Should we Give Repeat Courses of Antenatal Corticosteroids: What does the Evidence Show?

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TABLE 3. Overall Effect of Antenatal Corticosteroids Prior to Preterm Delivery on Respiratory Outcomes

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Deaths/Events</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liggins, 1972</td>
<td>15/11</td>
<td>0.37 (0.20-0.70)</td>
</tr>
<tr>
<td>Black, 1977</td>
<td>20/20</td>
<td>1.00 (0.64-1.56)</td>
</tr>
<tr>
<td>Schmidt, 1979</td>
<td>11-64</td>
<td>17.38</td>
</tr>
<tr>
<td>Tanouch, 1978</td>
<td>7-66</td>
<td>14.21</td>
</tr>
<tr>
<td>Barres, 1980</td>
<td>4-61</td>
<td>10.63</td>
</tr>
<tr>
<td>Dermott, 1980</td>
<td>5-30</td>
<td>5.42</td>
</tr>
<tr>
<td>Gamma, 1981</td>
<td>7-63</td>
<td>2.31</td>
</tr>
<tr>
<td>COST, 1984</td>
<td>21-30</td>
<td>14.59</td>
</tr>
<tr>
<td>Parras, 1971</td>
<td>12-15</td>
<td>14.35</td>
</tr>
<tr>
<td>Schmidt, 1972</td>
<td>22-20</td>
<td>22.40</td>
</tr>
<tr>
<td>Erensen, 1993</td>
<td>12-11</td>
<td>16.97</td>
</tr>
</tbody>
</table>

USE OF ANCS AFTER NIH CONSENSUS CONFERENCE

- Survey of US SPO members - n=1420, 60% response
- Rx at GA 24-34 weeks
- 91% would give weekly courses
- 28% would retreat even if PTL stops, and patient discharged
- 50% would give a maximum of 6+ courses; 23% 4-5 courses; 12% 3 courses; 6% 2 courses

Planer et al SPO 96
**Clinical Recommendations**

- All pregnant women between 24 and 34 weeks gestation who are at risk of preterm delivery within 7 days should be considered candidates for antenatal treatment with a single course of corticosteroids.
- Treatment consists of two doses of 12 mg of betamethasone given intramuscularly 24 hours apart or four doses of 6 mg of dexamethasone given intramuscularly 12 hours apart, as recommended by the consensus panel in 1994. There is no proof of efficacy for any other regimen.
- Because of insufficient scientific data from randomized clinical trials regarding efficacy and safety, repeat courses of corticosteroids should not be used routinely. In general, it should be reserved for patients enrolled in randomized controlled trials. Several randomized trials are in progress.

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**RCT: Single course vs weekly BMZ**

Guinn et al, JAMA 2001; 286:1581

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**Guinn et al’s conclusion:**

- Weekly courses of antenatal corticosteroids did not reduce composite morbidity compared with a single course of treatment
Conclusions

- Corticosteroids are potent drugs with multiple potential deleterious effects on the fetus in large doses, particularly at lower gestational ages, including effects on:
  - Growth
  - Neural development
  - Multiple hormones
  - Hemodynamics
  - Fetal behavioral states
  - Infection

Single vs weekly courses of antenatal corticosteroids: Evaluation of safety and efficacy

Primary Outcome: A Composite

The Occurrence of one of the following:
- Death: Stillborn or Neonatal
- Severe RDS
- Chronic Lung Disease
- IVH (Grade III / or IV)
- PVL

ACTORDS 2005

- Weekly BMZ until 32 wks vs saline, if risk of PTD persists
- Included twins & triplets
- Recruitment 1998 to July 2004
- N= 982 mothers & 1100 babies
- 25% received 4 or more courses


ACTORDS- Outcomes

- Primary:
  Incidence and severity of RDS

- Secondary:
  Newborn weight

ACTORDS 2005

Growth

<table>
<thead>
<tr>
<th>Weekly ANCS</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt g</td>
<td>1867</td>
</tr>
<tr>
<td>Head circ cm</td>
<td>29.6</td>
</tr>
<tr>
<td>Length cm</td>
<td>42.1</td>
</tr>
</tbody>
</table>

