.74)
- Neonatal Mortality Rate (NNM) (RR 0.69 95% CI 0.58-0.81)
- Systemic infection in the first 48 hours of life (RR 0.56, 95% CI 0.38-.085)
When to Administer?

- **< 22 weeks**
  - Reasonable if delivery in the next 7 days is anticipated
  - Unlikely to significantly improve lung function
  - Survive with severe impairment

- **23-34 weeks**
  - Recommend to all pregnant women who will deliver within the next 7 days
  - Significantly reduce risk of RDS, IVH, neonatal death
  - Reduction perinatal mortality at 23 weeks

- **> 34 weeks**
  - Controversial
  - Inconsistent data of efficacy
  - No data about long-term safety
Corticosteroid Use At 37-39 Weeks

- Empiric use of steroid has been recommended prior to CS at 37-39 weeks

- The ASTECS trial, 1000 women, betamethasone vs placebo, 48 hours before planned CS:
  - Reduction in overall incidence of respiratory problems (Transient tachypnea of the newborn and RDS) [RR 0.46]

- Similar trial, dexamethasone vs placebo, 48 hours before, 38 weeks planned CS:
  - Reduction in NICU admission for respiratory morbidity
  - Reduction in transient tachypnea of the newborn (RR 0.38)
  - No difference in RDS, need for mechanical ventilation
Corticosteroid Use At 34-36 Weeks

The Antenatal Late Preterm Steroids Trial (ALPS)

Methods:
Women at 34-36 weeks, risk of preterm birth, betamethasone vs placebo

Primary outcome:
Composite of neonatal respiratory treatment in the first 72 hours, stillbirth, or neonatal death within 72 hours of delivery

Result:
• Primary outcome occur less in treatment groups (RR 0.80; 95% CI 0.66-0.97)
• Severe respiratory complications, transient tachypnea of the newborn, surfactant use, and bronchopulmonary dysplasia, occurred significantly less frequently in the treatment group
• Neonatal hypoglicemia more frequently in treatment groups
• RDS and use of Mechanical Ventilation is similar

Gyamfi Bannerman et al, 2016. BEJM
Corticosteroid Use At 34-36 Weeks

Many approach

**The Society for MFM Specialists:**
Two doses of betamethasone for women 34-36 wk with symptoms of preterm labor, cervical dilatation > 3 cm, eff 75%, no tocolysis

**The American College of Obstetricians and Gynecologists:**
Administer betamethasone in women at 34-36 wk with imminent risk of preterm delivery within 7 days
Chorioamnionitis is contraindication
Tocolysis shouldn’t be used

**The Royal College of Obstetricians and Gynecologists:**
Routine administration of antenatal glucocorticoids for:
(1) All women at risk of preterm birth (include 34-36 weeks)
(2) All women who must undergo CS before 39 weeks
UPTODATE Recommendation:

- Administer first course corticosteroid for women scheduled CS at 34-36 weeks

- Not administer second course of corticosteroid for above condition, to women already received corticosteroid < 34 weeks

- Not administer corticosteroid for women undergoing CS at ≥ 37 weeks

- For vaginal delivery > 34 weeks, not administer steroid (TTN is less common in vaginal delivery)
Timing of Administration Before Delivery

- A statistical benefit was observed 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) (Crowley PA, 1995)

- In one study, only one-quarter of women delivered within the optimal window of after steroid administration (Mahkija NK et al, 2016)

- Observational data suggest neonatal benefits begin to accrue within a few hours of corticosteroid administration (Elimian et al, 2003)
**Choices of Drugs**

**Betamethasone**
- 2 x 12 mg im 24 hours apart

**Dexamethasone**
- 4 x 6 mg im 12 hours apart

**Why?**

These steroids are less extensively metabolized by the placental enzyme 11 β-hydroxysteroid dehydrogenase type 2.

The efficacy of alternative dosing regimen is unproven.
2013 Cochrane review of 12 trials:
No statistical differences between dexamethasone and betamethasone were observed for respiratory distress syndrome (RDS) or neonatal death

Both are effective, similar efficacy
Potential Side Effect of A Single Course of Antenatal Corticosteroid Therapy < 34 weeks

- Transient FHR changes (non-reassuring) within 2-3 days administration
- Transient improvement in umbilical artery end diastolic flow (EDF)

Fetal

Infants

Children

Maternal

Most women tolerate well

Transient hypoglycemia

No increase in risk of death, chorioamnionitis, & sepsis

No adverse effect on growth, lung function, psychosocial, cognitive, motor, neurologic & ophthalmologic

