PERINATAL JOURNAL

Opinion

Perinatal Journal 2022;30(1):240–243

Unresolved issues on the antenatal use of corticosteroids for fetal lung maturation

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Abstract

Antenatal corticosteroids (ACS) for fetal lung maturation is celebrating the 50th anniversary. The most recent Cochrane review concluded that there is robust evidence that a single course of ACS reduces the risk of perinatal death and respiratory distress syndrome. Some aspects of ACS remain unresolved, including variations in the steroids regimen, effectiveness in certain groups, long-term effects, optimal timing of ACS administration in elective cases. it is well established that a single course of betamethasone or dexamethasone is beneficial in cases of anticipated preterm birth and delivery eventually occurs between two and seven days from administration. The main focus for future research should be on limiting the unnecessary exposure in low-risk pregnancies and investigating the effect in specific groups, periviable and late preterm fetuses.

Keywords: Antenatal, corticosteroids, fetal lung maturation.

The use of antenatal corticosteroids (ACS) for fetal lung maturation is celebrating this year the 50th anniversary since the landmark study by Liggins and Howie.[1] Since then, several studies on ACS have been conducted; the most recent Cochrane review by McGoldrick et al. concluded that there is robust evidence that a single course of ACS reduces the risk of perinatal death and respiratory distress syndrome (RDS) and probably the risk of intraventricular hemorrhage (IVH).[2] Nevertheless, some aspects of ACS remain unresolved, including *(a)* variations in the steroids' regimen, *(b)* effectiveness in certain groups, *(c)* balance of risks and benefits in the periviable and late-preterm periods, *(d)* long-term effects of ACS in the offspring, *(e)* value of ACS in women on steroids for other indications, *(f)* optimal timing of ACS administration in elective cases, *(g)* impact of ACS administration in low- and high-income countries.

Variations in the Steroids' Regimen

Current guidelines uniformly recommend the use of either dexamethasone 6 mg in 4 doses every 12 hours or betamethasone 12 mg in two doses, the second 24 hours following the initial.[3] There is no clear advantage of one regimen over the other;[4] the incidence of survival without neurosensory disability at the age of 2 did not differ between dexamethasone and betamethasone treatments (aRR: 0.97; 95% CI: 0.83–1.13).[5] Furthermore, according to BETADOSE trial, a single dose (12 mg) of betamethasone may be as effective for the maturation of fetal lungs as the administration of two doses (2×12 mg).[6] Regarding repeated ACS, weekly doses of betamethasone have been correlated with lower risk of RDS (RR: 0.82; 95% CI: 0.71–0.95) and there were no adverse effects on neurocognitive function at early childhood (OR: 1.02; 95% CI: 0.81–1.29).[7,8] Moreover, according to the findings of an individual patient meta-analysis, a reduction in

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e-mail: iotsakir@gmail.com / **Received:** July 21, 2022; **Accepted:** July 28, 2022

How to cite this article: Tsakiridis I, Dagklis T, Şen C. Unresolved issues on the antenatal use of corticosteroids for fetal lung maturation. Perinat J 2022;30(3):240–243. doi:10.2399/prn.22.0303007

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the use of respiratory support was found in infants exposed to repeated ACS compared with infants not exposed (RR: 0.91; 95% CI: 0.85–0.97), but on the other hand lower birthweight z-score was identified in these cases (mean difference: -0.12; 95% CI: -0.18 to -0.06).[9] Therefore, more than two repeated courses of ACS should be discouraged.[10]

Effectiveness in Certain Groups

More data are needed regarding the effect of ACS in *(i)* multiple pregnancies, *(ii)* preterm premature rupture of membranes, *(iii)* fetal growth restriction, *(iv)* obese women and *(v)* diabetic women.

