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Mini Review

The Role of Antenatal Corticosteroid Administration in Lung Maturation in Anticipated Preterm Delivery

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Received: August 19, 2022; **Published:** August 23, 2022

Abstract

Preterm delivery is associated with complications in neonates, with respiratory distress syndrome being the most common. A review of published literature is provided regarding the positive effects of antenatal steroids when preterm delivery is anticipated. Recent bibliography on large cohorts of neonates was studied. Pubmed reference lists were searched using combination of the following terms: "antenatal corticosteroids", "corticosteroids and preterm delivery" and "prematurity and antenatal corticosteroids". Overall benefit in terms of neonatal outcomes has been proven, including lung function and cardiovascular health. Antenatal corticosteroid administration is beneficial when preterm delivery is anticipated, particularly when administered between 24 - 34 gestational weeks.

Keywords: *Antenatal Care; Corticosteroids; Preterm Birth; Respiratory Distress Syndrome; Betamethasone; Neonate*

Introduction

Preterm delivery, defined as delivery before 37 gestational weeks, is the most important determinant of adverse outcomes in newborns. Among them, respiratory distress syndrome (RDS) is one of the most important causes of morbidity and mortality. Other complications include intraventricular haemorrhage (IVH) and long-term neurodevelopmental deficits. A higher risk of RDS and mortality has been associated with premature birth particularly prior to 32 weeks' gestation [1].

Antenatal corticosteroid (ACS) administration represents one of the most substantial interventions in order to decrease the incidence of pulmonary immaturity. Glucocorticoids activate fetal pulmonary beta-receptors and promote surfactant production and pulmonary maturation. They improve maximal lung volume and compliance through accelerating the development of type 1 and type 2 pneumocytes, as well as gas exchange [2]. Reduced cerebral palsy and severe disability rates have also been described in children exposed to corticosteroids. Hence, it has been established that administration of ACS results in reduced neonatal morbidity and mortality.

The current article presents data on the benefits of ACS administration in anticipated preterm delivery (PTD) from experts in the field. Specifically, information on the efficacy and safety of corticosteroid administration during antenatal period when preterm delivery is anticipated is provided, and recent recommendations on the issue are summarized.

Timing of ACS administration

24 - 34 gestational weeks

Based on the universal consensus, antenatal administration of corticosteroids is recommended for fetal lung maturation in cases of anticipated PTD during the next seven days [3]. According to the updated Cochrane review conducted in 2017, including 30 randomised controlled studies of a total of 7,774 women and 8,158 infants, ACS was associated with a reduction in complications during the first 48 hours of life, such as perinatal death, infections, RDS, IVH and necrotizing enterocolitis (NEC) [4]. Whereas it is made clear that ACS administration between 24 and 34 weeks is substantial, the debate remains when it comes to neonates born before 25 weeks' gestation, known as very early preterm neonates, between 34 and 37 weeks, known as late preterm neonates and after 37 weeks, known as term neonates.

Periviable antenatal period (< 24 weeks of gestation)

According to several guidelines released between 2014 and 2017, the administration of corticosteroids is recommended between 22^{+0}-23^{+6} gestational weeks if PTD is expected within the next seven days. Favourable outcomes of ACS administration after 23 weeks' gestation in mortality and neurodevelopmental impairment of the offspring at 18 - 22 months of age have been reported by Carlo., *et al*. as well as a reduction in the risk for periventricular leukomalacia, intraventricular haemorrhage and necrotising enterocolitis [5]. Overall survival, but not fetal lung function, may also be improved by ACS administration before 22 weeks of gestation [6]. However, it is worth mentioning guidelines from two important Societies; NICE guidelines that state that ACS should be considered at 23^{+0} to 23^{+6} gestational weeks and the SOGC guidelines that state that ACS should be administered at 22^{+0} to 23^{+6} weeks [7].

Late preterm neonates (34 - 37 gestational weeks)

Regarding late preterm neonates, born between 34 and 37 weeks' gestation, the Antenatal Late Preterm Steroids study demonstrates that two 12 mg doses injected intramuscularly within 24 hours reduced the risk for stillbirth, neonatal death within 3 days of delivery and the need for respiratory support during the first 3 days after birth [8]. Nonetheless, neonatal hypoglycaemia occurred more frequently after ACS administration [8]. Hence, ACS should be considered with caution between 34^{+0} and 36^{+6} gestational weeks. However different recommendations vary slightly; the ACOG suggests ACS between 34^{+0} and 36^{+6} weeks at risk of preterm delivery within 7 days, if a previous course of ACS has not been administered and the SOGC states that ACS administration should be considered between 35^{+0} and 36^{+6} weeks [7].

