PREVENTION OF MORBIDITY IN THE PRETERM DELIVERY: ANTENATAL STEROIDS

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Global Health Problem

- 15 billion/year
- Leading cause of perinatal mortality and morbidity
  - 965,000/year neonatal death
  - 125,000/year under 5 years old

Global rate is 11-12%
Preterm Delivery
Distribution by Gestational Age

- Very early (<28 weeks): 6.4%
- Early (28^0–31^6 weeks): 10.5%
- Moderate (32^0–33^6 weeks): 13.0%
- Late (34^0–36^6 weeks): 70.1%
- **Morbidity**
  - RDS
  - IVH
  - Sepsis
  - NEC
  - Retinopathy
  - Broncopulmonary Dysplasia
  - Cerebral Palsy
  - Mental Retardation
Prevention of Morbidity in the Preterm Delivery

- Correct Diagnosis
- Tocolysis
- **Antenatal steroids**
- Transport to tertiary care units
- MgSO4
Antenatal Corticosteroids
Historical Background

• First RCT: Liggins G, Howie RN, Pediatrics, 1972
• Consensus by NIH and ACOG 1994
• Long 22 years

Sir Graham ("Mont") Liggins FRS
1926 - 2010
Antenatal Corticosteroids
Historical Background

National Institute of Health (1994)

Suggests antenatal corticosteroids between the 24 and the 34 weeks of gestation
• to reduce neonatal mortality and respiratory distress
• to prevention of intraventricular hemorrhage
Antenatal Steroids

Carla WA, JAMA, 2011
• Dexamethasone 6 mg (4 times, 12 hours apart) intramuscularly

• Bethametasone: 12 mg 24 hours apart intramuscularly

• Peak effect starts 24 hours following last dose and lasts 7 days
• Neonates with ACS exposure beyond 7 days were seven times more likely to have RDS

Sekhavat L, J Turk Ger Gynecol Assoc, 2011
Hester CQ, Arch Gynecol Obstet, 2017
Antenatal Corticosteroids
Maternal Side Effects

• Higher and repeated doses can cause adrenal insufficiency
  • Not in single course

• Chorioamnionitis- endometritis
  • No increase about maternal death, puerperal infection, sepsis
  COCHRANE DATABASE 2006

• Leucocytosis starts 24 hours following last dose and lasts 72 hours.
• Hyperglicemia and impaired glucose control in the diabetic subjects . Normoglycemia within 72 hours.

• Pulmonary Edema
  • Higher risk for the volume load and concurrent Beta-mimetics
Antenatal Corticosteroids
Neonatal Effects

» 6675 preterm delivery between the 32nd and 37th weeks of gestation (Retrospective Cohort)
» Hypoglycemia x1.6 times
» Hyperbilirubinemia x3.23 times higher than controls.
Antenatal Steroids Results

» 30 Trial; 7774 women ve 8158 infant
» Perinatal Death: RR 0,72 (0,58-0,89)
» Neonatal Death: RR 0,69 (0,59-0,81)
» RDS: RR 0,66 (0,56-0,77)
» Moderate-Severe RDS: RR 0,59 (0,38-0,91)
» IVH: RR 0,55 (0,4-0,76)
» NEC: RR 0,5 (0,32-0,78)
» Ventilator Assistance: RR 0,68 (0,56-0,84)
» Infection: RR 0,6 (0,41-0,88)
Antenatal Corticosteroids
Repeated or Single Course?

• Repeated corticosteroid administration decreases neonatal respiratory morbidity in the first weeks of life.
• Decreased birthweight and head circumference in the neonates

Murphy KE. Obstet Gynecol, 2012

• Repeated doses did not confirm as safe
• Repeated administration caused adverse neurologic outcome in the animal studies

Cochrane, Database 2011
Antenatal Corticosteroids
Repeated Doses

- Avoid from the repeated corticosteroid administration because of ongoing development of fetal brain

ACOG 2011
Umut bey selamlar,
Benim hala küçük kasımlarım oluyor ama yataşak uzanınca dinlenince geçiyor.
Simdi bu tarz rahatsızlıklarım baslayınca biraz tedirgin oldum,
Eğer extra bir zararı yoksa bana, celeston igneyi yaptrayım diyorum? Size danismak istediğim.
Antenatal Corticosteroids
Timing by Indication

