Antenatal Corticosteroids for Improving Preterm Newborn Survival in Low-Resource Countries

The WHO ACTION Trials Collaborators
The Panelists

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Global burden of preterm birth

Nearly 15 million babies are born preterm each year

Leading cause of neonatal and child mortality

Infants born preterm are at increased risk for a wide range of short-term and long-term respiratory, infectious, metabolic, and neurologic conditions, with higher risks among those born during the early preterm period.
Known effects of antenatal corticosteroids

Efficacy trials conducted largely in high-resource countries have demonstrated that antenatal corticosteroids for women at risk of preterm birth can reduce risk of:

- Neonatal deaths (RR 0.69, 95% CI 0.59 - 0.81)
- Intraventricular haemorrhage (RR 0.55, 95% CI 0.40 - 0.76)
- Respiratory distress syndrome (RR 0.66, 95% CI 0.56 - 0.77)
- Necrotizing enterocolitis (RR 0.50, 95% CI 0.32 - 0.78)
- Moderate and severe RDS (RR 0.59, 95% CI 0.38 - 0.91)
- Systemic infection in first 48 h (RR 0.60, 95% CI 0.41 - 0.88)

Efficacy trials conducted largely in high-resource countries have demonstrated that antenatal corticosteroids for women at risk of preterm birth can reduce risk of:

When administered antenatally, corticosteroids (dexamethasone or betamethasone) can cross the placenta and accelerate maturation of fetal lung

Roberts & Dalziel (2006)
Known effects of antenatal corticosteroids

Most trials were conducted in tertiary facilities in high-income countries

Often used heterogeneous or highly selected populations, which may not be generalizable

Generally old trials (most are over 20 years old), where risk of bias is often unclear

Generally small (<200 women)

No trials powered for neonatal mortality – often not measured post-discharge from hospital

Larger trials showed smaller or no clinical benefits
Antenatal Corticosteroid Trial (2015)

Cluster-randomized trial of a package of interventions to scale up antenatal corticosteroids in low- and middle-income countries

- **6 countries**: Guatemala, Kenya, Argentina, Zambia, India, Pakistan
- **102 clusters**
- **99,742 mothers enrolled**
- **100,705 babies**
- **18-month intervention**

**Primary outcome:**
neonatal death amongst neonates born at less-than-5th-percentile birth weight (as a proxy for preterm birth)
## Antenatal Corticosteroid Trial (2015)

<table>
<thead>
<tr>
<th>Group</th>
<th>Outcome</th>
<th>RR (95% CI)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Among births &lt;5th percentile infants</td>
<td>Neonatal death by 28 days</td>
<td>RR 0.96 (95% CI 0.99 – 1.06)</td>
<td>No benefit/harm</td>
</tr>
<tr>
<td></td>
<td>Stillbirth</td>
<td>RR 0.99 (95% CI 0.90–1.09)</td>
<td>No benefit/harm</td>
</tr>
<tr>
<td></td>
<td>Suspected maternal infection</td>
<td>OR 1.67 (95% CI 1.33–2.09)</td>
<td>Maternal harm</td>
</tr>
<tr>
<td>Among all births (population level)</td>
<td>Neonatal death by 28 days</td>
<td>RR 1.12 (95% CI 1.02 – 1.22)</td>
<td>Neonatal harm</td>
</tr>
<tr>
<td></td>
<td>Stillbirth</td>
<td>RR 1.11 (95% CI 1.02 – 1.22)</td>
<td>Fetal harm</td>
</tr>
<tr>
<td></td>
<td>Suspected maternal infection</td>
<td>OR 1.45 (95% CI 1.33–1.58)</td>
<td>Maternal harm</td>
</tr>
</tbody>
</table>
WHO recommendations on preterm birth (2015)

Recommendations developed according to WHO Guidelines Review Committee standards, and relevant to all settings.

