STRATEGIES TO IMPROVE ANTENATAL STEROID USAGE IN WOMAN AT RISK OF PRETERM LABOR IN INDIA

Showkat Hussain Tali ¹, Nandkishor S Kabra², Shagufta Yousuf³ and Amrit Jeevan⁴

¹Pediatrics, AIMSR, Bathinda, Punjab, India
²Neonatology Surya Child Care, Mumbai, India
³Gynecology and Obstetrics, AIMSR, Bathinda, Punjab, India
⁴Neonatology, Surya Child Care, Mumbai, India

ABSTRACT

One of the most effective means of preventing neonatal mortality is administration of antenatal steroids to mothers at the risk of preterm delivery. Antenatal steroid use in industrialized countries is about 95%. In India antenatal steroid coverage for eligible mothers in preterm labor in Govt sector hospital is estimated to be 20-40%. In private sector hospitals in India it is about 80%. Therefore there is an urgent need to devise strategies to address this key issue.

INTRODUCTION

As per the 2030 Agenda for Sustainable development (WHO), decreasing neonatal mortality is a priority to reach Goal 3 to ensure healthy lives and promote well-being for all at all ages, which calls for reduction in neonatal mortality to 12/1000 live births and under-5 mortality to at least as low as 25 per 1,000 live births by 2030¹. Each year more than one in ten babies are born preterm and over one million die due to complications of preterm birth, most commonly respiratory complications due to lung immaturity often called Respiratory Distress Syndrome [RDS]. This makes preterm birth the second most common cause of child deaths after pneumonia as of 2010, yet global attention and action is lacking. In addition to the mortality effects, millions of surviving preterm babies have long-term disability and higher risk of adult chronic diseases. Therefore, preterm birth is one of the highest burden conditions highlighted in the global burden of disease. It is also a major drain on families’ economic resources globally. The large survival gap for preterm babies born in high income compared to low income countries is due to lack of even simple newborn care let alone intensive care². In India of all live births 13 % infants are born preterm (before 37 completed weeks of pregnancy). Out of an estimated annual 26 million live births in India, 3.5 million babies are born preterm, and out of these 0.3 million babies die due to prematurity related complications. Preterm birth is estimated to be a risk factor in at least 50% of all neonatal deaths. As of 2015, In India the neonatal mortality rate is 28/1000 live births³. India accounts for 30 percent of neonatal deaths globally. Most of the deaths occur during the first days of life: 46 % occurring in the first two days of life and 73 % taking place within the first few weeks of life. Therefore, serious efforts must be made to address the needs of babies in the first few days of life⁴.

Antenatal corticosteroid [ANCS] injection for women at risk of preterm delivery is the most effective intervention to reduce the risk of RDS for preterm babies. Since its discovery in 1969, more than twenty convincing randomized controlled trials [RCTs] have helped to make ANCS standard of care for women with threatened preterm birth. Fluorinated Glucocorticoid hormones cross the placenta most efficiently and trigger a range of effects including the production of surfactant in the fetal lung. Surfactant enables babies to

*Corresponding author: Showkat Hussain Tali
Pediatrics, AIMSR, Bathinda, Punjab, India

Key Words:
Antenatal Steroids,
Preterm labor, Strategies
establish regular breathing without ventilator support or with reduced intensity of ventilation.

**Evidence from the literature regarding the usefulness of antenatal corticosteroids in women at risk of preterm labour**