• Antenatal corticosteroid timing was optimal in 40% (239/589)
• Women with hypertensive disorders were most likely to have steroids optimally timed (62%)
Antenatal Corticosteroids
Timing by Indication

• All those who received antenatal steroids 32.2 % delivered at term
• The majority of women (57 %) who received steroids >2 weeks prior to delivery received second course

Souter V, Am J Obstet Gynecol, 2017
Levin HI, Br J Obstet Gynaecol, 2016
Practice Patterns in the Timing of Antenatal Corticosteroids for Fetal Lung Maturity

• 345 patients were included. Only 20% received antenatal steroids within 7 days of delivery. Women who received AS less than 7 days before delivery were more likely to have a

- TV cervical length ≤2 cm
- Cervical dilatation ≥2 cm
- fFN positive

Adams MT, J Matern Fetal Med, 2015
Antenatal Corticosteroid Administration to Birth Interval

Table 3. Multivariable Analysis of the Association Between the Antenatal Corticosteroid Administration-to-Birth Interval and Adverse Neonatal Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No Antenatal Corticosteroids</th>
<th>Less Than 24 Hours</th>
<th>1–7 Days</th>
<th>Greater Than 7 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite outcome†</td>
<td>2.12 (1.69–2.65)</td>
<td>1.48 (1.22–1.80)</td>
<td>Reference</td>
<td>1.46 (1.20–1.77)</td>
</tr>
<tr>
<td>Mortality</td>
<td>2.56 (1.83–3.59)</td>
<td>1.59 (1.16–2.18)</td>
<td>Reference</td>
<td>1.40 (1.00–1.97)</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>1.45 (1.10–1.91)</td>
<td>1.26 (1.00–1.59)</td>
<td>Reference</td>
<td>1.39 (1.11–1.75)</td>
</tr>
<tr>
<td>Severe neurologic injury</td>
<td>2.67 (2.01–3.54)</td>
<td>1.74 (1.35–2.25)</td>
<td>Reference</td>
<td>0.88 (0.64–1.20)</td>
</tr>
<tr>
<td>ROP stage 3 or greater</td>
<td>1.63 (0.94–2.83)</td>
<td>1.15 (0.71–1.84)</td>
<td>Reference</td>
<td>1.49 (0.96–2.33)</td>
</tr>
<tr>
<td>NEC</td>
<td>0.97 (0.65–1.45)</td>
<td>0.99 (0.70–1.40)</td>
<td>Reference</td>
<td>1.32 (0.94–1.85)</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis. Bold indicates significant results.

* Model adjusted for gestational age at birth, neonatal sex, hypertension, and outborn status.
† Composite outcome included one or more of the following: mortality, bronchopulmonary dysplasia, severe neurologic injury (defined as intraventricular hemorrhage grade 3 or greater or periventricular leukomalacia), severe ROP (stage 3 or greater or requiring treatment).
Antenatal Corticosteroids Before 24th Weeks of Gestation

- No confirmatory or contradictory study to the antenatal corticosteroid treatment before the 26th weeks of gestation
  

- A meta-analysis of cohort studies suggested that antenatal corticosteroids may reduce the risk of neonatal in-hospital mortality by 52%
  
  Park CK, Obstet Gynecol, 2016
Antenatal Corticosteroids Promote Survival of Extremely Preterm Infants Born at 22 to 23 Weeks of Gestation

Rintaro Mori, MD, PhD, Satoshi Kusuda, MD, PhD, and Masanori Fujimura, MD, on behalf of the Neonatal Research Network Japan

Objective To evaluate the effectiveness of antenatal corticosteroid (ACS) to improve neonatal outcomes for infants born at <24 weeks of gestation.

Study design We performed a retrospective analysis of 11 607 infants born at 22 to 33 weeks of gestation between 2003 and 2007 from the Neonatal Research Network of Japan. We evaluated the gestational age effects of ACS administered to mothers with threatened preterm birth on several factors related to neonatal morbidity and mortality.

