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Review

50 YEARS OF ANTENATAL CORTICOSTEROIDS: A SYSTEMATIC REVIEW

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Summary

The administration of antenatal corticosteroids (ACS) to accelerate fetal lung maturation is considered one of the most valuable antenatal therapies in preterm labour. Although early indications that administering antenatal corticosteroids has a positive impact on fetal lung maturation and despite the widespread recommendations to use this treatment in women at risk of preterm birth, there is still some uncertainty regarding its effectiveness, particularly in lower-resource settings and in high-risk groups such as women with hypertension or multiple pregnancies. The optimal timing of administration has not improved in over 50 years. This assessment aimed to evaluate the effects of administering a course of corticosteroids to women before anticipated preterm birth (before 37 weeks of pregnancy) on fetal and neonatal morbidity and mortality, maternal mortality and morbidity, and the child's health later in life. It is advised that clinicians only administer a single course of ACS in high-risk cases of preterm birth likely to occur within the next seven days, and the gestational age is between 22+0 and 33+6 weeks. The diagnosis of preterm labour should be made based on available resources and expertise and supported by comprehensive protocols in the relevant setting.
Keywords: antenatal corticosteroids, fetal lung maturation, preterm birth, steroids

Introduction

Preterm neonates have complicated medical issues associated with an elevated risk of complications proportionate to an earlier birth. It is important to note that preterm birth is a risk factor in around 50% of all neonatal deaths [1]. Hence, early diagnosis and appropriate intervention are crucial for improving newborn outcomes, preventing mortality and reducing morbidity associated with preterm birth.

As mentioned above, preterm birth can result in various problems and long-term loss of human potential among survivors. Among these, respiratory distress syndrome, a severe complication due to immaturity of fetal lungs, is the primary cause of early neonatal mortality

and morbidity for the fetus in preterm labour [2]. Approximately 50% of premature neonates born before 28 weeks, and around 30% of premature neonates born before 32 weeks, have respiratory difficulties, and a vast majority of these premature neonates do not survive infancy [3]. Surviving neonates may become disabled and fail to thrive due to the hypoxia experienced at birth.

The administration of antenatal corticosteroids (ACS) to accelerate fetal lung maturation is considered one of the most valuable antenatal therapies in preterm labour [4]. Following the landmark study of Liggins and Howie in 1972, the impact of ACS on fetal lung maturation has been extensively studied [5]. Now, 50 years ahead of this milestone in neonatology, the study of antenatal corticosteroid therapy has altered the management of pregnant women experiencing preterm labour and significantly improved the life expectancies of prematurely born infants.

Aiming to learn how to halt premature labour, Liggins researched the factors responsible for initiating delivery using pregnant sheep [6]. During his experiments, he discovered that a pregnant sheep treated with corticosteroids delivered a live premature lamb, which was very frail and unlikely to survive, but contrary to what was expected, it was breathing. It was noted that the lambs respired with a strained and irregular breathing pattern and did not survive longer than several hours. Upon autopsy, Liggins fully inflated alveoli in the lungs of the newborn lambs, which starkly contrasted with the brittle and frail alveoli expected for lambs born in such a premature condition. This experiment led Liggins to postulate that antenatal corticosteroids he had administered on the pregnant sheep crossed the placenta and accelerated fetal lung maturation, thus allowing a lamb to breathe and continue life outside the womb, if only briefly. It was hypothesized that the corticosteroids induced some enzymes responsible for surfactant synthesis in the premature lungs of the fetal lamb.

Following this extensive study into the effect of antenatal corticosteroids on fetal lung maturity, Liggins formulated a double-blind, controlled clinical trial with Ross Howie, an expert in pediatrics [5]. Their trial included women experiencing premature labour around 24 to 36 weeks of gestation and for whom elective premature deliveries were planned before 37 weeks due to obstetric complications. The study's salient features were a 3.2% early neonatal mortality rate in the steroid-treated group and a 15% early neonatal mortality rate in the control group. Compared to the control group (25.8%), treated babies were less likely to develop respiratory distress syndrome (9.0%). No deaths were reported in infants whose mothers had been given corticosteroids at least 24 hours before delivery due to hyaline membrane disease or intraventricular cerebral haemorrhage.