Birth Z scores were different for the groups, but NS at discharge
ACTORDS 2005
Conclusions

- Decrease in RDS
- Decrease in weight, resolved by discharge
- No harmful effects noted
- No harmful effects on neurodevelopmental followup at 2 yrs

Status of RCTs of multiple course ANCS (1)

- USA (Guinn)
  - RCT published in JAMA in 2001
  - Concludes no benefit to weekly courses
  - BUT statistically significant less RDS in babies born <28 wks with multiple courses
- USA (NIH)
  - RCT published in AJOG in 2006
  - Single course + placebo, vs weekly courses
  - Trial stopped at 23% enrollment
  - Concludes no benefit
  - BUT less morbidity in babies born <32 wks

Status of RCTs of multiple course ANCS (2)

- United Kingdom
  - Single vs weekly courses
  - Effect on NB FRC, Pediatrics, 2002
- Australia
  - Single course + placebo vs weekly courses
  - Less RDS, and less severe in weekly group
- Canada
  - Single course + placebo vs repeat courses q14d
  - No respiratory function improvement

Who is at Continued Risk of PTD 24 – 34 Weeks?

- PPROM
- PTL, generally those requiring hospitalization with tocolysis
- Scheduled delivery for certain medical conditions:
  - Severe preeclampsia
  - Preeclampsia < 28 weeks
  - IUGR sufficiently severe to warrant delivery
  - Symptomatic abruptio placentae
  - Bleeding placenta previa
  - IUT’s > 24 weeks
  - Fetal surgery
Weekly vs Single Course of Antenatal Corticosteroids - Metaanalysis

- 5 RCTs
- One trial repeated q 2 wks
- In another pts were withdrawn if threat of PTD resolved
- Differences in GAs, inclusion of twins, etc

Metaanalysis of Repeat vs Single Course of ANCS - 5 RCTs

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>CI</th>
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<tbody>
<tr>
<td>RDS</td>
<td>0.82</td>
<td>0.72-0.93</td>
</tr>
<tr>
<td>Sev lung dz</td>
<td>0.46</td>
<td>0.48-0.75</td>
</tr>
<tr>
<td>Reduced birth wt &amp; incr IUGR</td>
<td>1.63</td>
<td>1.12-2.37</td>
</tr>
</tbody>
</table>

Cochrane Database 2007; 3:CD003935

Repeat ANCS - Metaanalysis

- Reduced growth predominantly with 5 or > repeats
- Dosing q 2 wks resulted in no reduction in RDS, or increased IUGR
- No adverse effects on growth or neurodevelopment with 2-5 doses

Why might redosing work?

- Initial dose may accelerate structural development of lung
- Initial & subsequent doses stimulate enzyme & surfactant production - but it wanes after 7 days
**EDITORIAL**

To rescue or not to rescue: that is the question

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**OBSTETRICS**

Impact of a ‘rescue course’ of antenatal corticosteroids: a multicenter randomized placebo-controlled trial

Thomas J. Garite, MD; James Kurtzman, MD; Kimberly Maured, MSN; Rose Clark, MD, for the Obstetric Collaborative Research Network

Background and Objective

The administration of antenatal corticosteroids (ANCS) to mothers who subsequently deliver prematurely is among the few clinical interventions that unequivocally improve outcome in premature babies. Benefits include reduced rates of mortality, respiratory distress syndrome (RDS), and intraventricular hemorrhage.

<table>
<thead>
<tr>
<th></th>
<th>Rescue</th>
<th>ANCS</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite morb</td>
<td>44%</td>
<td>64%</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>RDS</td>
<td>41</td>
<td>62</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Surfactant</td>
<td>38</td>
<td>56</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Ventilator</td>
<td>38</td>
<td>53</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

No sig diff in IVH III or IV, sepsis, perinatal death or IUGR
Potential Obstacles to Rescue Dosing

- 11% of enrollees delivered before 1 or both doses could be given
- 50% of enrollees went > 34wks
- Can we improve prediction of candidates, say with fFN or cervical length by US?
- But, 52% of enrollees were for reasons other than PTL & Cx Insufficiency

Conclusion: In this study rescue dosing resulted in under & overtreatment of selected candidates