Results By logistic regression analysis, ACS exposure decreased respiratory distress syndrome and severe intraventricular hemorrhage in infants born between 24 and 29 weeks of gestation. Cox regression analysis revealed that ACS exposure was associated with a significant decrease in mortality of preterm infants born at 22 or 23 weeks of gestation (adjusted hazard ratio, 0.72; 95% CI, 0.53 to 0.97; P = .03). This effect was also observed at 24 to 25 and 26 to 27 weeks of gestation and in the overall study population.

Conclusions ACS exposure improved survival of extremely preterm infants. ACS treatment should be considered for threatened preterm birth at 22 to 23 weeks of gestation. (J Pediatr 2011;159:110-4).
Can Antenatal Corticosteroids Create Survival Difference in Extremely Preterm Infants

Lower mortality
No difference for the BPD

Travers CP, Am J Obstet Gynecol, 2018
Chorioamnionitis

- 7 observational study were included. In histological chorioamnionitis (5 studies), antenatal steoroids were associated with reduced mortality (OR: 0.45), RDS (OR: 0.53), IVH (OR: 0.39).
- In clinical chorioamnionitis (in 4 studies), antenatal steroids were associated with reduced severe IVH (OR: 0.29) and PVL (OR: 0.35).
# Chorioamnionitis

## Antenatal Steroids

<table>
<thead>
<tr>
<th>Condition</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Distress Syndrome</td>
<td>0.58</td>
</tr>
<tr>
<td>Mild to Moderate IVH</td>
<td>0.41</td>
</tr>
<tr>
<td>Severe IVH</td>
<td>0.4</td>
</tr>
<tr>
<td>Neonatal Mortality</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Late Preterm Delivery - Respiratory Morbidity

- 75% of preterm deliveries are between the 34 and 37 weeks of gestation, 25% increase after 1990

- RDS prevalence 6.2% between the 34-36 weeks
- after 36 weeks 0.4% (Rubaltelli ve ark; Acta Pediatr, 1998)

- In comparison to deliveries between 38-40 weeks of gestation respiratory support need
  - 19.8 times higher before 34 weeks of gestation
  - 9 times higher in the 35th weeks of gestation
  - 5.2 times higher in the weeks of gestation

Escobar ve ark, Semin Perinatol, 2006
**Corticosteroids and Late Preterm Delivery**

100 cases, controlled study. Delivery following single dose of bethametasone. Less neonatal resuscitation (OR: 0.34), RDS (OR: 0.46) and higher Apgar scores at 1st and 5th min.

Balci O, Gynecol Obstet Invest, 2010

320 cases RCT; No difference about ventilatory support, transient tachypnea, hospitalization period

Porto AM, BMJ, 2011
Corticosteroids and Late Preterm Delivery


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Betamethasone (N = 1427)</th>
<th>Placebo (N = 1400)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>165 (11.6)</td>
<td>202 (14.4)</td>
<td>0.80 (0.66–0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>CPAP or high-flow nasal cannula for ≥2 continuous hr</td>
<td>145 (10.2)</td>
<td>184 (13.1)</td>
<td>0.77 (0.63–0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>Fraction of inspired oxygen of ≥0.30 for ≥4 continuous hr</td>
<td>48 (3.4)</td>
<td>61 (4.4)</td>
<td>0.77 (0.53–1.12)</td>
<td>0.17</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>34 (2.4)</td>
<td>43 (3.1)</td>
<td>0.78 (0.50–1.21)</td>
<td>0.26</td>
</tr>
<tr>
<td>ECMO</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Stillbirth or neonatal death ≤72 hr after birth</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Severe respiratory complication</td>
<td>115 (8.1)</td>
<td>169 (12.1)</td>
<td>0.67 (0.53–0.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPAP or high-flow nasal cannula for ≥12 continuous hr</td>
<td>93 (6.5)</td>
<td>147 (10.5)</td>
<td>0.62 (0.48–0.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fraction of inspired oxygen of ≥0.30 for ≥24 continuous hr</td>
<td>20 (1.4)</td>
<td>34 (2.4)</td>
<td>0.58 (0.33–1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Need for resuscitation at birth</td>
<td>206 (14.5)</td>
<td>260 (18.7)</td>
<td>0.78 (0.66–0.92)</td>
<td>0.003</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>79 (5.5)</td>
<td>89 (6.4)</td>
<td>0.87 (0.65–1.17)</td>
<td>0.36</td>
</tr>
<tr>
<td>Transient tachypnea of the newborn</td>
<td>95 (6.7)</td>
<td>138 (9.9)</td>
<td>0.68 (0.53–0.87)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Corticosteroids and Late Preterm Delivery

