Review Article

Antenatal Corticosteroids for Women at Risk of Preterm Labor - A Review

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ABSTRACT

Preterm is one of the leading cause of perinatal mortality and morbidity. As per estimates from World Health Organization (WHO), premature birth is one of the leading underlying cause of death in children under 5 years and over one million babies are dying each year worldwide due to complications of preterm birth. One of the mostcommon cause of deaths among preterm babies is respiratory distress syndrome (RDS). WHO has recommended the use of antenatal corticosteroids in the prevention of RDS and mortality in preterm new borns. Preterm infants often require respiratory support inthe form of prolonged oxygen support and positive pressure ventilation. There is an increased risk of hospitalizations in infants who are born preterm. The emotional as well as the personal costs for affected individuals and their families are high. Thus, preterm infants and preterm birth continue to remain a significant health issue worldwide. Most commonly used corticosteroids in pregnancies are prednisolone, betamethasone and dexamethasone. In this review the need for antenatal corticosteroids for women at risk of preterm labor is studied including their safety and efficacy. It is concluded that corticosteroids are used for more than three decades to accelerate lung maturation in antenatal treatment, and up to 34 weeks of pregnancies its effectiveness and safety is well established. However, administration of antenatal corticosteroids beyond 34 weeks of gestation is still controversial and prospective randomized trials are needed to illuminate this squabble area of antenatal care.

Keywords: Antenatal corticosteroids, Preterm labor, Respiratory distress syndrome.

INTRODUCTION

Preterm birth is defined as labor before 37 weeks of gestation[1] and is one of the leading cause of perinatal morbidity and mortality[2]. As per 2010 estimates, nearly 14.9 million neonates were born preterm which accounts for 11.1% of live births worldwide[3]. Majority of all the preterm births occur in the late preterm period (34 to <37 weeks). For example, in USA more than 70% of preterm births in 2014 were born in the late preterm period[4].It is estimated that more than 60% of the world's preterm births occur in South Asian and sub-Saharan African countries [3].

The risk factors for preterm birth can be previous history of preterm labor, multiple pregnancies, bacterial vaginosis, uterine over distension and anomalies, bleeding in early pregnancy, cervical incompetence, poor socio-economic status, elderly and adolescent age group and tobacco use[5].

As per estimates from World Health Organization (WHO), premature birth is one of the leading underlying cause of death in children under 5 years and over one million babies are dying each year worldwide due to complications of preterm birth.[link].

The preterm birth incidence is not equally distributed across all the gestational ages. Only 5% of preterm births occur at less than 28 weeks of gestation, nearly 15% at 28 to 31 weeks, 20% at 32 to 33 weeks of gestation and 60% to 70% at 34 to 36 weeks of gestation and these may vary depending upon the geographical location[7].

One of the most common cause of deaths among preterm babies is respiratory distress syndrome (RDS). RDS is an acute lung disease that occurs in newborn premature infants and is characterized by deficiency of surfactant coating the inner surface of lungs and is related to immaturity of the lungs[8]. Preterm infants often require respiratory support in the form of prolonged oxygen support and positive pressure ventilation. Some have intraventricular haemorrhages and associated "white matter brain injury", bronchopulmonary dysplasia, and severe retinopathy of prematurity and all these contribute significantly to adverse neurodevelopmental outcome in later life[9, 10]. There is an increased risk of hospitalizations in infants who are born preterm. The emotional as well as the personal costs for affected individuals and their families are high. Thus, preterm infants and preterm birth continue to remain a significant health issue worldwide[1].

WHO has recommended the use of antenatal corticosteroids (ACS) in the prevention of RDS and mortality in preterm new borns[11]. In obstetrics for pregnancies, antenatal glucocorticoids are widely used for those at risk for early preterm labor. However, the use of antenatal glucocorticoids has increased especially after a consensus conference held by the National Institutes of Health in 1994 and it concluded that there was strong

evidence that glucocorticoids could reduce adverse neonatal outcomes, including death, RDS, and other complications, when it is administered to women who are likely to deliver before 34 weeks of gestational period[12-14].

But this recommendation was not extended to women who are at risk of late preterm birth due to lack of data[15-16]. Infants who are born during the late preterm period (34 weeks 0 days to 36weeks 6 days) have more neonatal and childhood complications when compared with newborns who are born at term (37 weeks or later)[17-19]. But less attention has been paid to the outcome of neonates who were delivered outside the 24 week to 34 week window and especially among those who were delivered at term[15].

One of the major challenges faced by the physician managing a pregnancy which is at risk to deliver preterm is that the precise timing of delivery is often unknown, especially in cases of preterm premature rupture of membranes or preterm labor, the timing of delivery is often outside the control of the physician. In case of indicated preterm delivery, that is, for severe eclampsia or preeclampsia, progression of the disease may require delivery before attaining 24 hours of corticosteroid use. About half of women in preterm labor who appear to be at risk of imminent delivery may go on to deliver at term. All these conditions leads to a considerable number of neonates born outside the ideal window for corticosteroid delivery[20,21].