Concerns about harm led to inclusion of consensus-based criteria for antenatal corticosteroids use.
**WHO recommendations on preterm birth (2015)**

Antenatal corticosteroid therapy is recommended for women at risk of preterm birth from 24 weeks to 34 weeks of gestation when the following conditions are met:

- Gestational age assessment can be accurately undertaken.
- Preterm birth is considered imminent.
- There is no clinical evidence of maternal infection.
- Adequate childbirth care is available (including the capacity to recognize and safely manage preterm labour and birth).
- The preterm newborn can receive adequate care if needed (including resuscitation, thermal care, feeding support, infection treatment and safe oxygen use).

Strong recommendation based on moderate-quality evidence for newborn outcomes and low-quality evidence for maternal outcomes.
ACTION-I trial design

Multicountry, multicenter, parallel group, double-blind, individually randomized, placebo-controlled trial to compare intramuscular dexamethasone with identical placebo in women at risk of imminent preterm birth

Conducted at 29 secondary- and tertiary-level hospitals across six trial sites in Bangladesh, India, Kenya, Nigeria, and Pakistan
Participants
Pregnant women at risk of imminent preterm birth
26 weeks 0 days to 33 weeks 6 days

Primary Outcomes
- Neonatal death (until 28 days after birth)
- Any baby death (post-randomization stillbirth or neonatal death)
- Possible maternal bacterial infection – composite outcome defined as maternal fever (≥38°C) or clinically suspected or confirmed infection for which therapeutic antibiotics were used

Intervention
A course of 6mg dexamethasone IM injections every 12 hours, for a maximum of four doses, or until hospital discharge or birth
If undelivered by 7 days and still met the inclusion criteria, a single repeat course was used

Secondary outcomes
Maternal and newborn morbidity outcomes
Health care interventions and health service utilization outcomes

Comparison
Identical placebo (saline)
Trial setting

Resource-limited hospitals in Bangladesh, India, Kenya, Nigeria and Pakistan, selected based on assessment of available maternal and neonatal services

Minimal out-referral of women at risk of imminent preterm birth, or preterm newborns

Human resource, referral and health service equipment challenges that are common to many low-resource settings

Facilities could reasonably meet the WHO antenatal corticosteroid treatment criteria

- Emergency obstetric care available
- Preterm newborn care available: resuscitation at birth, thermal care, breastmilk feeding support, parenteral infection treatment, safe oxygen use, access to hygiene, access to CPAP

Hospitals were provided with Philips HD5 Ultrasound systems, CPAP systems, pulse oximeters and glucometers to ensure that at least minimum quality of care was received by trial participants
### Screening and recruitment

**Pregnant women who had confirmed live fetuses between 26 weeks 0 days and 33 weeks 6 days of gestation and who were at risk for preterm birth [defined as planned or expected birth in the next 48 hours (either provider-initiated preterm birth, or after PPROM or spontaneous labour)]**

**Gestational age must be determined by ultrasound (or an ultrasound was performed at admission),**

**Excluded if**
- Clinical signs of severe infection,
- Major congenital fetal anomalies
- Concurrent or recent (within the previous 2 weeks) use of systemic corticosteroids
- Contraindication to corticosteroids
- Participating in another trial

**Written informed consent was obtained from all the participants before randomization**
ACTION-I Trial

Antenatal Corticosteroids for Improving Outcomes in preterm Newborns
Key points

2852 women randomized – 1429 women to dexamethasone arm and 1423 women to placebo

Most common reason for exclusion – “birth not planned or expected in next 48 hours”

>99% completed follow up

Adherence to trial regimen:

- All women (except one) received at least 1 dose
- 57% and 53% of women got all four doses of the first course in dexamethasone and placebo groups, respectively
- Use of repeat course was minimal (<5%)
## Characteristics of the Participants at Trial Entry