- Antenatal corticosteroids reduce neonatal respiratory complications among women at risk of delivery between 34 weeks 0 days and 36 weeks 6 days (The NNT to prevent one case of severe respiratory morbidity was 25).
Antenatal Corticosteroids in Late Preterm and Near Term Fetuses

<table>
<thead>
<tr>
<th>Study</th>
<th>No of events/total</th>
<th>Risk ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stutchfield et al 2005\textsuperscript{11}</td>
<td>1/373 5/446</td>
<td>0.24 (0.03 to 2.04)</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>Porto et al 2011\textsuperscript{12}</td>
<td>2/143 1/130</td>
<td>1.82 (0.17 to 19.82)</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Ahmed et al 2015\textsuperscript{13}</td>
<td>0/228 2/224</td>
<td>0.20 (0.01 to 4.07)</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>Gyamfi-Bannerman et al 2016\textsuperscript{14}</td>
<td>20/1427 34/1400</td>
<td>0.58 (0.33 to 1.00)</td>
<td>80.9</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>23/2171 42/2200</td>
<td>0.55 (0.33 to 0.91)</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2=2.02$, $df=3$, $P=0.57$, $I^2=0\%$
Test for overall effect: $z=2.34$, $P=0.02$

Fig 6 | Forest plot for use of antenatal corticosteroids after 34 weeks’ gestation and risk of severe respiratory distress syndrome

Saccone G, BMJ, 2016
Imminent Late Premature Delivery

» Tocolysis should not be used in order to delay delivery to allow for administration of late antenatal corticosteroids

» Indicated delivery should not be postponed for steroid administration
Antenatal Corticosteroid Therapy for Fetal Maturation

**Abstract:** Corticosteroid administration before anticipated preterm birth is one of the most important antenatal therapies available to improve newborn outcomes. A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation who are at risk of preterm delivery within 7 days, including for those with ruptured membranes and multiple gestations. It also may be considered for pregnant women starting at 23 0/7 weeks of gestation who are at risk of preterm delivery within 7 days, based on a family’s decision regarding resuscitation, irrespective of membrane rupture status and regardless of fetal number. Administration of betamethasone may be considered in pregnant women between 34 0/7 weeks and 36 6/7 weeks of gestation who are at risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids. A single repeat course of antenatal corticosteroids should be considered in women who are less than 34 0/7 weeks of gestation who are at risk of preterm delivery within 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. Continued surveillance of long-term outcomes after in utero corticosteroid exposure should be supported. Quality improvement strategies to optimize appropriate and timely antenatal corticosteroid administration are encouraged.
SMFM recommendations

1. In women with a singleton pregnancy between 34 weeks 0 days and 36 weeks 6 days of gestation who are at high risk for preterm birth within the next 7 days (but before 37 weeks of gestation), we recommend treatment with betamethasone (2 doses of 12 mg intramuscularly 24 hours apart).

2. In women with preterm labor symptoms in the late preterm period, we recommend waiting for evidence of preterm labor, such as a cervical dilatation of at least 3 cm or effacement of at least 75%, before treatment with betamethasone.

3. In women with late preterm pregnancies receiving betamethasone, we recommend against the use of tocolysis in an attempt to delay delivery to complete the steroid course because it is unclear whether the benefits of betamethasone administration are outweighed by the risks of attempts to delay delivery.

4. In women with late preterm pregnancies with a potential medical indication for delivery, we recommend betamethasone not be given unless there is a definitive plan for late preterm delivery.
Antenatal Corticosteroids for Planned Cesarean Delivery?

» Multicentric RCT. Bethametasone completed 48 hours before planned cesarean delivery.

