Review Article :

Role of Antenatal Corticosteroids in preterm deliveries

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Abstract:

Globally, preterm birth is a serious public health problem and is a leading cause of perinatal death and disability. Care provided to mother during antenatal period has a significant bearing on the new born survival.Antenatal corticosteroids are usedfor accelerating foetal lung maturation for women at risk of pre-term birthwhich results in decrease of neonatal morbidity and mortality. Antenatal corticosteroids are effective in reducing respiratory distress syndrome (RDS) and other complications of premature deliveries. Govt. of India is placing it's efforts to bring this intervention into focus and also to empower ANMs to give a pre-referral dose of Antenatal Corticosteroid to a pregnant women going in to preterm labour to improve its access.

Keywords: Corticosteroids, preterm birth, gestational age, RDS, IVH, NEC

Preterm births and it'sdemographics:

As per World Health Organization (WHO), a preterm baby is defined as a baby who is born alive before 37 weeks of pregnancy are completed. Common causes of preterm birth include infections,multiple pregnancies and chronic conditionssuch as diabetes and high blood pressure.However, the most common cause of death among preterm babies of less than 34 weeks is Respiratory Distress Syndrome (RDS).An estimated 15 million babies are born preterm every year worldwide.As per the India New born Action plan prematurity contributes to 35% of all neonatal deaths in India.[29]

Preterm new born are classified on the basis of completed gestation period as: Extremely Preterm – Less than 28 weeks; Very Preterm – 28 to less than 32 weeks; Moderate to Late Preterm – 32 to less than 37 weeks. The relative proportion of these groups is 5%, 10% and 85%, respectively. The mortality rate among preterm new born increases with decreasing gestational age. It may be noted that even the moderate and late preterm neonates have an increased mortality risk as compared to those born at term gestation. Preterm birth occurs most commonly in economically disadvantaged communities1 and those with high rates of urinary and genital tract infection.

As per 2015 WHO statistics the rate of preterm birth ranges from 5% to 18% across 184 countries. India has the highest number of preterm births as well as neonatal deaths due to prematurity. Out of an estimated 2.6 crore live births in India each year, 35 lakh babies are born preterm, and out of these, 3.03 lakh babies (10% approximately) die due to complications of preterm births. Preterm birth is a risk factor in at least 50% of all neonatal deaths and is the second most common cause of death (after pneumonia) among children under the age of five1

Corticosteroids and it'snoteworthiness:

Steroid administration is one of the important maternal interventions to reduce impact of preterm deliveries on new-born outcome. Other beneficial effects included a reduction in neonatal death, cerebroventricular haemorrhage, and necrotising enterocolitis.RDS which is a common cause of

death of preterm babies can be largely prevented by administering corticosteroids to the pregnant woman as soon as she is diagnosed with threatened preterm labour or to pregnant woman who are at increased risk of preterm delivery (26-34 weeks of gestation). Corticosteroids when administered to the pregnant woman antenatally cross the placenta and reach the foetal lung and stimulate surfactant synthesis and maturation of other systems. If this foetus is now delivered prematurely, neonate will have a low risk of developing RDS and, therefore, much higher chance of surviving with supportive care.[2]

Corticosteroid types and their comparison:

Currently either Betamethasone or Dexamethasone is the recommended corticosteroid regimen used in clinical practice.

Betamethasone is available in two different forms:

a) Betamethasone sodium phosphate, a solution with a short biological half-life of 36 to 72 hours

b) Betamethasone acetate, a suspension with a relatively long half-life.

These forms of betamethasone are often used in combination to maximize the drug's efficiency while reducing the number of injections given to the mother.

Dexamethasone generally comes in the form of Dexamethasone sodium phosphate, a solution with a short biological half-life of 36 to 72 hours. Both betamethasone and dexamethasone are able to cross the placenta in their active form and have comparable properties. The chemical composition of betamethasone and dexamethasone are virtually identical except for the configuration of a methyl group in position 16. Some dexamethasone preparations contain a sulphite preservative. Sulphites have been linked to neurotoxicity in the newborn especially when in combination with peroxy nitrite[3].

The indirect subgroup comparison of betamethasone and dexamethasone in the Cochrane review indicated similar short-term neonatal outcomes for both drugs. Maternal outcomes were also similar although the risk of puerperal sepsis was higher in the dexamethasone versus placebo or no treatment group, while betamethasone did not show an increase in puerperal sepsis over placebo or no treatment. The optimal type of corticosteroid to be used for prenatal treatment remains unclear.[3,5] At this moment the consensus of opinion is that both dexamethasone or betamethasone can be used depending upon availability.