 Didn't increase any adverse infant outcome

No report any adverse effect on growth, lung function, psychosocial, motor, neurologic & ophthalmologic

• Transient FHR changes (non-reassuring) within 2-3 days administration
• Transient improvement in umbilical artery end diastolic flow (EDF)
Repeated Course of Corticosteroid Therapy

- Single VS Multiple Repeated Course
- Single VS Full dose
- Risk VS Benefit
Efficacy of Repeated Course of Steroid Therapy

- 2015 systematic review RCT, repeated doses betamethasone vs placebo

**RESULT**

- For the neonate:
  - Reduced risk of RDS (RR: 0.83)
  - Reduced risk composite serious infant outcome [RR 0.84] (perinatal death, bronchopulmonary dysplasia, IVH, NEC, sepsis, periventricular leukomalacia, & ROP)

- For the mothers: no difference in chorioamnionitis & puerpural sepsis

- For the young child: no significant benefit & harm
Concern About RISK in Multiple Course Corticosteroid Therapy

Maternal Fetal Medicine Networks Unit trial:
- Higher percentage of SGA fetuses in repeated course group
- Smaller placenta
- Increase incidence of cerebral palsy

Multiple Courses of Antenatal Corticosteroid for Preterm Birth Study:
- Dose response relationship between number of corticosteroid course with decrease in fetal growth
Multiple Course of Steroid Therapy

Risk

- SGA
- Reduced HC
- Smaller placenta
- Cerebral palsy?

VS

Benefit

- Reduced RDS
- Reduced composite infant morbidity
Salvage/Rescue/Booster Therapy

DEFINITION:
One additional course of therapy for women at high risk of delivering within 7 days

RATIONALE:
Reduction of RDS without increasing RISK of potentially adverse outcomes

EVIDENCE:
Three RCT, 2 report significant reduction in RDS, and 1 trial report significantly increased respiratory compliance
ACOG
Recommend single course of salvage steroids in women:
(1) Who remain at risk of preterm delivery < 34 weeks
(2) Whose prior course was administered at least 7 days previously

ACTORS
Weekly repeat dosing with single injection of betamethasone was effective after initial therapy

Single Dose <-> Two Dose
## Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal steroid (ANS) are associated with significant reduction in neonatal death, RDS, IVH and safe for mother</td>
<td>A</td>
</tr>
<tr>
<td>Single course of ANS to women 24-34 weeks who are at risk of preterm birth</td>
<td>A</td>
</tr>
<tr>
<td>ANS are most effective in reducing RDS in pregnancies that deliver 24 hours - t days after administration</td>
<td>A</td>
</tr>
<tr>
<td>ANS isn't associated with any significant short term maternal or fetal adverse effects</td>
<td>A</td>
</tr>
<tr>
<td>Caution when giving corticosteroid in women with systemic infection</td>
<td>A</td>
</tr>
<tr>
<td>ANS should be given to all women at risk of preterm birth up to 34 weeks</td>
<td>A</td>
</tr>
<tr>
<td>ANS should be given to all women for whom an elective CS planned prior to 39 weeks</td>
<td>A</td>
</tr>
<tr>
<td>Betamethasone 2 x 12 mg im or dexamethasone 4 x 6 mg im are the steroid of choice to enhance fetal lung maturity</td>
<td>A</td>
</tr>
<tr>
<td>Weekly repeat course of ANS isn't recommended</td>
<td>A</td>
</tr>
</tbody>
</table>
Take Home Messages

1. Steroid is beneficial in preterm labor
2. 22 - 34 weeks
3. Betamethasone = dexamethasone
4. Salvage/booster therapy: < 34 weeks in labor, already received steroid > 7 days before
5. Steroid > 34 weeks is optional for cesarean delivery
FIGO Recommendations

- All women between 24 to 34 weeks of gestation at risk of pre-term birth within 7 days, should receive a single course
- Pregnancy at less than 24 weeks of gestation with a risk of pre-term birth within 7 days - consider local limits of foetal viability
- Single course is recommended for pregnant women between 34 to 36.6 weeks with a risk of pre-term birth within 7 days and who have not received a previous course of AN steroids
- A single course of steroid for planned caesarean delivery at 37 to 38.6 weeks gestation
- Antenatal Steroids are most effective in deliveries within 24 hours after and upto 7 days
- Weekly repeat courses are not recommended
Cont..

- One course of AN steroids is indicated for pregnancies between 24 to 34 weeks at risk of delivery within 7 days irrespective of single or multiple births
- Recommended for women with pre gestational and gestational diabetes at risk of imminent pre-term birth
- Insufficient evidence on benefits or harm of AN steroid therapy in IUGR
Thanks