Glucocorticoid receptors are found in almost all human cells, allowing glucocorticoids to have widespread effects throughout the body, including the placenta and fetal tissues, resulting in pleiotropic effects. The binding of glucocorticoids to these receptors changes gene expression, transcription, and protein synthesis [7]. During pregnancy, the fetus is exposed to low levels of glucocorticoids early on, but towards the end of pregnancy, there is a rise in both maternal and fetal glucocorticoids to prepare for birth [8]. Drugs like betamethasone and dexamethasone are known to have an impact on the lungs by promoting surfactant production, but they also affect the heart, brain, hypothalamus, kidneys, and thyroid, simulating the natural rise in corticoids during late pregnancy.

The development of the fetal lungs can be divided into five stages, with alveoli increasing in number and maturing from 28 to 35 weeks of gestation. The surfactant, a combination of lipids and apoproteins, helps stabilize the alveoli and appears at 22 to 24 weeks. The use of corticosteroid treatments (ACS) leads to the acceleration of type 1 and 2 pneumocyte development, modification of alveolar structure, improved surfactant production, and enhanced airspace fluid clearance.

The increase in surfactant production is due to both transcriptional and post-transcriptional mechanisms, leading to increased phosphatidylcholine and fatty acids in the fetal lung. Both animal and human studies have shown that ACS improves lung compliance and volume and enhances the response to surfactant treatment.

Over the past several decades, the outcomes for preterm infants have greatly improved due to advancements in neonatal ventilation, surfactant treatments, and the administration of prenatal steroids. ACSs are given to women

at risk of premature labour and are typically administered in two injections. They can also be used before planned preterm birth; sometimes, a repeated course may be necessary. The most used glucocorticoids in clinical practice are dexamethasone and betamethasone [9]. There are two standardized courses of corticosteroid therapy to enhance fetal lung maturity:

The administration of 12 mg of betamethasone intramuscularly, followed by a repeat of the same dose 24 hours later.

The administration of 6 mg of dexamethasone intravenously, repeated every 12 hours for up to 4 doses.

Despite the early indications that administering antenatal corticosteroids has a positive impact on fetal lung maturation and the widespread recommendations to use this treatment in women at risk of preterm birth, there is still some uncertainty regarding its effectiveness, particularly in lower-resource settings and in high-risk groups such as women with hypertension or multiple pregnancies. Despite the widespread use of this treatment, the optimal timing of administration has not improved in over 50 years [10].

This assessment aims to evaluate the effects of administering a course of corticosteroids to women before anticipated preterm birth (before 37 weeks of pregnancy) on fetal and neonatal morbidity and mortality, maternal mortality and morbidity, and the child's health later in life. This assessment aims to provide further insights into indications, side effects, maternal health, and secondary outcomes of this treatment.

Materials and Methods

Herein we discuss the findings from over 80 publications, including scholarly articles, guidelines, systematic reviews, and other studies related to research on antenatal corticosteroids, mainly accessed through the PubMed and Cochrane library databases.

Our study involved the timing of the administration of ACS, the types and doses of ACS, and an analysis of single vs repeated doses of ACS. We have also evaluated the pertinence of ACS in scheduled caesarean sections and their use in specific gestational populations, namely, multiple gestations, obesity, PPROM, fetal growth restriction, and diabetes mellitus. The short and long-term health outcomes following the administration of ACS were also studied.

Results

Over 50 years after the publication of the benchmark study by Liggins and Howie (1972), assessing the impact of antenatal corticosteroids in reducing respiratory morbidity in premature neonates, we now have an expanse of studies and published trials that further delve into the effects of ACS on fetal lung maturation. Our objective was to put forth an updated review encompassing the impact of prophylactic corticosteroids for preterm birth and provide a definitive study incorporating all the new trials and studies that have previously been discussed.

Recently, more consensus has been needed about diagnosing preterm labour [11]. In elective situations, clinicians can administer ACSs when they believe they will be most effective. However, in many cases, such as PPROM, it is more complex, or some may deliver before the entire course of ACS is completed, and many may still need to be delivered for several weeks. The situation becomes even more complicated in spontaneous labour with intact membranes, where most women will not give birth prematurely.

It is important to note that there is no agreed definition of actual preterm labour, which leads to arbitrary and often unnecessary use of ACSs. This was evident from the first study by Liggins, as less than half of the women delivered within the predicted time frame of 2 to 7 days, with about one-third delivering later than seven days, most often later than 21 days after ACS administration [5].

The efficacy of ACSs has traditionally been thought to be most effective between 2 to 7 days, as shown by Liggins' first study and a Cochrane review that showed reduced rates of RDS in infants who received ACS in that time frame [12]. However, other evidence suggests that the benefits to the neonate may start as soon as a few hours after receiving ACS and could last beyond a week [12]. Some studies have found no difference in outcomes for infants born 8 to 14 days after treatment compared to those born within seven days [13, 14]. These results could be due to the arbitrary nature of the 7-day cutoff and a gradual decrease in the effectiveness of

ACS over time. Additionally, this decrease may not be uniform across all gestational ages or birth weights.