Gestation age at administration:

The available data strongly support the administration of antenatal corticosteroids to pregnant women who are at increased risk of preterm delivery within the next seven days.

Before 22 weeks -- It is unlikely that administration of antenatal corticosteroids at ≤22 weeks of gestation would significantly improve lung function, as there are only a few primitive alveoli at this gestational age on which the drug can exert an effect.[22]

23 to 34 weeks-- A 2006 meta-analysis of randomized trials of antenatal corticosteroids in women at risk of preterm birth provided strong evidence that respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and neonatal death are significantly reduced when corticosteroids are given at 26 to 34 weeks of gestation.[23] The benefit of administering antenatal corticosteroids before 26 weeks of gestation was suggested by a 2011 prospective cohort study including over 10,000 infants born at 22 to 25 weeks of gestation. Compared to no exposure to antenatal steroids, the composite outcome 'death or neurodevelopmental impairment at 18 to 22 months of age' was significantly lower for steroid exposed fetuses. Corticosteroid exposed infants born at 23, 24, and 25 weeks of gestation also had significant reductions in the outcomes of death by

18 to 22 months; hospital death; death by intraventricular hemorrhage or periventricular leukomalacia; and death or necrotizing enterocolitis.[24]

After 34 weeks -- Whether there is a significant improvement in outcome following antenatal corticosteroid use after 34 weeks of gestation is unclear since the baseline risks of RDS, IVH, and neonatal mortality are already low at that time.[25]A Brazilian placebo-controlled randomized trial found no benefit from administration of a course of betamethasone to women at 34 to 36 weeks of gestation at risk of imminent premature delivery.[26] There are limited long-term follow-up data on neurologic outcomes in children exposed to antenatal steroids after 34 weeks of gestation.

The American College of Obstetricians and Gynaecologists (ACOG) has not recommended antenatal corticosteroids for gestations >34 weeks.[27] However, the Royal College of Obstetrics and Gynaecology (RCOG) guidelines recommend routine administration of antenatal glucocorticoids for all women undergoing elective caesarean delivery before 39 weeks of gestation.28The Child health division, Govt. of India recommended single course of injection of Dexamethasone to women with preterm labour between 24 and 34 weeks of gestation.[2]

Corticosteroid dose, timing, frequency:

Type : Betamethasone

Two doses of Betamethasone having quantity of 12mg should be given. There should be a gap of 24hrs between each dose. Route and preferable site of application should be Intramuscular and Antero Lateral aspect of thigh respectively.

Type : Dexamethasone

Four doses of Dexamethasone having quantity of 6mg should be given. There should be a gap of 12hrs between each dose. Route and preferable site of application should be Intramuscular and Antero Lateral aspect of thigh respectively.

Rescue/Salvage doses:

Patients who have received an initial course of antenatal corticosteroid but do not deliver within 7-14 days may receive one repeat corticosteroid course know as rescue course.

There is increasing data in recent times that the rescue approach might be both effective and safe. Vermillion and colleagues published a retrospective cohort study of 152 women at risk for preterm delivery, who received a corticosteroid course before 28 weeks. Outcomes were compared for women re-admitted for preterm labour after 28 weeks who received a single rescue dose (2nd dose) of corticosteroid versus those who did not. Rescue corticosteroid administration was significantly associated with a reduction in frequency of RDS as well as mean days of ventilator.[19]

More recently Garite and colleagues published the results of randomized trial with a rescue approach.

There was a significant reduction in the primary outcome of composite neonatal morbidity of < 34 weeks in the rescue steroid group when compared to placebo and significantly decreased respiratory distress syndrome, ventilator support, and surfactant use.Administration of a single rescue course of antenatal corticosteroid before 33 weeks improves neonatal outcome without apparent increased short-term risk.[20]

Efficacy of Antenatal corticosteroids:

Most recent Cochrane reviews included [21] trials of3885 patients and 4269 infants, provided evidence on the use of antenatal corticosteroids for reducing adverse neonatal outcomes associated with prematurity across different categories. This review includes trails that compared corticosteroid treatment with placebo in women expected to deliver between 24 and 37 weeks of gestation as a result of either spontaneous preterm labour, preterm premature rupture of membranes (PPROM) or elective preterm birth. Treatment with single course of antenatal corticosteroids decreased

the risk of neonatal deaths by 31%, the risk of RDS by 34%, IVH by 46%, NEC by 54% and infections in the first 48hrs by 44%. Need for respiratory support and admission to the neonatal intensive care unit were also reduced by corticosteroid therapy.[5]

Side effects:

When pregnant women took a single course of steroids, no adverse effects were observed in the newborns. Studies that followed the development of preterm babies into childhood or adulthood did not find any clear differences in growth and development between those who received steroids before birth and those who did not. Shortly after being born, children who had more than one course are somewhat smaller than children who only had one course. But they "catch up" in size within a few months. The studies did not find any evidence of long-term negative consequences.