<table>
<thead>
<tr>
<th></th>
<th>Dexa vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication for trial entry</strong></td>
<td></td>
</tr>
<tr>
<td>Spontaneous PTB</td>
<td>61.2% vs 60.3%</td>
</tr>
<tr>
<td>Provider-initiated PTB</td>
<td>38.8% vs 39.7%</td>
</tr>
<tr>
<td><strong>Mean GA at trial entry</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30.8 vs 30.7 weeks</td>
</tr>
<tr>
<td><strong>Trimester ultrasound performed</strong></td>
<td></td>
</tr>
<tr>
<td>1st trimester</td>
<td>10.9% vs 10.3%</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>24.1% vs 23.1%</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>65.0% vs 66.5%</td>
</tr>
<tr>
<td><strong>Medication before randomization</strong></td>
<td></td>
</tr>
<tr>
<td>Tocolytic prior to randomization</td>
<td>17.6% vs 18.8%</td>
</tr>
<tr>
<td>Magnesium sulfate for FNP</td>
<td>9.9% vs 12.6%</td>
</tr>
</tbody>
</table>
## Primary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dexamethasone n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Relative risk (95% CI)*</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal death</td>
<td>278/1417 (19.6)</td>
<td>331/1406 (23.5)</td>
<td>0.84 (0.72-0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>Stillbirth or neonatal death</td>
<td>393/1532 (25.7)</td>
<td>444/1519 (29.2)</td>
<td>0.88 (0.78-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Possible maternal bacterial infection‡</td>
<td>68/1416 (4.8)</td>
<td>89/1412 (6.3)</td>
<td>0.76 (0.56-1.03)</td>
<td>0.002§</td>
</tr>
</tbody>
</table>

* Relative risks and 95% confidence intervals, calculated from modeling, were adjusted for trial sites and accounted for clustering due to multiple births.

† P values were adjusted for multiplicity for the three primary outcomes with the use of the false-discovery-rate approach.

‡ Possible maternal bacterial infection was defined as the occurrence of fever (temperature ≥38°C) or clinically suspected or confirmed infection for which therapeutic antibiotics were used. Suspected or confirmed infection included obstetrical infection (chorioamnionitis, postpartum endometritis, or wound infection) or nonobstetrical infection (respiratory tract infection [pneumonia, pharyngitis, sinusitis, or a similar infection], urinary tract infection [excluding pyelonephritis], pyelonephritis, acute cholecystitis, or other system infection) captured during hospital admission or admissions only.

§ This P value was calculated for noninferiority.
# Neonatal secondary outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dexamethasone n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth</td>
<td>115/1544 (7.4)</td>
<td>113/1526 (7.4)</td>
<td>1.00 (0.78-1.30)</td>
</tr>
<tr>
<td>Early neonatal death (≤ 7 days)</td>
<td>218/1417 (15.4)</td>
<td>268/1406 (19.1)</td>
<td>0.81 (0.68-0.96)*</td>
</tr>
<tr>
<td>Severe respiratory distress‡</td>
<td>116/1245 (9.3)</td>
<td>141/1223 (11.5)</td>
<td>0.81 (0.64–1.03)</td>
</tr>
<tr>
<td>Severe respiratory distress at 24 h</td>
<td>34/1122 (3.0)</td>
<td>58/1065 (5.5)</td>
<td>0.56 (0.37-0.85)*</td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>183/1284 (14.3)</td>
<td>197/1264 (15.6)</td>
<td>0.92 (0.76-1.11)</td>
</tr>
<tr>
<td>Hypoglycaemia‡</td>
<td>301/1242 (24.2)</td>
<td>328/1217 (27.0)</td>
<td>0.91 (0.80–1.04)</td>
</tr>
<tr>
<td>Hypoglycaemia at 6 hours</td>
<td>92/1224 (7.5)</td>
<td>123/1194 (10.3)</td>
<td>0.73 (0.56-0.95)*</td>
</tr>
</tbody>
</table>

‡ Measured from the initial postnatal hospitalization until death, discharge, or completed day 7

