Antenatal corticosteroids for preterm Labour

Where are we now?

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Outline

• History of ACS use for preterm labour
• What are their benefits and risks?
• When to give – gestation, duration to delivery.
• Choice of drug – betamethasone vs dexamethasone?
• Society recommendations
• Limited resource settings – what is the evidence?
THE ACT TRIAL .... Althabe et al 2015
1969 ‘the EUREKA moment’

PREMATURE DELIVERY OF FOETAL LAMBS INFUSED WITH GLUCOCORTICOIDs

G. C. LIGGINS

1972 ‘the Landmark paper’

A CONTROLLED TRIAL OF ANTEPARTUM GLUCOCORTICOID TREATMENT FOR PREVENTION OF THE RESPIRATORY DISTRESS SYNDROME IN PREMATURE INFANTS


1990

The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials

PATRICIA CROWLEY, IAIN CHALMERS, MARC J. N. C. KELLER

2006

[Intervention Review]

Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Devender Roberts¹, Stuart R Dalziel²

2017
Benefits and Risks of ACS

Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Devender Roberts¹, Stuart R Dalziel²

21 studies – 3885 women and 4269 infants

In the NEONATES – reduction in:

NEONATAL DEATH - RR 0.69, 95% CI 0.58 to 0.81, 18 studies, 3956 infants
RDS - RR 0.66, 95% CI 0.59 to 0.73, 21 studies, 4038 infants
IVH - RR 0.54, 95% CI 0.43 to 0.69, 13 studies, 2872 infants
NEC - RR 0.46, 95% CI 0.29 to 0.74, eight studies, 1675 infants

Resp Support and NICU admission - RR 0.80, 95% CI 0.65 to 0.99, two studies, 277 infants)
Systemic infections in the 1st 48hrs of life - RR 0.56, 95% CI 0.38 to 0.85, five studies, 1319 infants

No evidence for increased risk of maternal death, chorioamnionitis or puerperal sepsis.
2017 update.....

- **Reduction** in the most serious adverse outcomes related to prematurity
  - **Perinatal Death** – av. RR 0.72, CI 0.58 to 0.89
  - **Neonatal Death** - RR 0.69, CI 0.59 to 0.81
  - **RDS** – av. RR 0.66, 95% CI 0.56 to 0.77
  - **IVH** – av. RR 0.55, CI 0.40 to 0.76
  - **NEC** - RR 0.50, 95% CI 0.32 to 0.78
  - Need for mechanical Ventilation - RR 0.68, 95% CI 0.56 to 0.84
  - Systemic infections in the 1st 48hrs -RR 0.60, 95% CI 0.41 to 0.88

- **No obvious benefit** for:
  - CLD
  - Neurodevelopmental delay

- **No associated increase** in chorioamnionitis, endometritis, Maternal Death
When to give ?gestation

• **26 - 34 weeks**.....Roberts et al Cochrane 2006
  *WHO – 24 -34wks, RCOG 24 -34wks, ACOG 24 -36wks

• **24 -26 weeks**.....scarce data only 1 trial 49 infants contributed to the above review.

• 34 - 36 weeks....inconsistent data (esp HMIC vs LMIC) on efficacy no data on long term safety

• 37 – 39 weeks (elective CS)

Evidence for benefit ...Saccone et al metaanalysis BMJ 2016 reduced resp morbidity (RDS, TTN, Mechanical ventilation duration) 6 trials 5698 singleton pregnancies.
When to give duration to delivery

**48hrs – 7days**
peak of effect from the initial 1972 trial subgroup analysis.

**Salvage/ Rescue therapy/Repeat therapy.**
single repeat course where preterm delivery is imminent within 7days.
(for mother who did not deliver within the initial 7 days).

some evidence of short term benefits- reduced RDS, however small reduction in BWT, long term benefits and risks are unknown.....Crowther et al cochrane review 2015
• ACS is recommended for women at risk of preterm birth from 24-34wks if:
  – Gestational age can be accurately determined
  – Preterm birth is imminent
  – Adequate childbirth care and preterm care is available.
1. ACS should be given to all women at risk of iatrogenic or spontaneous preterm birth up to 34+6 weeks of gestation (24 0/7 to 34 6/7).

1. ACS can be considered for women between 23+0 and 23+6 weeks of gestation who are at risk of preterm birth.

1. ACS should be given to all women for whom an elective caesarean section is planned prior to 38+6 weeks of gestation.
• A single course of corticosteroids – for pregnant women 24 0/7wks to 36 6/7 at risk of preterm delivery.

• Single repeat course of ACS for women less than 34 0/7 at imminent risk of preterm delivery within 7 days whose prior ACS was given more than 14 days previously.

• Consider ACS for pregnant women from 23 0/7 who are at risk of preterm delivery within 7 days based on family’s decision regarding resuscitation.
Betamethasone vs Dexamethasone

12 trials – 1557 women 1661 infants

Dexamethasone – LESS IVH (RR 0.44 95%CI 0.21 – 0.92) 4 trials 549 infants.

