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ANTENATAL CORTICOSTEROIDS and the Management of PRETERM BIRTH

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Earlier studies: Meta-analysis ACS reduces neonatal mortality by half in low and middle-income countries

ACS significantly decreases neonatal mortality and morbidity

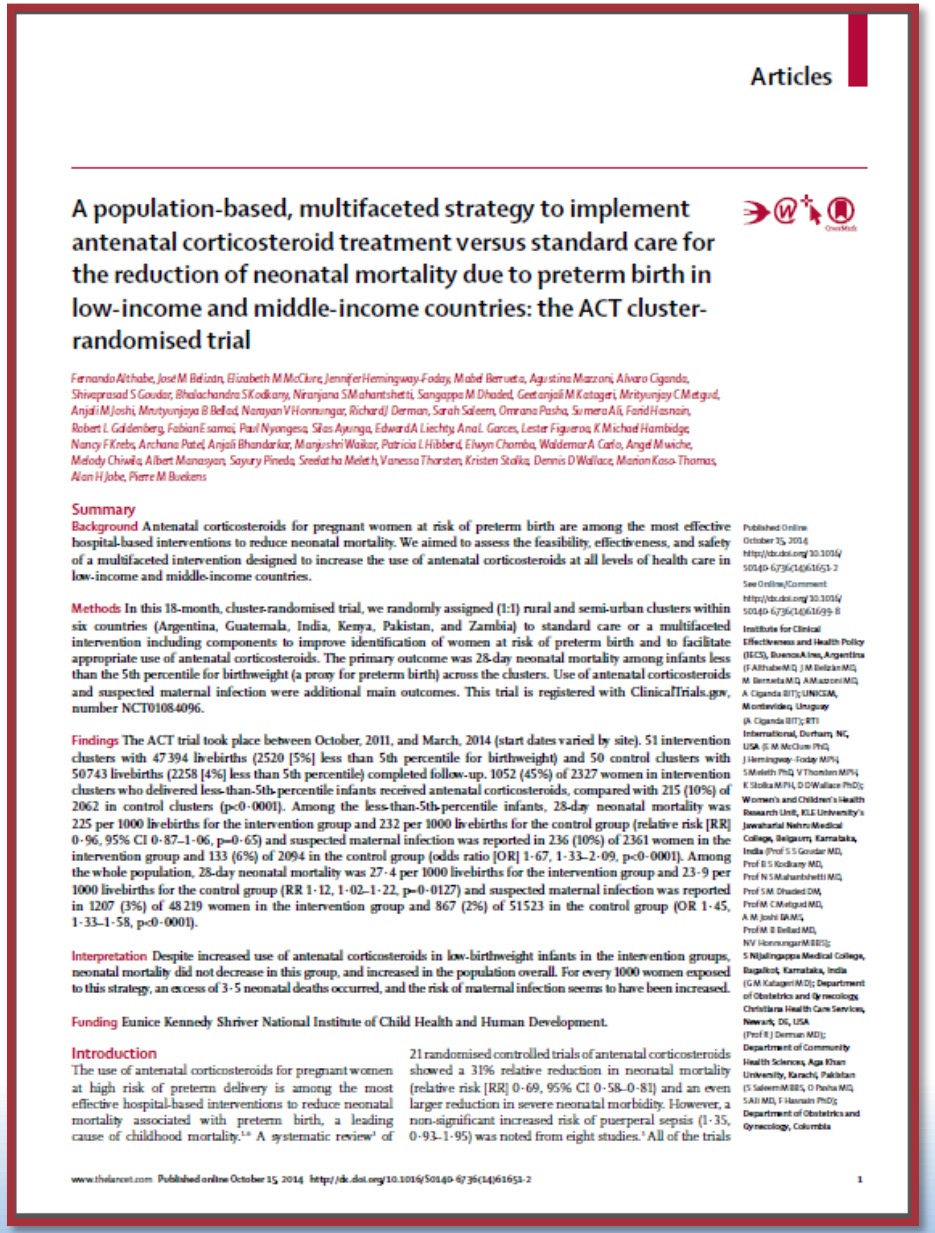
- 34% reduction in **respiratory distress syndrome**
  - 46% reduction in **intracranial hemorrhage**
  - 54% reduction in **necrotizing enterocolitis**
    - 31% reduction in **neonatal death**

Effect of ACS is not exclusively pulmonary – it is multi-organ

Source: Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database of Systematic Reviews* 2006,Issue3.Art.No.:CD004454. DOI:10.1002/14651858.CD004454.pub2.

Use of Antenatal Corticosteroids: New Data

- Well-designed cluster randomized trial
- Published 15 Oct 2014
- 100,000 pregnant mothers across 6 low and middle income countries
  - Argentina, Guatemala
  - India, Pakistan
  - Kenya, Zambia
- Followed all treated women up to delivery



Articles

A population-based, multifaceted strategy to implement antenatal corticosteroid treatment versus standard care for the reduction of neonatal mortality due to preterm birth in low-income and middle-income countries: the ACT cluster-randomised trial

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Summary

Background Antenatal corticosteroids for pregnant women at risk of preterm birth are among the most effective hospital-based interventions to reduce neonatal mortality. We aimed to assess the feasibility, effectiveness, and safety of a multifaceted intervention designed to increase the use of antenatal corticosteroids at all levels of health care in low-income and middle-income countries.