Eventhough the evidence of benefit for the use of ACS has been available for many years[22,23], widespread adoption of this treatment into routine clinical practice was significantly delayed and implementation of their use remained suboptimal in developed countries for many years[24]. However, there is limited information on how well this practice has been implemented in developing countries[25].

Action and Usage of Corticosteroids

In pregnancy, the three most commonly used corticosteroids are prednisolone, betamethasone and dexamethasone.

The target organ of antenatal corticosteroids (ACS) when given to women at risk of preterm labor is immature fetal lung. The most important effect of ACS is stimulation of pulmonary surfactant. Also, ACS can alter lung fluid absorption and alveolar development by inducing genes associated with the synthesis of surfactant proteins, the membrane protein sodium/potassium ATPase, the epithelial sodium channel, and fatty acid syntheses[26,27]. The enhancement of all these mechanisms causes an accelerated maturation of the fetal lung and thereby reduces the severity of RDS in the first few days after a preterm birth.[28]

Most commonly used oral corticosteroid in pregnancy is prednisolone with multiple formulations available. It is mainly used for treatment of autoimmune conditions and for immunosuppression[29]. Prednisolone is a pharmacologically active synthetic steroid and it undergoes reversible metabolism to prednisone. Prednisone is both the inactive metabolite and the prodrug of prednisolone. Both prednisone and prednisolone are rapidly absorbed after oral administration with peak plasma concentrations between 1 to 3 hours[30]. Prednisolone binds to albumin and transcortin and slightly to alpha 1-acid glycoprotein, in plasma[29]. Prednisone and prednisoloneare cleared from the body primarily by hepatic metabolism, however the renal tissue may also contribute to metabolism[30].

In case of healthy pregnant women taking prednisolone, prednisolone concentrations in fetus are 8 to 10 fold lower than those found in the mother[31]. Prednisolone is lipophilic, so it can easily cross the placenta[32].

Dexamethasone and betamethasone are synthetic corticosteroids, have a similar molecular structure and have an ability to cross the human placenta from mother to fetus[33]. The total recommended treatment dose for betamethasone in anticipated preterm birth is 24 mg[12]. Betamethasone is administered as two 12 mg intramuscular injections ofa 1:1 preparation of betamethasone acetate and betamethasonephosphate, and is given 24 hours apart[12, 34]. Even though use of lower doses of the acetate form has also been reported, dexamethasone is usually prescribed as dexamethasone sodium phosphate[35, 36, 37, 38]. Dexamethasoneis given in four doses of 6 mg im 12 hours apart [36].

Candidates for Antenatal Corticosteroid Therapy

- Indicated to all women at high risk of preterm delivery between 24 and 34 weeks of gestation.
- Also indicated for women over 34 weeks of gestation when there is evidence of pulmonary immaturity[15].

Timing of Corticosteroids Use

For women at risk of preterm labor, a single course of antenatal corticosteroids has been identified as a highly effective and safe intervention to reduce neonatal morbidity and mortality[15, 23].

Antenatal corticosteroid administration is usually recommended in pregnant women at 24 to 34 weeks of gestation for those at risk of preterm labor[15]. All pregnant women who are at high risk for preterm labor should receive antenatal corticosteroids, if birth is not expected within 1 or 2 hours[24]. Antenatal corticosteroids administered within 24 hours to 7 days before extremely preterm birth was found to be associated with significantly higher survival when compared to those exposed to antenatal corticosteroids at shorter or longer administration to birth intervals[39].

The use of antenatal corticosteroids before 22 weeks of gestation has limited beneficial effect on lung maturation[40]. Due to this reason, if delivery is expected

after 23 weeks of gestation, antenatal corticosteroids should be given in 22 weeks of gestation.[41].

In case of late preterm infants (infants born between 34 to 37 weeks of gestation) also corticosteroid administration can be considered for the reduction of high mortality and morbidity. However, most of the studies show that in case of newborns born after 34 weeks of gestation, administration of antenatal corticosteroids did not reduce respiratory morbidity[42-45].

Risk factors associated with antenatal corticosteroid use

No serious side effects have been reported after administration of corticosteroids during pregnancy however, some studies reported reduction in fetal breathing movements, fetal body movements and heart rate variation after betamethasone administration[46,47]. These effects are found to be more obvious with betamethasone than dexamethasone. However, the repeated courses of steroids have been associated with increased risk of fetal growth restriction[48].

The most commonly observed side effect is the induction of hyperglycaemia due to increased insulin resistance[49,50]. This may increase the risk of neonatal hypoglycaemia and hyperbilirubinaemia if this hyperglycaemia occurs close to delivery[51].

