Frequently asked questions (FAQ) regarding antenatal corticosteroids for fetal maturation

UN Commission / Born Too Soon Care Group on Antenatal Corticosteroids

Frequently Asked Questions

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7. Are there any generics of Beta-Ac+PO4?
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10. Can ACS be used in women with hypertension?
11. Can ACS be used in diabetic women?
12. Can ACS be used in women with preterm premature rupture of membranes (pPROM)?
13. Are tocolytics required for efficacy?
14. Do partial doses confer any benefit?
15. Can caregivers provide multiple courses of ACS?
16. Can ACS be used in community level care, when referral is not feasible?

Intervention and Efficacy

1. **What are antenatal corticosteroids (ACS)?** Antenatal corticosteroids have been used since 1972 to accelerate fetal maturation in threatened pre-term birth. This includes maturation of the lungs (reducing respiratory distress syndrome), the brain (reducing intracranial hemorrhage), the skin (reducing infection) and the kidneys (reducing fluid/electrolyte imbalance). In high income countries, ACS are used in nearly 90% of cases where indicated, but in low income countries coverage rates are estimated at 5% in Africa[1] and 9-73% in SE Asia[2] . Their low cost and high efficacy make them an attractive tool to improve outcomes for pre-term infants, especially 27-34 weeks gestation.

2. **How are ACS used?** All effective ACS are intramuscular injections given during threatened preterm birth. Oral administration is not effective. A full course of ACS requires 2-4 injections over 36 hours, but partial courses have also been proven effective (Question #14) . The table below summarizes the dosage and administration of antenatal corticosteroids in threatened preterm labor

Drug	Betamethasone (Phosphate+Acetate)	Dexamethasone
Dose / Injection	12 mg	6 mg
# Injections	2	4
Interval btwn injections	24hrs	12hrs
Complete Course	24 mg	24 mg

3. **How effective are ACS?** As of January 2013, there were 19 randomized controlled trials with mortality endpoints to evaluate the impact of ACS. Pooling together both dexamethasone and betamethasone data, a single course of antenatal steroids is associated with a 31% mortality reduction where ventilation and/or surfactant is standard of care, RR 0.69 (95% CI 0.58 to 0.81)[3]. In four studies from middle income countries, the mortality effect is even higher at 53% reduction [RR 0.47 (95% CI 0.35 to 0.64)][4]. This makes ACS one of the most effective interventions to save the lives of premature newborns.

4. **What is the WHO position on ACS? What about institutions and professional associations?** The WHO recommends the use of ACS in the management of preterm labor and premature rupture of membranes[5]. ACS are additionally on the WHO list Priority live-saving medicines for women and children 2012[6], and dexamethasone is under review for addition to the WHO list of essential medicines[7]. Beyond the WHO, there have been United States National Institute of Health (NIH): Consensus Statements in 1994[8] and 2000[9] supporting ACS usage, as well as guidelines of the American College of Obstetrics and Gynecology (ACOG)[10], Royal College of Obstetrics and Gynecology (RCOG)[11], World Association of Perinatal Medicine (WAPM)[12], and a joint statement of support from International Federation of Gynecology and Obstetrics (FIGO) and International Pediatric Association (IPA)[13].

Drug and Dosage

5. **Which ACS is best?** Betamethasone acetate + phosphate (Celestone) and dexamethasone sodium phosphate are the only two drugs with multiple randomized controlled trials to demonstrate their safety and efficacy. Both drugs are safe and effective. Neither has been definitively shown to be superior to the other[14]. Dexamethasone is broadly available as a generic drug costing <$1USD per dose, and frequently available in facility settings for multiple indications. It is on the WHO essential medicines list and many national essential medicines lists for multiple indications other than fetal maturation. Celestone is a proprietary product retailing for around $75USD which has suffered from production shortages in recent years. It is not sold as widely as dexamethasone, and Celestone is entirely unavailable in some countries, such as India.

6. **Can betamethasone phosphate (Beta-PO4) be used instead of betamethasone acetate suspended in betamethasone phosphate (Celestone)?** There is no data to support the substitution of Beta-PO4 for Celestone, and Beta-PO4 alone is not recommended in any guidelines. However, there is one 1989 study using Beta-PO4 in 251 women which shows a positive effect to Beta-PO4[15]. Subsequent work in 2007 and 2009 in sheep has shown that Beta-PO4 is ineffective as a single dose, but can decrease work of breathing in a four dose regimen[16 17].