22+0 – 23+6 weeks

The outcomes in over 3,500 neonates born before 24 weeks of gestation found that administering ACS reduced the mortality rate by 52% compared to a control group with no treatment or a placebo [15]. Another study found that receiving ACS improved neurodevelopmental outcomes or reduced the risk of death in neonates born at 23, 24, and 25 weeks but not in neonates born at 22 weeks [16]. In general, neonates born at 22-25 weeks of gestation had higher survival rates post-ACS exposure [17]. A meta-analysis of neonates born between 22+0 and 22+6 weeks found that ACS doubled the survival rate compared to those without it [18].

Therefore, a course of ACS can be considered for women at high risk of preterm birth within the next seven days between 22+0 and 23+6 weeks of gestation. This decision should be based on local standards regarding peri-viable neonatal support and neonatal facility availability and involve appropriate consultation with parents and perinatal specialists.

24+0 – 33+6 weeks

A meta-analysis of 27 randomized controlled trials found that the use of ACS in cases of imminent preterm birth reduced rates of respiratory distress syndrome (RDS), intraventricular haemorrhage (IVH), and perinatal and neonatal death [19]. The analysis also showed that ACS did not increase the risk of chorioamnionitis or endometritis. The meta-analysis included 11,272 women and covered 27 studies, 20 conducted between 24 and 34 weeks of gestation. It included studies conducted in high, middle or low-income countries and focused on singleton pregnancies or multiples. Some of these studies used a single dose of steroids, while others used either single or repeated doses and a placebo. The meta-analysis concluded that further data is required for high-risk groups, including women with multiple pregnancies, diabetes or hypertension.

In 2015, the ACT study raised concerns about the use of ACS in low-income countries as it indicated that it may increase neonatal mortality [20]. However, this study faced criticism for its limitations, and the subsequent WHO study (2020) found that dexamethasone resulted in lower risks of neonatal death and stillbirth compared to placebo, without increasing the risk of maternal bacterial infection [21]. This supports the use of ACS in both high- and low-income countries.

34+0–36+6 weeks

During the first decade of ACS research between 1972 and 1981, most studies covered cases until 36 weeks and six days. Later, all studies only focused on cases up to 34 weeks and 6 days. But from 2010 to 2018, a few studies re-examined the potential benefits of steroids in late preterm fetuses [22]. The Antenatal Late Preterm Steroids (ALPS) study was a large, randomized, controlled study that evaluated the impact of ACS on fetuses between 34 and 36 weeks and 5 days of gestation, using strict criteria for the definition of threatened preterm labour. The study found a significant decrease in the primary composite adverse outcome, which included neonatal respiratory treatment within 72 hours, stillbirths, or neonatal deaths within 72 hours of birth, as well as a decrease in other undesired outcomes such as severe respiratory complications, surfactant administration, and bronchopulmonary dysplasia [23]. There was no significant difference in the incidence of chorioamnionitis or neonatal sepsis.

Interestingly, subgroup analysis showed that only female fetuses benefited from ACS regarding the primary outcome, and ACS also reduced the rate of the primary adverse effect in cases of elective cesarean section during the late preterm period. However, neonatal hypoglycemia was more common in the steroid group. It's worth noting that hypoglycemia may be linked to future neurodevelopmental problems.

Discussion

Given the current uncertainty about the balance of benefits and risks, a single course of ACS is not routinely recommended between 34 and 36 weeks and six days of gestation for women at high risk of preterm labour within the next seven days.

The effectiveness of ACS in promoting fetal lung maturation relies on its transfer from the mother to the fetus via the placenta.

The extent to which drugs pass through the placenta varies among different compounds and during various stages of pregnancy, which is why beta or dexamethasone are used [24, 25]. The most commonly used regimen involves 24 mg of either two doses of 12 mg IM of betamethasone or four doses of 6 mg IM of dexamethasone. These doses can occupy up to 80% of corticosteroid receptors, stimulating the fetal corticosteroid response. Higher doses of betamethasone do not increase its efficacy, while a shorter dosing interval of corticosteroids may increase the risk of NEC and should be avoided [26, 27]. Compared to dexamethasone, betamethasone is associated with a lower risk of chorioamnionitis and RDS, but the risk of IVH is lower, and hospitalization time in the NICU is shorter in the dexamethasone group [28]. In vitro and in vivo observations suggest that beta and dexamethasone have similar biological activity and exposure, so the choice between the two often depends on availability or cost [29].