Sometimes in women with Type 1 or Type 2 diabetes mellitus and gestational diabetes, diabetes ketoacidosis may be precipitated by corticosteroid administration[52,53].

The evaluation of fetal well-being after maternal corticosteroid administration with Doppler examination of blood flow velocity waveforms is therefore essential to investigate the fetal hemodynamic effects of exogenous corticosteroids[35,54]. A single course of ACS is not associated with any significant short-term fetal or neonatal adverse effects[15].

In 1951 there was a finding that treatment of pregnant mice with corticosteroids caused cleft palate in the offspring[55]. There were concerns that corticosteroids could lead to more severe adverse pregnancy outcome, mainly because corticosteroids affect almost every cells in the body[56] and also because of the higher potency of the synthetic corticosteroids[57].

Active tuberculosis has been suggested as a potential contraindication for ACS treatment, although there is no evidence for this. Clearly this will not be a common problem in developed countries when compared to developing countries, where ACS administration is still a rare practice[58].

Topical corticosteroids are assumed to be safer when compared to systemic corticosteroids[59].

Contraindications to the Administration of ACS

- Therapy is contraindicated in case of maternal systemic infections including tuberculosis.
- Caution is advised in women with chorioamnionitis.[15].

DISCUSSION

Preterm birth is the leading cause of neonatal morbidity and mortality in both high and low income countries[13].

Pregnant women who are at risk of preterm birth continue to be a major clinical obstetrical issue. So a single course of ACS remains the standard of care in this clinical setting to optimize fetal lung maturity[48].

The use of ACS is associated with decreased neonatal morbidity and mortality among preterm infants[60].

In a prospective study by Colm PT et al., they found that infants exposed to antenatal corticosteroids (n=81 832), at each gestation 29 weeks or less, 31 weeks, and 33-34 weeks had a significantly lower rate of severe intracranial haemorrhage, bronchopulmonary dysplasia, severe retinopathy, necrotizing enterocolitis or death compared with infants without exposure[61].

In an audit across four South East Asian countries by Pattanittum P et al., they found that antenatal corticosteroids given to women prior to preterm birth had significant health benefits for their babies[62]

In 2016, Berrueta M. et al., conducted a study to assess the rates of ACS use at all levels of health care in low and middle income countries. They found that in hospitals with maternal and neonatal care capabilities meeting the WHO preterm guidelines criteria, ACS use is likely to be lower than expected[63].

In a review by Judith MK et al., they concluded that antenatal steroid treatment was associated with reductions in neonatal mortality and mortality in very preterm babies, yet remains at low coverage in low/middle-income countries[64].

Though the efficacy of ACS to improve outcomes after preterm birth may be established for singleton infants, there remain questions about efficacy in specific patient populations such as multiple gestations, pregnancies complicated by intrauterine growth restrictions, very early preterm and late preterm pregnancies[58].

Also, there is still uncertainty remaining about the length of corticosteroid effectiveness and the need for repeat or rescue courses (Patients who have received an initial course of ACS but do not deliver within 7 to 14 days may receive one repeat corticosteroid course known as the “rescue” course) [58].

However, in a randomized triple blind clinical trial by Porto AM et al., (2011) they found that ACS at 34-36 weeks of pregnancy does not reduce the incidence of RDS in newborn infants[65].

But in the randomized, multicenter trial conducted by Gyamfi BC et al., (2016) they found that antenatal administration of betamethasone to women at risk for late preterm delivery decreased the need for substantial

respiratory support during the first 72 hours after birth. Betamethasone administration also resulted in reduced rates of severe respiratory complications, bronchopulmonary dysplasia, and transient tachypnea of the newborn infants along with reduced rates of surfactant use, resuscitation, and a prolonged stay in a special care nursery[51].

Also, in the systematic review with meta-analysis by Saccone G. et al., they concluded that a single course of corticosteroids; either dexamethasone or betamethasone, should be considered for women at risk of imminent late premature delivery at 34-36 weeks' gestation and for women undergoingplanned cesarean at 37 or more weeks' gestation[66]. Also, in a multicentric pragmatic randomized trial by Stutchfield P. et al., (2005), they found that antenatal betamethasone is effective in reducing admission to special care baby unit with respiratory distress after elective caesarean section at term[67].

CONCLUSION

Up to 34 weeks of pregnancies effectiveness and safety is well established for Antenatal treatment with corticosteroids and it has been used to accelerate lung maturation for more than three decades [15,22,23]. But qualms remains about the duration of corticosteroid administration and need for repeat doses[58]. A single course of antenatal corticosteroids in 24 to 34 weeks of gestation has been identified as a highly effective and safe intervention to reduce neonatal morbidity and mortality[40]. However, 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[40].

Also further studies are required on optimal corticosteroid to use, the optimal dose to delivery interval, long term effects into adulthood, effects in multiple pregnancies, effects in groups not well studied, including those who previously had received a course of corticosteroids and women with pregestational diabetes[66].

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