REVIEW ARTICLE

Antenatal Corticosteroids – Is it a Panacea for the Fetus and the Newborn?

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ABSTRACT

A single course of corticosteroids for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation at risk of preterm delivery within 7 days is the standard antenatal therapy to accelerate fetal lung maturation and prevent respiratory distress syndrome. The benefits include not only a reduction in the risk of RDS (34%) but also a substantial reduction in mortality (32%), Intra-ventricular hemorrhage (IVH) (45%), Necrotizing enterocolitis (NEC) (nearly 50%) and mechanical ventilation need (30%) and systemic infections in the first 48 hours (40%). Extrapolation of this therapy to late preterm and elective Caesarean section for early term deliveries may reduce respiratory distress and transient tachypnea of newborn but may lead to undesirable effects like hypoglycemia, neuro-sensory and behavioral disabilities.

INTRODUCTION

Corticosteroid administration before anticipated preterm birth is one of the most important antenatal therapies available to improve newborn outcomes. A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation who are at risk of preterm delivery within 7 days. It has been one of the most important advances in perinatal care. Antenatal corticosteroids (ANCS), when administered to a pregnant woman before delivery of a very premature infant, accelerate fetal lung maturation and prevent neonatal mortality, respiratory distress syndrome and brain injury.

Liggins in 1969 showed that lambs delivering prematurely who received glucocorticoids had lungs that remained partially expanded.[1]

Liggins and Howie published the first randomized controlled trial of antenatal corticosteroids (ANCS) in Pediatrics in 1972 that demonstrated a reduction in respiratory distress syndrome (RDS) in infants less than 32 weeks of gestation from 69.6 to 11.8%.[1]

A 1995 meta-analysis demonstrated an approximately 50% reduction in RDS in infants whose mothers were treated with ANCS, with the best treatment-to-delivery interval of 24 hours to 1 week after ANCS treatment.[2]

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The benefits of antenatal administration of corticosteroids to fetuses at risk of preterm delivery vastly outweigh the potential risks. Cockrane database has shown that these benefits include not only a reduction in the risk of RDS (34%) but also a substantial reduction in mortality (32%), Intraventricular hemorrhage (IVH)(45%), Necrotizing enterocolitis (NEC) (nearly 50%) and mechanical ventilation need(30%) and systemic infections in the first 48 hours (40%).[2]

ACOG 2016 Recommendations for Antenatal Steroids[2]:

- All fetuses between 24 and 34 weeks gestation at risk of preterm delivery within 7 days should be considered candidates for antenatal treatment with corticosteroids. A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation who are at risk of preterm delivery within 7 days, including for those with ruptured membranes and multiple gestations.
- Those mothers at 22-23 weeks at risk of delivery within 7 days may also receive ANCS based on family's decision for resuscitation and care irrespective of membrane rupture status and regardless of fetal number.
- As treatment with corticosteroids for less than 24 hours is still associated with significant reductions in neonatal mortality, RDS, and IVH, it is advocated that antenatal corticosteroids should be given unless immediate delivery is anticipated.
- In preterm premature rupture of membranes at less than 30 to 32 weeks' gestation in the absence of clinical chorioamnionitis, antenatal corticosteroid use is recommended because of the high risk of IVH at these early gestational ages.
- Administration of ANCS may be considered in pregnant women between 34 0/7 weeks and 36 6/7 weeks of gestation (Late preterms) who are at risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids.
- A single repeat course may be advocated for gestation less than 34 weeks and at risk of delivery within 7 days if ANCS was received 14 days prior
- Rescue course corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario. Whether to administer a repeat or rescue course of corticosteroids with preterm prelabor rupture of membranes (PPROM) is controversial, and there is insufficient evidence to make a recommendation for or against.
- Multiple courses of steroid are not advocated, because of the risk of decrease in birth weight, head circumference, neurodevelopmental impairment and Cerebral palsy
- ANCS for elective LSCS in term gestation, if not received previously, found to have decreased incidence of respiratory distress and transient tachypnea of Newborn (TTN)

Treatment consists of:

Betamethasone 12 mg 24 hours apart intramuscular(IM) x 2 doses or Dexamethasone 6 mg 12 hours apart IM x 4 doses

Optimal benefit begins 24 hours after initiation of therapy and lasts 7 days

Betamethasone versus dexamethasone :Which is better?

RCT's reviewed by Cochrane database[2] showed no evidence of benefit of one over other. Less intra-ventricular hemorrhage (IVH) was seen withDexamethasone while Betamethasone showed less frequent neurodevelopmental abnormality at 18 – 22 months.