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

This Cochrane review was updated in 2017, with the inclusion of 30 studies (involving 7774 women and 8158 infants). Gestational age at trial entry was 24 0/7 to 37 0/7 weeks. The review found that the administration of ANCS to women at risk of preterm delivery produces a considerable reduction in the risks of complications of prematurity such as perinatal death, neonatal death, and respiratory distress syndrome, cerebro-ventricular hemorrhage, necrotizing enterocolitis, need for mechanical ventilation and systemic infections in the first 48 hours of life. There was no increase in chorioamnionitis, endometriosis or maternal death; there was no obvious benefit for chronic lung disease, mean birth weight, death in childhood, neurodevelopmental delay in adulthood or death into adulthood. There was no definitive evidence to suggest that antenatal corticosteroids work differently in any pre-specified subgroups (singleton versus multiple pregnancy; membrane status; presence of hypertension) or for different study protocols (type of corticosteroid; single course or weekly repeats). There was no evidence that gestational age at trial entry (< 35 0/7 weeks or >34 0/7 weeks) led to different rates of chorioamnionitis in women exposed to corticosteroids. There were insufficient studies in the later gestational age group to evaluate endometritis. For the infant, there was no evidence that gestational age at trial entry led to different rates of death (perinatal; neonatal; fetal), RDS, IVH or birth weight in infants exposed to corticosteroids.

Authors concluded that the evidence from this update supports the continued use of a single course of antenatal corticosteroids to accelerate fetal lung maturation in women at risk of preterm birth. A single course of antenatal corticosteroids could be considered routine for preterm delivery. It is important to note that most of the evidence comes from high income countries and hospital settings; therefore, the results may not be applicable to low-resource settings with high rates of infections.

**Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease**

Cochrane review published in 2011 included 10 trials (4730 women and 5650 babies) with low to moderate risk of bias. Treatment of women who remain at risk of preterm birth seven or more days after an initial course of prenatal corticosteroids with repeat dose(s), compared with no repeat corticosteroid treatment

1. Reduced the risk of their infants experiencing the primary outcomes respiratory distress syndrome (risk ratio (RR) 0.83, 95% confidence interval (CI) 0.75 to 0.91, eight trials, 3206 infants, numbers needed to treat (NNT) 17, 95% CI 11 to 32)

2. Reduced risk of serious infant outcome (RR 0.84, 95% CI 0.75 to 0.94, seven trials, 5094 infants, NNT 30, 95% CI 19 to 79).

3. Treatment with repeat dose(s) of corticosteroid was associated with a reduction in mean birth weight (mean difference (MD) -75.79 g, 95% CI -117.63 to -33.96, nine trials, and 5626 infants). However, outcomes that adjusted birth weight for gestational age (birth weight Z scores, birth weight multiples of the median and small-for-gestational age) did not differ between treatment groups. At early childhood follow-up no statistically significant differences were seen for infants exposed to repeat prenatal corticosteroids compared with unexposed infants for the primary outcomes (total deaths; survival free of any disability or major disability; disability; or serious outcome) or in the secondary outcome growth assessments.

Authors of Cochrane review conclude that the short-term benefits for babies of less respiratory distress and fewer serious health problems in the first few weeks after birth support the use of repeat dose(s) of prenatal corticosteroids for women still at risk of preterm birth seven days or more after an initial course. These benefits were associated with a small reduction in size at birth. The current available evidence reassuringly shows no significant harm in early childhood, although no benefit. Further research is needed on the long-term benefits and risks for the woman and baby. Individual patient data meta-analysis may clarify how to maximise benefit and minimise harm.

Cochrane review published in 2017 concluded that there was no evidence that protocols that allowed weekly repeat doses of corticosteroids led to different rates of chorioamnionitis or endometritis in women exposed to corticosteroids. There were also no different rates of death (perinatal, neonatal, fetal), RDS, IVH or birth weight in infants exposed to corticosteroids.

**Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth**

This review published in 2013, 12 trials (1557 women and 1661 infants) were included. Dexamethasone was associated with a reduced risk of intraventricular hemorrhage (IVH) compared with Betamethasone (risk ratio (RR) 0.44, 95% confidence interval (CI) 0.21 to 0.92; four trials, 549 infants). No statistically significant differences were seen for other primary outcomes: respiratory distress syndrome (RDS) (RR 1.06, 95% CI 0.88 to 1.27; five trials, 753 infants) and perinatal death (neonatal death RR 1.41, 95% CI 0.54 to 3.67; four trials, 596 infants). Similarly, very few differences were seen for secondary outcomes such as rate of admission to the neonatal intensive care unit (NICU) although in one trial, those infants exposed to Dexamethasone, compared with Betamethasone, had a significantly shorter length of NICU stay. Median and small differences were seen for growth assessments. Between treatment groups. At early childhood follow-up no statistically significant differences were seen for infants exposed to repeat prenatal corticosteroids compared with unexposed infants for the primary outcomes (total deaths; survival free of any disability or major disability; disability; or serious outcome) or in the secondary outcome growth assessments.
215 women), no differences in maternal or neonatal outcomes were seen between the different Betamethasone dosing intervals assessed. Similarly, no significant differences in outcomes were seen when Betamethasone acetate and phosphate was compared with Betamethasone phosphate in one trial.

Authors of the review conclude that it remains unclear whether one corticosteroid (or one particular regimen) has advantages over another. Dexamethasone may have some benefits compared with Betamethasone such as less IVH, and a shorter length of stay in the NICU. The intramuscular route may have advantages over the oral route for dexamethasone, as identified in one small trial. Apart from the suggestion that 12-hour dosing may be as effective as 24-hour dosing of Betamethasone based on one small trial, few other conclusions about optimal antenatal corticosteroid regimens were able to be made. No long-term results were available except for a small subgroup of 18 month old children in one trial. Trials comparing the commonly used corticosteroids are most urgently needed, as are trials of dosages and other variations in treatment regimens. Cochrane review 2017 concluded that there was no evidence that type of corticosteroid used led to different rates of endometritis. Betamethasone appeared to result in less maternal choorioamnio-nitis than dexamethasone. There was no evidence that type of corticosteroid used led to different rates of death (perinatal (neonatal or fetal), RDS, IVH, birth weight, moderate/severe RDS or chronic lung disease.

**Product definitions**

Both Betamethasone [beta-] and Dexamethasone [dexamethasone] are administered as intramuscular injections. The effect is higher if there is 24 hours between the first dose of ANCS and the time of birth. Both drugs have a long history of wide use, strong efficacy and safe administration. Fourteen RCTs have used Betamethasone, and 6 used Dexamethasone. There is no definitive evidence to recommend one of these two options over the other. A very large trial or series of trials would be required in order to make definitive recommendations on choice of steroid and confidently measure risk of rarer outcomes, but it is clear that current evidence supports the use of either product to save lives safely. An advantage for Betamethasone is that it requires only two injections compared to four injections of Dexamethasone. This might be an important consideration especially at the lower levels of the health system. However, Dexamethasone is currently far less expensive and far more widely available than Betamethasone.

Antenatal steroid use in industrialized countries is about 95%. In India antenatal steroid coverage for eligible mother in preterm labor in Govt sector hospital is estimated to be 20-40%. In private sector hospitals in India it is about 80%. Therefore there is an urgent need to devise strategies to address this key issue.

**Strategies to improve antenatal steroid usage in woman at risk of preterm Labor in India**

There are many steps involved in translating valid research in to practice. There could be many leaks at each stage.

The following strategies may be applied and could be immensely helpful in developing countries like India to increase the antenatal steroid coverage. In pregnant woman at risk of preterm labor.

**Increasing Awareness of benefits of use of ANCS: Increasing awareness amongst Obstetricians, Pediatricians, Medical officers, ANMs, District Hospital, Rural Hospital and PHC staff involved in management of pregnant women. There is an urgent need to publicize the benefits of ANCS widely in pregnant women and society at large. This can be achieved through involvement of Federation of Obstetrical and Gynecological Society of India (FOGSI), Indian Academy of Pediatrics (IAP), National Neonatology Forum (NNF) of India, Indian Medical Association (IMA), Ministry of Health and Family welfare. NRHM and INAP have already incorporated use of ANCS in its program. This is a major tool for making a new programme a success. A new intervention no matter how useful it may be, in reality won’t have a substantial impact in actual world unless the people who are supposed to offer the intervention and the ones who are the beneficiary subjects are made aware of its benefits. So both health care professionals including doctors and the supporting staff and all pregnant women may be made aware about the beneficial use of ANCS through special education sessions. Even electronic and print media may be used to create a general public awareness in this regard to get the best possible impact.