The ACTORDS study found that giving weekly doses of betamethasone after an initial course in cases where delivery has not occurred after seven days was associated with fewer respiratory complications, including RDS [30]. This was confirmed by a Cochrane review, which found that repeated doses were linked to lower rates of RDS and a decrease in serious adverse neonatal outcomes [31]. However, repeated doses were also linked to a reduction in mean birth weight. Neonates treated with repeated ACS during pregnancy had lower rates of respiratory support than no treatment and a lower birthweight [32]. Another study found repeated doses (≥4 courses) were associated with increased rates of small for gestational age (SGA) [33]. Additionally, repeated corticosteroids were associated with reduced placental weight [34]. A secondary analysis of data from the ACTORDS study, which looked at neurocognitive function at 6 to 8 years old as the primary outcome, found that repeated betamethasone treatment did not have any adverse effects on neurocognitive function at that age, even in cases of fetal growth restriction (FGR) [35]. Despite some evidence of short-term respiratory benefits, the long-term effects of repeated ACS doses are unclear and highlight the continued inability to predict imminent preterm birth accurately.

As a consequence of those reviews, it is not advised to administer repeated doses of ACS after the first course due to uncertainties regarding its benefits and potential adverse effects. A repeated course of ACS is not typically prescribed, and it may only be given to women who are at a high risk of preterm labour and have reached up to 33 weeks and six days of gestation and have received a previous course of ACS at least two weeks prior.

A meta-analysis showed that administering ACS 48 hours before a planned C-section at full term could lead to a lower risk of TTN, RDS, and needing mechanical ventilation, resulting in a shorter stay in the NICU and higher Apgar scores [36]. However, based on data from only one trial, the most recent Cochrane review on the subject is still being determined if ACS reduces the risk of RDS or TTN [37, 38]. ACS likely reduces the risk of admission to neonatal care for respiratory issues but does not impact the risk of requiring mechanical ventilation.

Results from the EPIPAGE-2 trial showed that giving ACS to women with high-risk twin pregnancies reduced the rates of periventricular leukomalacia or severe IVH and in-hospital deaths [39]. However, the recent Cochrane review found no significant impact of ACS on the outcomes of fetal death, perinatal death, neonatal death, RDS, and IVH in twin pregnancies. It is limited by the number of studies and participants. Despite the idea that multiple gestations may require higher doses of corticosteroids, research shows that cord blood levels of steroids in twins are similar to those seen in single pregnancies [40, 41]. Therefore, in cases of multiple pregnancies, the same amount and reasons for administering ACS should apply as in single pregnancies.

There is limited evidence to support modifying the doses of ACS based on body mass index (BMI). A study of 55 participants found that cord blood levels of corticosteroids were similar between obese and non-obese pregnant women [40].

The criteria for diagnosing PPROM are still unclear, and there is very little evidence predicting which women with PPROM are more likely to deliver within seven days [42]. Furthermore, there has been concern about the possibility that ACS may increase the risk of perinatal infections in women with PPROM. A meta-analysis of more than 1,400 PPROM cases found that ACS

reduces RDS, IVH and NEC without increasing the risks of maternal or neonatal infection [43]. The latest Cochrane review's subgroup analysis also showed no difference between both groups in perinatal, neonatal, and fetal mortality, RDS, endometritis, or chorioamnionitis [22]. Repeat ACS courses were not associated with a higher risk of chorioamnionitis or neonatal complications in cases with PPROM, but the risk of chorioamnionitis may increase with multiple ACS courses [44, 45].

For this reason, a single course of ACS is recommended at the time of diagnosis of PPROM when gestational age criteria are met.

No studies have been conducted to determine the effect of ACS on fetuses with FGR. Some research suggests that these fetuses may not benefit as much from ACS because they may already have enhanced lung maturation due to chronic stress and the breakdown of 11-B-HSD II or even be negatively affected, as some animal studies have shown. Some studies have reported that ACS may decrease birth weight while reducing head size. However, recent research has indicated that the decrease in weight may only result from repeat courses and that maternal health conditions may have influenced some poor outcomes in fetuses with FGR. A secondary analysis from the ACTORDS trial found no adverse effects on neurocognitive function in 139 FGR fetuses that received repeated betamethasone treatment compared to a placebo group aged 6 to 8 years [46].