* Statistically significant
# Neonatal secondary outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dexamethasone n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apgar score &lt;7 at 5 min</td>
<td>276/1359 (20.3)</td>
<td>293/1368 (21.4)</td>
<td>0.95 (0.82-1.10)</td>
</tr>
<tr>
<td>Major resuscitation at birth</td>
<td>101/1382 (7.3)</td>
<td>144/1383 (10.4)</td>
<td>0.70 (0.55-0.88)*</td>
</tr>
<tr>
<td>Use of oxygen therapy‡</td>
<td>726/1429 (50.8)</td>
<td>756/1413 (53.5)</td>
<td>0.95 (0.88-1.02)</td>
</tr>
<tr>
<td>Use of CPAP‡</td>
<td>265/1429 (18.5)</td>
<td>337/1413 (23.9)</td>
<td>0.78 (0.67-0.90)*</td>
</tr>
<tr>
<td>Use of mechanical ventilation‡</td>
<td>83/1284 (6.5)</td>
<td>103/1264 (8.2)</td>
<td>0.79 (0.59-1.05)</td>
</tr>
<tr>
<td>Use of parenteral therapeutic antibiotics</td>
<td>527/1245 (42.3)</td>
<td>494/1175 (42.0)</td>
<td>1.00 (0.91–1.10)</td>
</tr>
<tr>
<td>Use of surfactant</td>
<td>9/1284 (0.7)</td>
<td>18/1264 (1.4)</td>
<td>0.49 (0.22-1.08)</td>
</tr>
<tr>
<td>Admission to a special care unit</td>
<td>905/1287 (70.3)</td>
<td>897/1268 (70.7)</td>
<td>0.99 (0.94-1.04)</td>
</tr>
<tr>
<td>Newborn readmission</td>
<td>39/1429 (2.7)</td>
<td>48/1413 (3.4)</td>
<td>0.81 (0.53-1.25)</td>
</tr>
</tbody>
</table>

*Measured from the initial postnatal hospitalization until death, discharge, or completed day 7
## Maternal secondary outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dexamethasone n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>5/1429 (0.4)</td>
<td>4/1423 (0.3)</td>
<td>1.23 (0.33-4.57)</td>
</tr>
<tr>
<td>Fever</td>
<td>78/1417 (5.5)</td>
<td>70/1406 (5.0)</td>
<td>1.10 (0.80-1.50)</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>17/1429 (1.2)</td>
<td>18/1423 (1.3)</td>
<td>0.93 (0.48-1.80)</td>
</tr>
<tr>
<td>Endometritis</td>
<td>5/1429 (0.4)</td>
<td>3/1423 (0.2)</td>
<td>1.65 (0.39-6.92)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>8/1429 (0.6)</td>
<td>15/1423 (1.1)</td>
<td>0.53 (0.22-1.25)</td>
</tr>
<tr>
<td>Nonobstetrical infection</td>
<td>34/1429 (2.4)</td>
<td>42/1423 (3.0)</td>
<td>0.81 (0.52-1.26)</td>
</tr>
<tr>
<td>Use of therapeutic antibiotics</td>
<td>68/1427 (4.8)</td>
<td>89/1422 (6.3)</td>
<td>0.76 (0.56-1.03)</td>
</tr>
<tr>
<td>Any antibiotic use</td>
<td>1205/1353 (89.1)</td>
<td>1216/1355 (89.7)</td>
<td>1.00 (0.97-1.02)</td>
</tr>
<tr>
<td>Postpartum readmission</td>
<td>14/1429 (1.0)</td>
<td>13/1423 (0.9)</td>
<td>1.07 (0.50-2.26)</td>
</tr>
</tbody>
</table>
## Cause of neonatal death

