Notes on the Antenatal Corticosteroids Trial (ACT)—October 15, 2014[1]

UN Commission of Life Saving Commodities Antenatal Corticosteroids Working Group

Evidence before ACT: Antenatal corticosteroids (ACS) have been used since 1972 to accelerate fetal lung maturation in threatened preterm birth. A Cochrane review of 21 randomized controlled trials conducted in hospitals in high and middle income countries, found that ACS reduced neonatal mortality by 31% (RR 0.69; 95% CI 0.58-0.81).[2] There was no evidence of benefit at gestational ≥34 weeks (RR 1.58; 95% CI 0.71-3.50). Of these 21 trials, four were in middle income countries (Brazil, Jordan, Tunisia and South Africa), including a high proportion of HIV positive women in South Africa. A meta-analysis of these four trials showed higher effect on reducing neonatal deaths.[3] In some high income countries, ACS are routinely used in nearly 90% of cases where indicated, but coverage estimates are just 5% in the 42 low income countries where 90% of under-5 deaths occur[4].

Findings from ACT: ACT was a cluster randomized trial, published 15th October 2014. The study was a commendable feat, enrolling over 100,000 pregnant mothers across 6 low and middle income countries (Argentina, Guatemala, India, Kenya, Zambia, and Pakistan). ACT assessed a strategy for provision of ACS in more peripheral settings, especially outside hospitals. Of women receiving ACS, 20% were given their first injection in the community, 63% in health centers, and 17% in hospitals. The sites where women gave birth included hospitals (51%), clinics (25%) and homes (23%). Babies born in home or primary care settings typically do not have access to specific care for preterm infants (e.g. Kangaroo mother care). Since the study was not designed to reliably determine gestational age for all participants, the proxy outcome used was mortality among those born below the 5th percentile for birth weight, using the weight distributions of their respective study site populations. This was only a rough approximation of the target group, since the group of low birth weight babies includes many small for gestational age infants as well as preterm infants. Of all women receiving ACS, only 16% gave birth to a <5th percentile newborn. Of all women giving birth to a <5th percentile newborn, only 45% received steroids. ACT did not collect data on cause-specific mortality or potential risk factors so the mechanisms driving the results are not yet fully understood.

> **Newborn outcomes:** Prior to the ACT Trial, most studies focused on the positive effect in preterm babies and few studies report effects for term or near-term babies. Two studies (n=498 infants) found higher risk of fetal and newborn death when ACS was administered to mothers whose infants were born >36 weeks estimated gestation (RR 3.25, 95% CI 0.99 to 10.66). The ACT trial also found significantly higher mortality among babies in the intervention arm born at an estimated gestation ≥37 weeks compared with the control arm (RR 1.21, 95% CI: 1.07-1.36). ACS was also associated with higher risk of stillbirth. The study demonstrated no benefit from ACS for babies born small (<5th percentile) or any other birth weight, comparing intervention with control arms. This mixing of the SGA and preterm infants in the low birth weight categories analysis could mask the benefit to preterm infants if ACS had no benefit for SGA infants.
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> **Maternal outcomes:** Prior to the ACT trial, meta-analysis of 8 trials which tracked maternal infection showed a non-statistically significant trend towards increased risk of maternal infection associated with ACS (RR 1.35 95%CI: 0.93-1.95). The ACT trial reported an increased risk of suspected maternal infection (OR 1.45; 95%CI: 1.33-1.58).

Programmatic Implications: The full body of evidence available to date, including ACT, suggests that ACS should only be used for gestational age between 24 and 34 weeks, and only where the following three conditions can be met:

1. Ability to accurately assess gestational age (GA) and determine risk of imminent preterm birth.
2. Adequate care available for preterm newborns (e.g. resuscitation, Kangaroo Mother Care, adequate feeding support, treatment of infection, etc.)
3. Reliable, timely and appropriate identification and treatment of maternal infection

The WHO is aware of the ACT results and plans to convene an additional consultation of an already ongoing preterm guidelines expert committee to review the new evidence and make recommendations with regard to guidelines for ACS use.

Research Implications: The ACT trial raises several important questions, answers to which will help improve the safety, effectiveness, and potential reach of ACS programs.

> **Further analysis of ACT trial data:** Secondary analyses may reveal differences in maternal and newborn outcomes between the countries and the levels of care available.
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> **Further analysis by the Cochrane Collaboration of data from ACS RCTs:** Most of the studies summarized in the current Cochrane systematic reviews do not report outcomes for women treated with ACS who did not give birth preterm. Increased risks may occur also in high and middle income countries and may have been under-estimated in the previous meta-analyses.
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> **Innovation to improve gestational age assessment:** Currently available methods for GA assessment during pregnancy in resource-limited settings compromise both the quality of care provided and the quality of research conducted. Innovation in this area requires continued investment.
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> **Rigorous testing of effectiveness and safety of ACS in middle and low income countries in settings that meet the three key diagnostic and care process requirements (listed above).**

For more information: See http://www.healthynewbornnetwork.org/topic/antenatal-corticosteroids

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