- *(i)* Regarding twin pregnancies, the EPIPAGE-2 study showed that ACS administration reduced the risk of IVH or periventricular leukomalacia (aOR: 0.2; 95% CI: 0.1–0.5).[11] However, a recent meta-analysis could not demonstrate any effect of ACS on the risk of IVH, RDS and perinatal death in multiple pregnancies.[2]
- *(ii)* Although there were concerns regarding a possible increase in the rates of infection following ACS administration in preterm premature rupture of membranes, this was not confirmed in the latest Cochrane review.[2]
- *(iii)* A reduction of about 3% in the rates of neonatal mortality in the ACS group in pregnancies complicated by fetal growth restriction has been found by a meta-analysis (OR: 0.63; 95% CI: 0.46–0.86).[12] However, no randomized trials have been conducted, so far, on this topic.
- *(iv)* Limited published data exist on the titration of ACS dose according to maternal body mass index. Evidence on less than 60 women found that ACS levels in the umbilical cord were similar between obese and non-obese women (p>0.05).[13]
- *(v)* Regarding diabetes, pregnant women with this condition are almost always excluded from the studies, so, to date, no data exist on this topic.

Balance of Risks and Benefits in the Periviable or Late Preterm Periods

According to data from two meta-analyses, ACS administration before 24 weeks of gestation reduced the risk of IVH and periventricular leukomalacia, as well as mortality rate by about 50% compared to no treatment or placebo.[14,15] Furthermore, neurodevelopmental impairment or death at the first two years of age was lower in neonates receiving ACS in utero and born at 23 weeks (83.4% vs. 90.5%), but not at those born at 22 weeks.[16]

Regarding late preterm period, a large randomized trial assessed the effect of ACS administration at 34+0–36+5 weeks and found a reduction in neonatal respiratory complications or death (RR: 0.80; 95% CI: 0.66–0.97), but higher risk of hypoglycemia in the ACS group (RR: 1.60; 95% CI: 1.37–1.87).[17]

Long-Term Effects of ACS in the Offspring

In the original report by Liggins and Howie,[1] it was already noted that less than half of the cases received ACS 2–7 days before delivery and about one in three delivered at least seven days later, in fact most of them more than three weeks following ACS. According to data from a Finnish population-based study, ACS treatment increased mental and behavioral disorders in infants by about 30% and this effect was more prominent in term neonates exposed to ACS (HR: 1.47; 95% CI: 1.36–1.69).[18] Moreover, according to a recent cohort study, ACS-exposed infants had no difference in attention deficit disorder (p=0.54) or developmental delay (p=0.10).[19] The latest Cochrane review found that ACS given prior to anticipated preterm delivery reduced the risk of developmental delay by about 50%.[2]

Value of ACS in Women Already on Steroids for Other Indications

Women of reproductive age suffering from autoimmune diseases may be prescribed corticosteroids for immunosuppression. These women usually continue their treatment during pregnancy. To date, there is no evidence on the effect of the long-term steroids' use on fetal lung maturation; these women usually receive ACS for obstetrical indications in addition to their treatment.

Optimal timing of ACS Administration in Elective Cases

According to data from the largest multicenter randomized trial, there was no significant benefit in women receiving ACS before elective cesarean section at term

with regards to the outcomes of transient tachypnea of the neonates (RR: 0.54; 95% CI: 0.26–1.12), RDS (RR: 0.21; 95% CI: 0.03–1.32).[20]

Impact of ACS Administration in Low- and High- Income Countries

Access to medications may be restricted in low-income countries. Since prematurity affects a high proportion of women living in these countries, it is important to assess the effect of ACS on perinatal outcomes. According to data from a multi-country, randomized trial involving pregnant women at risk of preterm delivery between 26+0 and 33+6 weeks of gestation in low-income countries, the administration of ACS was associated with reduced risk of neonatal death (RR: 0.84; 95% CI: 0.72–0.97), without increasing the risk of bacterial infection (RR: 0.76; 95% CI: 0.56–1.03).[21]

To conclude, it is well established that a single course of betamethasone or dexamethasone is beneficial in cases of anticipated preterm birth and delivery eventually occurs between two and seven days from administration. The main focus for future research should be on limiting the unnecessary exposure in low-risk pregnancies and investigating the effect in specific groups, periviable and late preterm fetuses.

Funding: This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with Ethical Standards: The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

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