Betamethasone acetate + Phosphate (Celestone) is the drug used abroad which is not available in India. We have only Betamethasone Phosphate, which is less stable with shorter half life. Acetate salt has a higher stability with a longer half-life. As per WHO and Ministry of Health and Family Welfare Guidelines in India, Dexamethasone is advocated (cheaper and freely available globally).

ANCS action on the lung: causes maturation of developing fetal lung by.

1. Stimulating development of both type I and type II pneumocytes
2. Helping in lung fluid clearance by increasing number of epithelial Na channels→ clear fluid from alveolar lumen to interstitium, preventing ventilation/perfusion mismatch
3. Increase lung compliance and maximise lung volume
4. Decrease Protein extravasation
5. Thinning of the mesenchyme of alveolar-capillary structure
6. Increase saccular and alveolar gas volumes
7. Decrease alveolar septation
8. Increase antioxidant volumes
9. Increase surfactant production → decreasing surface tension within the alveoli
10. Activation of endothelial nitric oxide synthase, effecting pulmonary blood flow, improving pulmonary adaptation at birth.
11. Effect on gene expression

DISCUSSION

A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation who are at risk of preterm delivery within 7 days, including for those with ruptured membranes and multiple gestations.

Neonates whose mothers received antenatal corticosteroids have significantly lower severity, frequency, or both, of respiratory distress syndrome (relative risk [RR], 0.66; 95% confidence interval [CI], 0.59–0.73), intracranial hemorrhage (RR, 0.54; 95% CI, 0.43–0.69), necrotizing enterocolitis (RR, 0.46; 95% CI, 0.29–0.74), and death (RR, 0.69; 95% CI, 0.58–0.81), compared with neonates whose mothers did not receive antenatal corticosteroids.[2]

Special Situations:

- Can ANCS be given in cases of PPROM? Answer is yes.
- Concern of increased risk of maternal and neonatal infections is there but Cochrane meta-analyses show reduced death, RDS, IVH, NEC in this subgroup and no increased risk of sepsis.[2] Whether to administer a repeat or rescue course of corticosteroids with preterm prelabor rupture of membranes (PPROM) is controversial, and there is insufficient evidence to make a recommendation for or against.
- Frankchorioamnionitis – may be the only contraindication
- Maternal hypertension and maternal diabetes also are not contraindications for ANCS.
- In twins/ multiple gestation, and in obesity also the same dose of ANCS to be administered.
- **Antenatal corticosteroids in the late preterm period.**
- Recent data suggest that ANCS can be beneficial in pregnant women at high risk of late preterm birth, between 34 0/7 weeks and 36 6/7 weeks of gestation who have not received a prior course of antenatal corticosteroids. Because treatment also reduces neonatal morbidity when administered beyond 34 weeks, updates to US guide lines in 2016 recommended treatment for pregnant women between34 weeks 0 days to 36 weeks 6 days who are at risk for preterm delivery within 7 days and who have not received a previous course of antenatal corticosteroids. However, many questions about optimal use of antenatal corticosteroids remain unanswered.[3,4,5]
- **ANCS before Elective Cesarean Section.**[3,4,5]
- The Antenatal Steroids for Term Elective Cesarean Section (ASTECS) study, by Stutchfield et al evaluated ANCS for 998 women with planned elective cesarean delivery at 37 weeks of gestation. Neonatal admission to the special care unit for respiratory distress decreased from 5.4% in the control group to 2.9% in the treatment group and RDS was reduced between control and treatment groups (1.1% vs 0.2%). 3 trials demonstrated a low incidence of respiratory related adverse outcomes such as RDS after cesarean delivery at term, and the greatest effect of ANCS exposure in reduction of respiratory morbidity is related to transient tachypnea of newborn (TTN).
- An unanticipated finding was an increased incidence of hypoglycemia, (glucose level <40mg/dl) in the ANCS group (24% vs 15%)
- The hypoglycemia was increased in infants whose mothers had pre-gestational diabetes mellitus.

Challenges for administration of ANCS

There are clear benefits to the administration of ANCS in preterm gestation 24 to 34 weeks when delivery occurs 24 hours to 7 days after treatment. But, recent guidelines have recommended consideration of antenatal corticosteroids for women with threatened late preterm birth and for women undergoing full-term elective cesarean delivery (37-39 weeks; early term).[5,6,7]

Under such guidelines, the proportion of infants who may be exposed to exogenous corticosteroids increases from less than 2% to more than 10% of all births. In the setting of these expanded indications, it is imperative to go beyond evaluation of short-term benefits and determine the long-term safety of this fetal exposure.