<table>
<thead>
<tr>
<th></th>
<th>Study</th>
<th>Control</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDS</td>
<td>0.002</td>
<td>0.011</td>
<td>0.21</td>
</tr>
<tr>
<td>Transient Tachypnea</td>
<td>0.021</td>
<td>0.04</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Stutchfield ve ark, BMJ, 2005
Antenatal Corticosteroids for Planned Cesarean Delivery?

- Study group receive two i.m dexamethasone 24 hours apart at 37 weeks of gestation.
- Respiratory distress was 7.3% in study, 23% in control group.
- Transient tachypnea was 7% vs 19.6%.
- The most significant benefit of steroid administration was noted in those babies 37-37 weeks plus 6 days.

Antenatal Corticosteroids for Planned Cesarean Delivery?

- 645 cases; 645 control
- Dexamethasone 8 mg 12 hours apart (3 dose) 48 hours later planned cesarean
- Planned cesarean between the 38th and 38 weeks plus 6 days
- NICU admission by respiratory problems 2.5 times less than controls (1.6 % vs 3.9 %); RR: 0.41; NNT: 44

Antenatal Corticosteroids for Multiplets

- Same protocol
- Only in case of threatened preterm labor/delivery
- RDS is more prevalent if the antenatal corticosteroid to delivery interval over 7 days from the last dose (54, 5% vs 74,1%)

Antenatal Corticosteroids for Multiplets

SMFM PAPERS

Optimal time interval between a single course of antenatal corticosteroids and delivery for reduction of respiratory distress syndrome in preterm twins

Jin-Yi Kuk, MD; Jung-Ju An, MD; Hyun-Hwa Cha, MD; Suk-Joo Choi, MD, PhD; Juan E. Vargas, MD; Soo-young Oh, MD, PhD; Cheong-Rae Roh, MD, PhD; Jong-Hwa Kim, MD, PhD

OBJECTIVE: The objective of the study was to investigate the effect of a single course of antenatal corticosteroid (ACS) therapy on the incidence of respiratory distress syndrome (RDS) in preterm twins according to the time interval between ACS administration and delivery.

STUDY DESIGN: We performed a retrospective cohort study of twins born between 24 and 34 weeks of gestation from November 1995 to May 2011. Subjects were grouped on the basis of the time interval between the first ACS dose and delivery: the ACS-to-delivery interval of less than 2 days (n = 166), 2-7 days (n = 114), and more than 7 days (n = 66). Pregnancy and neonatal outcomes of each group were compared with a control group of twins who were not exposed to ACS (n = 122). Multiple logistic regression analysis was used to examine the association between the ACS-to-delivery interval and the incidence of RDS after adjusting for potential confounding variables.

RESULTS: Compared with the ACS nonexposure group, the incidence of RDS in the group with an ACS-to-delivery interval of less than 2 days was not significantly different (adjusted odds ratio [aOR], 1.089; 95% confidence interval [CI], 0.524–2.262; P = .819). RDS occurred significantly less frequently when the ACS-to-delivery interval was between 2 and 7 days (aOR, 0.419; 95% CI, 0.181–0.968; P = .042). However, there was no significant reduction in the incidence of RDS when the ACS-to-delivery interval exceeded 7 days (aOR, 2.205; 95% CI, 0.773–6.292; P = .139).

CONCLUSION: In twin pregnancies, a single course of ACS treatment was associated with a decreased rate of RDS only when the ACS-to-delivery interval was between 2 and 7 days.

Key words: antenatal corticosteroids, preterm delivery, respiratory distress syndrome, steroid-to-delivery interval, twin pregnancy

Questions

» Neonatal morbidity following antenatal corticosteroids who were undelivered within 7 days?

» Antenatal corticosteroid treatment between 22 and 24 weeks of gestation

» For the planned cesarean delivery between the 37-39 weeks of gestation?
Conclusion

Antenatal corticosteroids accelerate fetal lung maturation and reduce rates of neonatal death, respiratory distress syndrome, intraventricular hemorrhage.
Take Home Messages

• A single course of antenatal corticosteroids should be offered to all women at risk of preterm delivery.
• The benefits of antenatal corticosteroids outweigh the risks
• A single course of antenatal corticosteroids may be considered in women at risk of delivery between 34–36 and 22–24
• A single course of “rescue” corticosteroids may be considered in women still at risk of preterm delivery seven days after completing the initial course.