**Increasing Acceptance of benefits of use of ANCS:** Still a lot of Obstetricians, Pediatricians, Medical officers, ANMs, District Hospital, Rural Hospital and PHC staff involved in management of pregnant women have not accepted that ANCS have substantial benefits. This group needs to be better educated by varieties of tools like training by leaders and experts in the field. Other big barrier in developing countries for implementation of a service is the illogical social taboos and deeply rooted some poor cultural values. Educating the masses in general and woman in reproductive age group and pregnant women in particular may help greatly to overcome this kind of a barrier. Another barrier in acceptance is inaccessibility of the intervention either because of unavailability or non affordability. It may be overcome by making the intervention available close to the door steps of the target population.

---

![Figure 1](image-url) **Figure 1** Many steps involved in translating valid research in to practice
For that matter all health institutions including PHCS and dispensaries are to be well equipped with trained personal and adequate ANCS stocks that are available 24x7. Empowering midwives to provide ANCS for women in preterm labor would be a boon to the success of this programme.

**Identifying Target Population:** The target population of ANCS use is women at risk for preterm labour between 24 to 34 weeks of gestation. The major barrier to implementation of corticosteroid therapy is the difficulty of identifying women at risk of preterm delivery in time to administer corticosteroids. This requires effective and well-utilized antenatal services. Successful implementation of this intervention would involve: education of health-care providers regarding the identification of warning signs of a preterm birth; identification of women at risk, including effective antenatal screening for hypertension and proteinuria [pre-eclampsia is an important cause of preterm delivery in low-income countries] and providing information to pregnant women. The information to pregnant women would need to focus on early reporting to a health facility at the first signs of pregnancy complications such as preterm uterine contractions, preterm rupture of membranes and symptoms of pre-eclampsia.

**Doable intervention:** making Dexamethasone and Betamethasone and required disposables (syringe, needle, alcohol swabs) freely available at all health centers from primary to tertiary wherever pregnant women are likely to deliver. Health care providers then fill that this is an doable intervention.

**Which and what medicine to use:** Both Dexamethasone and Betamethasone are used worldwide for this purpose. Current evidence does not support clear cut superiority of one to the other in all the aspects. However WHO recommends Dexamethasone over Betamethasone for being less costly and for its easy availability in developing countries. Dexamethasone: 4 doses of 6 mg each administered 12 hrs apart, intramuscularly, is the current recommendation. At present administration of just one course of ANCS may be aimed at till robust evidence of effectiveness and adequate data on risk benefit ratio for repeated courses is available.

**Increasing recall rate:** This may be made possible by introducing a column in antenatal care checklist in the medical records of the woman attending outpatient departments for antenatal visits. Furthermore commonly used recall aids like posters and alerts may be used in health care facilities at important locations including Antenatal OPDs, labor rooms and emergency rooms for the same purpose.

**Making eligible patient agreeing to take ANCS:** Many of the times it is not the availability of intervention that is the limiting factor but the poor utilization of the intervention by the recipients for not being fully aware about the possible risks and actual benefits of the intervention. For that matter the administrators of the services may be fully trained in proper counseling and upgrading motivation skills so that the recipients don’t have unfounded fears and inappropriate apprehensions in utilizing the beneficial effects of ANCS administration.

**ANCS given to eligible pregnant women in preterm labor-Done:** For the ultimate success of an intervention, ensuring that the services are actually provided to the target population is of paramount importance. For that proper auditing system must be put in place. Proper record of all pregnant women, who are at the risk of preterm delivery, women who actually received the intervention, the missed out cases, availability and extent of utilization of stocks of steroids at health facilities etc may be the essential elements that can be audited for. Increase policy awareness and provider support to correctly administer ANCS: in the wealthy world, strong policy promotion and provider education was crucial to the adoption of ANCS. It is a key opportunity now for rapid adoption in the developing world as well.