Adverse effects of ANCS:

Maternal effects: Glycemic abnormalities and leukocytosis are seen especially in diabetic mothers but returns to baseline in 3 days . In the fetus, transient decrease in fetal heart rate variability and decrease in biophysical profile are seen.

Neonatal effects: Repeated weekly doses have been associated with decreased birth weight and poor fetal head growth (decreased head circumference) and increased risk of neurodevelopmental impairment by 5 years and is not recommended.[8]

In experimental animal studies ANCS caused hippocampal degeneration and HPA axis dysfunction and decreased fetal and brain growth. These findings were consistent with observational studies showing that ANCS impaired fetal growth and decreased neuronal density in the hippocampus of newborns.

Hypoglycemia and its effect on child neurodevelopment are of particular concern, as corticosteroids cross the placenta and the blood-brain barrier and may harm fetal brain development.

In late preterm and in term elective LSCS, an associated increased frequency of hypoglycaemia (24% versus 15%) was noticed in the ALPS study.[9] Hypoglycemia was noted in late preterm infants whose mothers were treated with ANCS in several studies.[7,8,9] Cord blood levels of C-peptide and glucose were higher in ANCS-exposed fetuses, which indicates that these fetuses were hyper insulinemic and thus at higher risk for neonatal hypoglycemia.[9]

In the late preterm and term period, the greatest effect of ANCS is a decrease in the rate of TTN, which is normally a self-limiting process.

An unintended consequence of the use of ANCS to improve respiratory symptoms in late preterm infants is that it may unmask other morbidities, such as hypoglycemia. It should be noted that the risk of hypoglycemia in the late preterm infants in the ALPS study was higher than the benefit that was derived from decreased respiratory morbidity (TTN and need for CPAP/Oxygen). These babies still require close observation for other preterm morbidities that include hypoglycemia, jaundice, hypothermia, and feeding difficulties.

Finally, ANCS therapy in 210 preterm survivors who were observed until age 14 years had higher systolic and diastolic blood pressures in adolescence, which could lead to clinical hypertension later in life.

Mental and behavioral problems

Prenatal exposure to exogenous corticosteroids is thought to be associated with alterations in developmental programming of the fetus, with downstream effects on cardiovascular, metabolic, and endocrine functions and neurologic outcomes. Five-year follow-up of the multicenter Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study[8,10] demonstrated that increased corticosteroid exposure was associated with increased risk for neurosensory disability among the children subsequently born at term. Small cohort studies have also demonstrated increased risk for psychiatric symptoms among young adults born extremely preterm who had been exposed to ANCS.[8,10,11] A large number of treatment-exposed children are not delivered within 7 days and go on to be born at term. 45% of steroid-exposed infants were delivered at term and an increased risk for childhood mental and behavioral disorders associated with antenatal corticosteroid exposure were particularly seen in them.[11] In these infants, minor short-term benefit have been outweighed by significant long-term risks. Prior work has emphasized potential long-term risks secondary to hypoglycemia in late preterm born children exposed to this therapy.

Current guidelines that expand recommendations for use of antenatal corticosteroids to late preterm and early term deliveries should be reconsidered until long-term safety has been more thoroughly evaluated.[8-10]

Findings in a population-based retrospective cohort study that included 674877 children followed up for 11years, exposure to maternal antenatal corticosteroid treatment, compared with non-exposure, was significantly associated with mental and behavioral disorders in children (hazard ratio: 1.33).[10]

Reduction in short-term risk may be counter-balanced by higher long-term risk for mental and behavioral disorders, at least in children born at term after the treatment exposure. Mental and behavioral disorders were statistically significantly higher for the treatment-exposed compared with the non-exposed child.

In the entire cohort and in term-born children, treatment exposure, compared with non-exposure, was significantly associated with psychological development disorders; attention-deficit/hyperactivity or conduct disorders; mixed disorders of conduct and emotions, emotional disorders, disorders of social functioning or tic disorders; other behavioral or emotional disorders; and sleep disorders.[10]

CONCLUSION

A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation who are at risk of preterm delivery within 7 days, including for those with ruptured membranes and multiple gestations. It is the standard antenatal therapy to accelerate fetal lung maturation and prevent respiratory distress syndrome and benefits far outweigh the risks. A single repeat course may be advocated for gestation less than 34 weeks and at risk of delivery within 7 days if ANCS was received 14 days prior. But recommendations to administer this therapy in the late preterm window and extension of treatment to women scheduled for cesarean delivery at term before 39 weeks may need to be re-examined until sufficient safety data are available.

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