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Should antenatal corticosteroids be done after 34 weeks of gestation? Review article

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ABSTRACT

Late preterm infants constitute the majority of preterm labors. The neonatal morbidity and mortality among late preterm infants are serious problems of obstetrical practice. This arises the question of antenatal corticosteroid administration beyond 34 week of gestation. In this review, need for antenatal corticosteroids after 34 weeks of gestation is studied.

Key Words: Antenatal corticosteroids, 34 weeks of gestation

Introduction

Labor before 37 weeks of gestation defined as preterm birth is the main determinant of postnatal mortality and morbidity (1). Preterm labors constitute 11% of all labors and cause two thirds of infant mortalities in USA (2). Medical interventions for obstetric causes (preeclampsia, eclampsia, preterm rupture of membranes, intrauterine growth restriction) led to increase in preterm labors.

The use of antenatal corticosteroids in management of preterm labor came into obstetrical practice by the paper reported by Liggins and Howie in which reduction in the incidence and severity of respiratory distress syndrome (RDS) and mortality in offspring have been shown (3). Antenatal corticosteroids usage unprecedentedly promotes survival of preterm infants by reducing the risks of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC) and systemic infections without adverse effects in adulthood (4,5).

The use of antenatal corticosteroid is recommended in women at risk of preterm labor within 7 days between 24 and 34 weeks of gestation (4). The use of antenatal steroids beyond 34 weeks of gestation is an area of conflict. In this review literature on this issue is evaluated.

Action and usage of antenatal corticosteroids: The development of type 1 and type 2 pneumocytes is stimulated by antenatal corticosteroids leading to increase in maximal lung volume, compliance and gas exchange (6-10). Increase in production of surfactant proteins and phospholipid synthesis enzymes cause type 2 pneumocytes to produce more surfactant. Not only the endogenous surfactant but also the neonatal response to postnatal exogenous surfactant is increased by antenatal corticosteroids. Antenatal corticosteroids also induce pulmonary beta receptors (increase surfactant release and absorption of alveolar fluid) (7), fetal lung antioxidant enzymes (11), up regulates gene expression of epithelial sodium channels (important for lung fluid absorption) (12).

The drugs of choices in antenatal corticosteroid use are betamethasone and dexamethasone. Cochrane review of 12 trials in 2013 revealed no statistical differences between dexamethasone and betamethasone for RDS or neonatal death (13).

Betamethasone is given in two doses of 12 mg intramuscularly 24 hours apart or Dexamethasone is given in four doses of 6 mg intramuscularly 12 hours apart (14-17).

Timing of antenatal corticosteroids: After the second dose of antenatal corticosteroids, maximum benefit is achieved in between 24 hours to 7 days. The beneficial effects begin within few hours of administration. Single dose given infants (born before the second dose) had better outcomes than ones who did not receive antenatal corticosteroids (18). All women at high risk for preterm labor should take antenatal corticosteroids if birth is not expected within one or two hours (19).

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Antenatal corticosteroid administration is recommended in pregnant who are at risk of preterm labor at 24 to 34 weeks (4). Since there are few primitive alveoli antenatal corticosteroids before 22 weeks of gestation has limited beneficial effect on lung function (20). For this reason in 22 week antenatal corticosteroids should be given if delivery is expected after 23 weeks of gestation (21).

Discussion

Antenatal corticosteroids after 34 weeks: Infants born between 34-37 weeks can be defined as late preterm. Late preterm infants constitutes majority of preterm labors and they were thought to be mature as term infants but it is known that high morbidity and mortality risk is present (22-29). For reduction of high mortality and morbidity among late preterm infants corticosteroid administration can be considered.

In the study conducted by Shanks et al. (30) women with singleton gestations between $34^{0/7}$-$36^{6/7}$ weeks with an immature TDx-FLM-II test (<45 mg/g) after a clinically indicated amniocentesis to test for fetal lung maturity were participated. Ten women had antenatal corticosteroids 15 women did not receive any drugs. Although the study was stopped due to difficulty in patient recruitment, no statistical improvement in neonatal morbidities were reported. Tdx-FLM-II test is a way of fluorescence polarization for assessment of surfactant levels. The study revealed a statistically significant increase in between Tdx_FLM-II tests results after one week of corticosteroid administration in treatment group compared with non-treatment group. Since this study had a low number of participants, it is limited to show effect of antenatal corticosteroids in late preterm labors.

In a similar study retrospective cohort of pregnant women who underwent amniocentesis to determine fetal lung maturation at 34-37 weeks was studied. Tdx-FLM-II test result lower than 50 mg/g was accepted as an immature test. Treatment group was given two dose of betamethasone 12 mg 24 hours apart, control group did not take any medications. The neonatal outcomes such as RDS, transient tachypnea of newborn (TTN), need for admission to neonatal intensive care unit (NICU), hypoglycemia, hyperbilirubinemia requiring treatment, sepsis and length of hospital stay were recorded. Composite respiratory morbidity (RDS, TTN or need for respiratory support) was defined as primary outcome. The rate of the composite respiratory morbidity outcome was significantly higher in the non-treatment group compared with patients who received corticosteroid therapy (21% vs 8.4%, respectively; P .02). Significantly in non-treatment group more infants required respiratory support. The two groups did not differ significantly with regard to the rates of RDS, TTN, hypoglycemia, and hyperbilirubinemia (31).

In a well-designed trial, effect of corticosteroids in between $34^{0/7}$-$36^{6/7}$ weeks of gestation was studied. The study is carried as a randomized, triple blind, placebo controlled clinical trial. Sample size was calculated as 80% power to detect a reduction of 50% in rate of respiratory disorders with the use of corticosteroids. Treatment group received standard dose of betamethasone and control group received placebo. In both groups low rates of RDS and high rates of TTN was found. The treatment with corticosteroids failed to reduce the risk of any respiratory morbidity. A further analysis was performed to detect any differences in the effect of corticosteroids by gestational age (34, 35, 36 weeks and more). By adjusting results in respect to gestational week, no significant differences between groups were reported. Only the rate of jaundice requiring phototherapy was lower in babies whose mother received antenatal corticosteroids (32).

In a retrospective study, three groups were analyzed; the study group included neonates born to women between $34^{0/7}$ and $38^{6/7}$ weeks of gestation who received antenatal corticosteroids after an amniocentesis with immature fetal lung indices and delivered within 1 week. The reference group included neonates born between $34^{0/7}$ and $38^{6/7}$ weeks of gestation whose mothers had an amniocentesis with mature fetal lung indices and also collected data on a second reference group of neonates, whose mothers were managed expectantly after an amniocentesis performed with immature fetal lung indices. Administration of antenatal corticosteroids did not reduce respiratory morbidity in newborns born after 34 weeks of gestation (33).

The antenatal steroids for term caesarean section (ASTECS) trial studied 998 women who had a planned cesarean delivery after 37 weeks of gestation. One group received antenatal corticosteroids the other group received no treatment. Respiratory problems were found to be low in neonates treated with antenatal corticosteroids (34). Similarly the Royal College of Obstetrics and Gynecology (RCOG) recommend antenatal corticosteroids for women at risk of

preterm labor up to $34^{6/7}$ and women who will undergo elective cesarean section up to $38^{6/7}$weeks of gestation (35).

Results

As a conclusion, administration of antenatal corticosteroids beyond 34 weeks of gestation is still controversial and prospective randomized trials are needed to enlighten this conflicted area of antenatal care.

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