Early term neonates

Neonates born at 37 weeks' gestation or beyond by elective caesarean section, showed lower rates of admission to NICU for respiratory distress when betamethasone was administered within 48 hours from delivery [9]. Therefore, ACS has been proven beneficial at all time points.

However, a counterargument has been presented by Skoll., *et al*. who advocate to not treat with ACS in the presence of regular contractions without cervical change or a short cervical length without regular contractions [7].

Drugs

Betamethasone and dexamethasone have been shown to have similar effect on lung maturation [4]. However, betamethasone administration resulted in a greater reduction in chorioamnionitis and RDS rates compared to dexamethasone according to Roberts., *et al* [4]. In contrast, the risk of IVH was lower and the length of NICU stay was shorter in neonates treated with dexamethasone in a study by Brownfoot., *et al* [10].

Intramuscular administration of betamethasone and dexamethasone is recommended for lung maturation at a total dose of 24 mg in

divided doses: either 2 doses of betamethasone 24 hours apart or 4 doses of dexamethasone [7].

The maximum effect of corticosteroids on neonates is observed when the first dose is administered 48 hours to one week prior to delivery, according to Dagklis., *et al*. [2], or one to seven days prior to delivery according to a meta-analysis [11]. In contrast, ACS administration less than 24 hours before delivery shows no favourable outcome [11]. Furthermore, reduced rates of perinatal mortality, RDS and IVH have been associated with repeated ACS courses, however they are not universally recommended due to potential reduction in mean birthweight and severe neuromotor, neurosensory or neurocognitive disability or death [12]. In addition, a Finnish prospective study also showed that repeat ACS exposure resulted in reduced birth weight in preterm neonates, born between 30 and 34 weeks' gestation), near term neonates, born between 35 and 37 weeks' gestation or full term neonates [13]. Therefore, most guidelines suggest a single repeat course of ACS in pregnancies threatened by preterm labor before 34 gestational weeks if seven days have passed from the prior dose.

Multiple gestation

Preterm delivery and complications are common in twin pregnancies. Although it has been proposed that ACS metabolism may be different in the presence of two fetoplacental units and that similar betamethasone serum concentrations in twins are probably achieved with three, instead of two, betamethasone doses of 12 mg, 18 hours apart [14], the cord blood levels of steroids in multiple gestations have been found similar to those seen in singleton pregnancies [2]. In addition, ACS therapy has been shown to have no significant effect on RDS, perinatal death, IVH, chorioamnionitis or birth weight in multiple gestations [4]. Hence, ACS should be administered in the same dosage in multiple gestation and singleton pregnancies. It is also worth adding that the WHO, ACOG and SOGC recommend that ACS therapy is recommended when PTD is anticipated in both single and multiple gestations, whereas NICE makes no recommendation for multiple gestations.

PPROM (Preterm prelabor rupture of membranes)

In case of PPROM and no clinical signs of infection, ACS administration reduces neonatal mortality, RDS, IVH and NEC. In the case of women with PPROM and chorioamnionitis, ACS also reduce the rates of neonatal mortality. Therefore, all the guidelines recommend ACS for fetal lung maturation [3].

An important parameter to be considered is that although repeat prenatal corticosteroid doses are beneficial to neonatal lung function and cardiovascular system, they may have negative effects on the mother, including risk of infection and suppression of the hypothalamic-pituitary-adrenal axis. In addition, corticosteroids inhibit cell growth and DNA replication in humans, whereas in animals they inhibit fetal growth and increase fetal blood pressure [15]. Myelination of the nervous system and alveolar septa formation may also be affected in animals [16].

Conclusion

The role of ACS in anticipated preterm delivery has thoroughly been investigated. The present article contributes to enhancing our understanding of the role of corticosteroid administration, which according to the most recent recommendations demonstrates overall benefit in terms of neonatal outcomes.

Conflict of Interest

The author declares no financial interest or any conflict of interest.

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Volume 11 Issue 9 September 2022