**Key Strategies put in place by Govt of India**

**ANMs empowered to administer ANCS**

1. Pre-referral dose to a pregnant woman in preterm labour (24-34 weeks of gestation).
2. Complete the full course, in case the referral is delayed, refused, or referral is not possible.
3. Appropriate and timely referral of women in preterm labour to facilities with provision of C-section and SNCUs to promote adequate and quality care of pregnant women and newborn
4. All elective C-section or induction of labour in uncomplicated deliveries should be done at or after 39 weeks of gestation to ensure that the baby is mature and of normal weight

**Administration of ANCS is an integral part of comprehensive management of preterm labour**

1. Oral preparations are not to be used
2. Repeated courses /more frequent doses not useful
3. ANCS to be used even if surfactant therapy is available

**State Level Activities**

1. Ensure that all levels of both public and private health facilities use ANCS in preterm labour
2. Use of ANCS in the management of preterm labour is to be emphasized in Skilled Birth Attendant (SBA)/ BEmOC and CEmOC (Emergency Obstetrics Care) trainings
3. Orientation to focus on diagnosis of true preterm labour, indications/contraindications and safe injection practices
4. Ensure availability of Injection Dexamethasone in the ANMK it which is already an essential drug.
5. Establish robust referral linkages with tertiary level neonatal care simultaneously for critical care (ventilatory support) required by a preterm.

**Record keeping and reporting**

1. Facilities to carry out correct forecasting of the supplies and provide timely feed back to districts on the stock out situation
2. Quarterly data may be collected by the Block MO and from the districts compiled at the state level
3. Validation of record keeping of ANCS administration will be done from delivery room registers, case sheets, discharge tickets, referral registers.
References

1. United Nations (2015) Transforming our world: the 2030 agenda for sustainable development. New York, NY, USA: United Nations. Available at: http://tinyurl.com/od9mens. Accessed on 4th April 2017
2. Born too soon: The Global Action report on preterm Birth. March of Dimes, PMNCH, Save the Children, WHO, Publication May 2012. New York.
3. http://www.unicef.org/infobycountry/indiastatistics.html accessed 04th April 2017.
4. Multi-centric Home Based Intervention Project of the Indian Counsel of Medical Research [ICMR annual report 2005-2006]
5. National Institutes of Health. Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consensus Statement 1994; 12: 1–24.
6. Robert D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database of Systemic Reviews 2017, doi: 10.1002/14651858.CD004454.pub3.
7. Crowther CA, McKinlay CJ, Middleton P, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. Cochrane Database Syst Rev. 2011 Jun 15; (6):CD003935.
8. Brownfoot FC, Gagliardi DI, Bain E, Middleton P, Crowther CA. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2013 Aug 29; (8):CD006764.
9. Lawn J, Segrè J, Buekens P, et al. Antenatal Corticosteroids for the reduction of deaths in preterm babies. Prepared for the United Nations Commission on Live--Saving Commodities for Women and Children. March 2012.
10. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, Luptook AR, et al.. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010; 362 (21):1970-9.
11. Shinde S, Kabra NS, Sharma SR, Avasthi BS, Ahmed J. Glycerin suppository for promoting feeding tolerance in preterm very low birth weight neonates: a randomized controlled trial. Indian Pediatr. 2014; 51(5):367-70.
12. http://nrhm.gov.in/images/pdf/programmes/childhealth/guidelines/Operational_Guidelines-Use_of_Antenatal_Corticosteroids_in_Preterm_Labour.pdf. accessed 15th January 2017

How to cite this article:
Showkat Hussain Tali et al. 2017, Strategies to improve antenatal steroid usage in woman at risk of preterm labor in India. Int J Recent Sci Res. 8(3), pp. 16107-16111. DOI: http://dx.doi.org/10.24327/ijrsrc.2017.0803.0076

******