Primary outcomes - NO SIGNIFICANT DIFFERENCE (Dexamethasone vs Betamethasone) in:

- RDS (1.06 CI 0.88 – 1.27). 5 Trials 753 infants

- NEONATAL DEATH (1.41 CI 0.54 – 3.67) 4 Trials 596 infants

Conclusion – ‘It remains unclear whether one corticosteroid (or one particular regimen) has advantages over another’.
Limited resource settings – ?Evidence

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


The ACT trial.....Althabe et al

Aim – To assess feasibility effectiveness and safety of a multifaceted intervention to increase the use of ACS at ALL levels of healthcare in LMIC.

How - 18mo clustered randomised trial 6 countries - Argentina, Guatemala, India, Kenya, Pakistan, and Zambia.
The ACT trial.....Althabe et al

• Population – pregnant women at risk for preterm birth in LMIC.

• Intervention – multifaceted aimed to increase antenatal corticosteroid use

• Comparator – standard care.

• Outcomes – 28day neonatal mortality in infants less than 5\textsuperscript{th} percentile for birthweight. Frequency of maternal infection, use of antenatal steroids, maternal mortality.
102 clusters randomly assigned

51 allocated to intervention
51 clusters recruited participants

0 clusters withdrew
3 women withdrew
1501 women lost to follow-up
24 babies (from 21 women) less than 500 g and less than 20 weeks’ gestational age at birth

51 clusters included in analysis
48,219 women, 48,698 total births*, 47,394 livebirths

Primary analysis population (less-than-5th-percentile birthweight livebirths)
2361 women, 2520 infants

51 allocated to control
50 clusters recruited participants

1 cluster withdrew
0 women withdrew
1833 women lost to follow-up
21 babies* (from 17 women) less than 500 g and less than 20 weeks’ gestational age at birth

50 clusters included in analysis
51,523 women, 52,007 total births*, 50,743 livebirths

Primary analysis population (less-than-5th-percentile birthweight livebirths)
2094 women, 2258 infants

Figure 1: Trial profile
The ACT trial.....Althabe et al

• More women received ACS

1052 (45%) of 2327 women in intervention clusters who delivered less-than-5th-percentile infants vs 215 (10%) of 2062 in control clusters (p<0.0001).

• Higher 28day neonatal mortality in the whole population.

27.4/1000 live births for the intervention group vs 23.9 /1000 live births for the control group (RR 1.12, 1.02–1.22, p=0.0127)

• Increased suspected maternal infection

1207 (3%) of 48 219 women in the intervention group and 867 (2%) of 51 523 in the control group (OR 1.45, 1.33–1.58, p<0.0001).
The ACT trial.....Althabe et al

• For every 1000 women exposed to ACS: excess 3.5 neonatal deaths occurred.

• For mothers of infants in the <5th percentile weight exposed to ACS there was a 3.6% absolute increase in suspected infection.
Reducing neonatal mortality associated with preterm birth: gaps in knowledge of the impact of antenatal corticosteroids on preterm birth outcomes in low-middle income countries

Elizabeth M. McClure¹, Robert L. Goldenberg², Alan H. Jobe³, Menachem Miodovnik⁴, Marion Koso-Thomas⁴, Pierre Buekens⁵, Jose Belizan⁶ and Fernando Althabe⁶
Reflections on the results....following secondary analysis

- Increase in neonatal and maternal infections
- ACT conducted in lower level facilities, and homes, previous trials in hospitals with good obstetric and neonatal care.
- Large study (nearly 100,000 deliveries) well powered to detect smaller baseline risks of ACS
- Duration of follow up – 42days.
- The < 5\textsuperscript{th} percentile for weight as a proxy for preterm birth
- Dexamethasone vs Betamethasone.
McCure et al suggested further research directions:

1) Gestational age assessment: What is the best way to determine gestational age and which outcomes associated with ACS use are impacted in different gestational age windows?

2) Risk population: Which factors predict preterm delivery in LMIC and what is the best way to ensure that providers can identify signs of risk?

3) Obstetric and neonatal care: What is the impact of ACS when administered to women delivering at different levels of obstetric and neonatal care?

4) Infectious outcomes: What maternal and newborn infectious outcomes are associated with ACS?
Administer ACS to mothers 24 -34wks if:

• Gestational age can be accurately determined
• Preterm birth is imminent
• *Adequate childbirth care and preterm care* is available.

Administer at 24hrs – 7days.
The need for further research in the area of ACS use for preterm labour in LMIC settings cannot be overemphasized, as we have seen overwhelming evidence of benefit and absence of risk of an intervention is not always automatically reproducible in a different setting.
References


• Crowther et al Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal outcomes. Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.:CD003935


• Saccone et al Antenatal Corticosteroids for maturity of term or near term fetuses: systematic review and meta analysis of randomized controlled trials. BMJ 2016;355:i5044


• Others referenced in the slides
The WHO ACTION-II (Antenatal Corticosteroids for Improving Outcomes in preterm Newborns) Trial