Methods In this 18-month, cluster-randomised trial, we randomly assigned (1:1) rural and semi-urban clusters within six countries (Argentina, Guatemala, India, Kenya, Pakistan, and Zambia) to standard care or a multifaceted intervention including components to improve identification of women at risk of preterm birth and to facilitate appropriate use of antenatal corticosteroids. The primary outcome was 28-day neonatal mortality among infants less than the 5th percentile for birthweight (a proxy for preterm birth) across the clusters. Use of antenatal corticosteroids and suspected maternal infection were additional main outcomes. This trial is registered with ClinicalTrials.gov, number NCT01084096.

Findings The ACT trial took place between October, 2011, and March, 2014 (start dates varied by site). 51 intervention clusters with 47 394 livebirths (2520 [5%] less than 5th percentile for birthweight) and 50 control clusters with 50 743 livebirths (2258 [4%] less than 5th percentile) completed follow-up. 1052 (45%) of 2327 women in intervention clusters who delivered less-than-5th-percentile infants received antenatal corticosteroids, compared with 215 (10%) of 2062 in control clusters (p<0·0001). Among the less-than-5th-percentile infants, 28-day neonatal mortality was 225 per 1000 livebirths for the intervention group and 232 per 1000 livebirths for the control group (relative risk [RR] 0·96, 95% CI 0·87–1·06, p=0·65) and suspected maternal infection was reported in 236 (10%) of 2361 women in the intervention group and 133 (6%) of 2094 in the control group (odds ratio [OR] 1·67, 1·33–2·09, p<0·0001). Among the whole population, 28-day neonatal mortality was 27·4 per 1000 livebirths for the intervention group and 23·9 per 1000 livebirths for the control group (RR 1·12, 1·02–1·22, p=0·0127) and suspected maternal infection was reported in 1207 (3%) of 48 219 women in the intervention group and 867 (2%) of 51523 in the control group (OR 1·45, 1·33–1·58, p<0·0001).

Interpretation Despite increased use of antenatal corticosteroids in low-birthweight infants in the intervention groups, neonatal mortality did not decrease in this group, and increased in the population overall. For every 1000 women exposed to this strategy, an excess of 3·5 neonatal deaths occurred, and the risk of maternal infection seems to have been increased.

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Introduction

The use of antenatal corticosteroids for pregnant women at high risk of preterm delivery is among the most effective hospital-based interventions to reduce neonatal mortality associated with preterm birth, a leading cause of childhood mortality.[1–6] A systematic review[1] of 21 randomised controlled trials of antenatal corticosteroids showed a 31% relative reduction in neonatal mortality (relative risk [RR] 0·69, 95% CI 0·58–0·81) and an even larger reduction in severe neonatal morbidity. However, a non-significant increased risk of puerperal sepsis (1·35, 0·93–1·95) was noted from eight studies.[1] All of the trials

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The Intervention

- Assessment and provision of ACS in more peripheral settings, especially outside hospitals
- Could not reliably determine gestational age
  - proxy outcome: mortality among births < 5th percentile for birth weight
- No improvements made in newborn care for preterm newborns

The trial tested the efficacy of ACS alone

The Results

- Of women receiving ACS, 20% were given their first injection in the community, 63% in health centers, and **17% in hospitals**
  - Meaning: **dosing successfully pushed out of hospital**
- Of all women receiving ACS, only 16% delivered a <5th percentile newborn, so **5 out of 6 women treated did not have a very small baby**
  - Meaning: **Diagnostic approach not specific**
- Of all women delivering a <5th percentile newborn, only 45% received steroids so **less than half of the target group were treated**.
  - Meaning: **Only half the population covered**

Newborn and Maternal Outcomes

- The study demonstrated **no benefit from ACS for small newborns** (<5th percentile)
  - *Meaning: use of ACS did not reduce preterm newborn mortality*
- Neonatal **mortality among all live births was higher**
  - *Meaning: overall mortality increased*
- Significantly **higher mortality** among babies born at estimated gestation **≥37 weeks**
  - *Meaning: ACS to babies in late gestation increased mortality*
- Associated with **higher risk of stillbirth**
  - *Meaning: in utero exposure to ACS might be harmful*
- ACT demonstrated **increased risk of maternal infection**

WHY did mortality increase?

- Some **theories**

1. ACS were administered alone – not part of a preterm care package
2. Large overtreatment – many women got who did not need
   - Are stressed and non-stressed fetuses different?
3. Many older (35 weeks or above) babies got ACS
   - Is there something different about the lungs in older fetuses?
4. Proximity of treatment to delivery
   - Is there some harm when there is a long gap between treatment and delivery?
   - Does ACS benefit become harm after some period?
5. Is there more maternal subclinical infection?
   - How can we be more careful in assessing women for infection?

Way Forward: Program Recommendations

- In hospitals, where ACS use is currently the practice, continue current use. However, put greater emphasis on
  1. Accurate assessment of gestational age
  2. Accurate determination of risk of imminent preterm birth
  3. Adequate care of preterm newborns (e.g. resuscitation, KMC, treatment of infection, intensive newborn care)
  4. Reliable, timely and appropriate treatment of maternal infection
- Put on hold plans for expanding the use of ACS and any work on first dose of ACS prior to referral
- Anticipate new WHO recommendations
- Develop a holistic package of care for preterm births

For more information, please visit
www.mcsprogram.org

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