A review conducted in 2009 that analyzed five studies with 664 fetuses did not find any significant differences in terms of morbidity, mortality, respiratory distress syndrome, IVH, or NEC [47]. However, the results may have been limited in their ability to detect outcome differences. A more recent meta-analysis in 2020, which included 13 studies with 6,387 fetuses of FGR and small for gestational age, showed that neonatal mortality was significantly lower in infants who received ACS, with significant variations between studies [48]. There were no significant differences in respiratory distress syndrome, NEC, IVH, periventricular leukomalacia, bronchopulmonary dysplasia, chronic lung disease of prematurity, or neonatal sepsis.

Lastly, a small sub-study from the TRUFFLE 2 feasibility study showed no improvement from administering ACS after 32 weeks of pregnancy [49]. However, due to its small sample size, it was only possible to assess partially all outcomes in this matched case-control study.

In conclusion, the most recent studies suggest that administering antenatal corticosteroids (ACS) to women at risk of preterm birth (before 37 weeks of pregnancy) leads to a reduction in neonatal mortality in cases of fetal growth restriction (FGR). However, no significant impact has been found on neonatal morbidity in the short or long term. These results were based on studies including a considerable number of FGR infants, but further research with larger sample sizes is needed to understand the effect of ACS in this population. Therefore, when it comes to preterm delivery cases complicated by fetal growth restriction, administering antenatal corticosteroids should follow the same guidelines and dosages as in cases where the fetus is of appropriate gestational age.

It is important to note that administering a single course of antenatal corticosteroids (ACS) to women with single or multiple pregnancies before preterm birth may interfere with the natural cortisol levels and have both short-term and long-term effects [50]. While immediate side effects, such as postnatal hypoglycemia, have been observed, long-term consequences, such as reduced fetal growth or poor academic performance, are only evident with repeated administration of ACS [51]. Exposure to ACS was linked to an increased risk of mental and behavioural disorders in children.

The findings from these meta-analyses suggest that a single course of ACS in women with singleton or multiple pregnancies before anticipated preterm birth does lead to a reduction in the incidence of developmental delay in childhood and improves most neurodevelopmental outcomes in the offspring, especially in cases where deliveries occur before 34 weeks of gestation. There was no increase in intellectual, visual, or hearing impairment in childhood or adulthood. In addition, it was noted that a substantial proportion of deliveries occurred at >37 weeks of gestation. However, further studies with larger sample sizes and more extended follow-up periods are needed to establish the long-term effects of ACS on children born preterm.

It is important to note that repeated courses

of ACS, whether second or weekly doses after an initial course, can negatively affect fetal growth and development. Children exposed to repeated courses of ACS delivered after 37 weeks of gestation showed a significant increase in neurosensory disability at 5 years of age. Additionally, there was a trend towards an increase in cerebral palsy at 2-3 years of age following repeat ACS in a National Institute of Child Health and Development trial. However, the study approach to determine the gestational age-specific risks and benefits of repeated courses of ACS for preterm labour found that below 29 weeks of gestation, a repeat course in the case of anticipated preterm birth is beneficial, while after 29 weeks, the long-term side effects, including growth retardation and neurodevelopmental delay, become more prominent.

Conclusions

Despite the benefits of administering ACS in improving neonatal outcomes, there are still some unresolved issues regarding its use [52]. The main challenge is the inability to accurately predict which women who present with preterm contractions or PPROM are most likely to deliver within the next 7 days. Given the uncertainty surrounding the long-term effects of ACS and neonatal hypoglycemia, especially in late preterm neonates, the World Association of Perinatal Medicine recommends that strict protocols should guide the use of ACS.

Until more data becomes available from prospective studies, it is advised that clinicians should only administer a single course of ACS in high-risk cases of preterm birth that are likely to occur within the next 7 days, and the gestational age is between 22+0 and 33+6 weeks. The diagnosis of preterm labour should be made based on available resources and expertise and supported by comprehensive protocols in the relevant setting.

There are many more critical unresolved issues related to the use of ACS in preterm labour, and further research is needed to address these questions and provide more explicit guidelines for the benefit of ACS in clinical practice. Some key questions include the accuracy of diagnosis and prognosis of preterm labour, the timing of ACS administration for maximum effectiveness, the impact of ACS on multiple pregnancies, the effects of previous steroid treatment, and the long-term cardiovascular and neurodevelopmental outcomes of the offspring exposed to ACS. These are all critical areas of investigation that will help provide a clearer understanding of the benefits and risks associated with using ACS in preterm labour.

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