7. **Are there any generics of Celestone?** American Regent produces a suspension of Beta-Ac in Beta-PO4 which Is "AB" rated by the FDA , indicating that a study has been submitted demonstrating bioequivalence to Celestone. However, for antenatal use, Jobe and others have identified the potential importance of a milling process used in the production of Celestone to ensure Beta-Ac particle size of 4-12um. It is not known whether the American Regent product has this same characteristic, or to what extent this characteristic could affect outcomes.

Special circumstances

8. **What are the contraindications for ACS?** ACS should not be used in presence of frank or systemic infection including tuberculosis or sepsis, systemic fungal infections, cerebral malaria, or with administration of live virus vaccines.

9. **Can ACS be administered in women with advanced preterm labor?** Yes. Meta-analysis shows a 47% reduction in mortality among newborns born less than 24 hours after their first dose of ACS [RR 0.53 (0.29-0.96)]. This is very similar to the 51% mortality drop observed in babies born within 48 hours of their first dose [RR 0.49 (0.30-0.81)]. (3)

10. **Can ACS be used in women with hypertension?** Yes. In a meta-analysis of 278 women live births from women with hypertension, newborn mortality was 50% lower among newborns exposed to ACS [RR 0.50 (0.29, 0.87)] with no evidence of increased maternal morbidity. (3)

11. **Can ACS be used in diabetic women?** Yes. Although diabetic women were mostly excluded from early studies on ACS, most professional guidelines advocate the use of ACS in diabetic women. They do note, however, that women with impaired glucose tolerance or diabetes who are receiving fetal steroids should have additional insulin and be closely monitored.(12)

12. **Can ACS be used in women with preterm premature rupture of membranes (pPROM)?** Yes, in a meta-analysis of 984 live births from women with complications of pPROM, newborn mortality was 42% lower among babies exposed to ACS versus those who were

not [RR 0.58 (0.43 - 0.80)]. Among these same women, the rate of purpeural sepsis was virtually identical in the ACS and non-ACS groups. (3)

13. **Are tocolytics required for efficacy?** No. Tocolytics are not required for ACS to be effective, but may prolong the time to delivery and therefore allow more time for ACS to act, or for an additional dose to be given. However, some note that tocolytics complicate the care algorithm and are not available in many settings. Concurrent administration of ACS and tocolytics using beta-mimetics in the presence of maternal infection increases the risk of development of pulmonary edema[18].

14. **Do partial courses of ACS confer any benefit?** Yes. Studies of dexamethasone[19] and betametashone[20] show a dose dependent effect whereby subjects receiving the full course have the best outcomes, but subjects receiving only partial dosing have better outcomes than those who received no ACS at all.

15. **Can caregivers provide multiple courses of ACS?** Several trials have demonstrated that repetitive courses of ACS are not advised, as fetuses exposed to multiple courses are receive marginal or no benefits but assume added risks (9). However, there is some evidence to suggest that for mothers who had completed a single course of ACS before 30 weeks, a single additional, rescue course of betamethasone before 33 weeks gestation improves neonatal outcomes[21].

16. **Can ACS be used in community level care, when referral is not feasible?** All data collected on ACS use and effectiveness to date comes from facility settings. However, The Global Network for Women's and Children's Health Research are currently conducting a trial due to complete in 2013 which will include women cared for with ACS in facilities and communities across several low resource settings[22].

About the UN Commission / Born Too Soon Care Group on Antenatal Corticosteroids

The Antenatal Corticosteroids Working Group is an international collaboration of organizations committed to advancing the use antenatal steroids for fetal maturation in threatened preterm labor through advocacy and technical assistance. The members include individuals representing the United States Agency for International Development, the Maternal and Child Health Integrated Program, Save the Children/Saving Newborn Lives, The, Bill & Melinda Gates Foundation, The World Health Organization, The United States National Institute of Health, The American College of Nurse Midwives, Cincinnati Children's Hospital Medical Center, The Global Alliance to Prevent Prematurity and Still birth at Seattle Children's, and the Instituto de Efectividad Clínica y Sanitaria.

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