Corticosteroids in special cases:

Mothers with Diabetes:Antenatal women with diabetes are at higher risk of experiencing various obstetric and medical complications. Foetal lung maturity is delayed in pregnancies where euglycemia is not achieved. These facts imply that ACS (Antenatal Corticosteroids) may be required to improve neonatal survival in preterm pregnancies complicated by diabetes.9Gestational diabetes is not considered a contraindication for ACS. In fact, women with gestational diabetes were more likely (odds ratio 1.21; 95% confidence interval 1.05-1.40) to receive ACS in a study conducted in British Columbia, Canada.[10]

Hypertension and Pre-eclampsia are not a contradiction for administration of antenatal corticosteroid in pregnant women.[7]

Mothers with twins and triplet pregnancies:

Patients with multiple gestations are at significant higher risk of delivering preterm. Some of the reasons for preterm in these cases are higher rates of obstetrical complications such as preterm labour and preterm rupture of membranes, and the increased incidence of maternal complications such as preeclampsia. It has been observed twin and triplet gestations exposed to antenatal corticosteroids has reduced risk of RDS. It is also found that plurality is an effect modifier.[11]

There may be physiological reasons for the diminished effectiveness of antenatal corticosteroids in multiple gestations. Larger volume of distribution in the maternal and fosetal compartments in multiple gestations would have dilution effect on the concentrations of drug reaching the foetuses.[8]

However, one study has shown that volume of distribution was actually same between singleton and twin pregnancies.[18]

Recently a study has shown that in patients receiving multiple courses of antenatal corticosteroids who delivered within one week, maternal and umbilical cord serum betamethasone concentrations at delivery did not differ between singleton and twin gestations, which suggests that an apparent decrease in effectiveness of steroids in twin pregnancies is not due to inadequate foetal drug levels.[19]As on today there is no consensual recommendation for the dose of ANC in multiple gestations. So it should be administered as per the schedule of singleton pregnancy

Mothers with Tuberculosis:

Caution should be exercised when giving corticosteroid therapy to women with systemic infection including tuberculosis

Corticosteroids suppress the immune system, so there is a risk that their use may activate latent infections or exacerbate fungal infections. In a woman with systemic infection, it may theoretically suppress the immune response to infection. However there is no evidence to suggest that a single course of corticosteroids would have a profound effect in women with systemic infection, however extra care should be taken in its use.[14]

Mothers with preterm premature rupture of membranes (PPROM):

Data from Cochrane review demonstrates reduction in neonatal deaths, RDS, IVH and NEC in the subgroup of infants whose mothers received antenatal corticosteroids for preterm premature rupture of membranes.[5] There is no increase in maternal or neonatal infection in this setting. However concern remains about the use of corticosteroids in this population, because of increased risk of chorioamnionitis and the strong association between clinical chorioamnionitis and cystic periventricular leukomalacia as well as cerebral palsy. Infection and inflammation are believed to be important pathophysiological factors. It is recommended that delivery not be delayed in the setting of clinical chorioamnionitis for administration of antenatal corticosteroids.[21] But evidence overall supports administration of antenatal corticosteroids for patients with PPROM up to 32-34 weeks in absence of overt infection.

Activities at national level:

In 2013, as a part of Indian government initiative (India New-born Action Plan-INAP) Auxiliary Nurse Midwives (ANMs) are authorized to administer pre-referral dose of antenatal corticosteroids (ANCS) to women in preterm labour, improving the chances of survival of premature babies.

India has set a target to bring Neonatal Mortality RateandStill Birth Ratestobelow 10(per 1000 live births) by the year 2030. As part of INAP (India New Born Action Plan) Antenatal corticosteroid administration is one of the coverage target, to achieve impact targets. As per this plan the coverage of women with preterm labour receiving at least one dose of antenatal corticosteroids should be 75% by 2017, 90% by 2020, 95% by 2025 and 100% by 2030.[16]

Conclusion:

Neonatal deaths due to prematurity has reduced dramatically in last couple of decades. This is largely due to better neonatal care, availability of surfactants and more than that the antenatal administration of corticosteroids. Awareness among paramedical staff about antenatal corticosteroids administration at village level will further reduce the neonatal mortality in India.The studies are being carried out on the benefits and risks of repeated courses of corticosteroid therapy, the optimal drug, doses, route of administration, dosage to mothers with multiple gestations.At the moment carry home message is to give steroids to all mothers in preterm labour or threatened preterm labour unless there is specific contraindication.

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