<table>
<thead>
<tr>
<th>Final cause of death</th>
<th>Dexamethasone (N=1417)</th>
<th>Placebo (N=1406)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal asphyxia – no. (%)</td>
<td>61 (4.3)</td>
<td>78 (5.5)</td>
<td>0.78 (0.56-1.07)</td>
</tr>
<tr>
<td>Respiratory distress synd. – no. (%)</td>
<td>113 (8.0)</td>
<td>156 (11.1)</td>
<td>0.72 (0.57-0.90)*</td>
</tr>
<tr>
<td>Neonatal sepsis – no. (%)</td>
<td>77 (5.4)</td>
<td>74 (5.3)</td>
<td>1.03 (0.76-1.41)</td>
</tr>
<tr>
<td>Other specific causes – no. (%)</td>
<td>18 (1.3)</td>
<td>12 (0.9)</td>
<td>1.49 (0.73-3.16)</td>
</tr>
<tr>
<td>Indeterminate – no. (%)</td>
<td>9 (0.6)</td>
<td>11 (0.8)</td>
<td>0.81 (0.33-1.96)</td>
</tr>
</tbody>
</table>
Subgroup analyses

Prespecified subgroup analyses of the primary outcomes

- whether preterm birth was planned (yes vs no) – **no interaction**
- GA at first dose – **no interaction**
- no. of fetuses – **no interaction**
- study site – **no interaction**
- mode of birth – **no interaction**
- time from first dose to birth – **no interaction**
- use of tocolytic agent before preterm birth – **interaction (P=0.03)**
### Summary of findings

- **Reduced incidence of neonatal death alone and stillbirth or neonatal death**
- **No increase in maternal bacterial infection**
- **No effect on stillbirth**
- **No evidence of maternal or newborn harms**
- Benefits observed even though 45% of participants received less than 4 doses of trial medication
- **Need to treat 25 women to prevent 1 newborn death**

#### Reduced risks of the following outcomes support primary outcome findings:

- **Early neonatal death**
- **Severe respiratory distress at 24 hours**
- **Resuscitation at birth**
- **Use of CPAP**
- **Neonatal hypoglycemia at 6 hours reduced, but no difference at 36 hours**

Updated global evidence base – RDS
# Updated global evidence base - summary

## Antenatal corticosteroids for women at risk of preterm birth

### What is this systematic review about?
Antenatal steroids, compared with placebo or no treatment, given to pregnant women at risk of giving birth before 37 weeks.

### What evidence did we find?
- **27 randomised trials** including 11,272 women
  - **15 trials**: singleton pregnancies only
  - **12 trials**: included multiple pregnancies
  - **10 trials**: from middle- and low-income countries
  - **17 studies**: high-income countries
  - **19 studies**: used a single course of steroids
  - **8 studies**: used either single course or repeated doses

### What are the effects of antenatal corticosteroids?

<table>
<thead>
<tr>
<th>For babies: high-certainty evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 2.3% fewer perinatal deaths</td>
</tr>
<tr>
<td>- 2.6% fewer neonatal deaths</td>
</tr>
<tr>
<td>- 4.3% fewer cases of respiratory distress syndrome</td>
</tr>
<tr>
<td>Little to no difference in birthweight</td>
</tr>
</tbody>
</table>

### For babies: moderate-certainty evidence
- 1.4% fewer cases of intraventricular haemorrhage

### For mothers: moderate-certainty evidence
- Probably little to no difference in:
  - Maternal deaths
  - Chorioamnionitis
  - Endometritis

### What does this mean?
A single course of antenatal steroids reduces the risk of **serious respiratory illness and death** in neonates in low-middle- and high-income countries.

More detailed data are needed for certain high-risk groups (e.g., multiple pregnancies, pregnant women with diabetes or hypertension).

**Evidence up to date: Sept 2020**
Implications for national policies and implementation in LMIC

- Firm government commitment to safely scale up ACS administration where ACS treatment criteria can be met
- Well planned and participatory consensus-driven processes of adaptation and implementation
- Development or updating of national guidelines and protocols based on latest research evidence
- Creation of enabling environment for safe ACS use (avoiding stock-outs, upgrading facilities for care of women and preterm newborns)
- Training of healthcare staff of determination of GA and clinical features of imminent preterm birth
- Clear referral pathways for women at risk of preterm birth should be established within and across health care facilities

Reduced adverse events from preterm birth will only be achieved through:

- Government commitment
- Updating of national guidelines
- Enabling environment
- Health care staff training
- Network of care
The WHO ACTION Trials Collaborators

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