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Controversies in antenatal corticosteroids

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ABSTRACT

Antenatal corticosteroids (ACS) successfully reduce the rates of neonatal mortality and morbidity after preterm birth. However, this translational success story is not without controversies. This chapter explores some contemporary controversies with ACS, including the choice of corticosteroid, use in threatened preterm birth less than 24 weeks' gestation, use in late preterm birth, use at term before cesarean delivery, and issues surrounding repeated and rescue dosing of antenatal corticosteroids. The use of ACS in special populations is also discussed. Finally, areas of future research in ACS are presented, focusing on the ability to individualize therapy.

Practice Points

- Antenatal corticosteroids are recommended for women with threatened preterm birth between 24^{+0} and up to 33^{+6} weeks gestational age.
- Consideration is now extended toward therapy for women beginning at 23^{+0} weeks and between 34^{+0} and 36^{+6} weeks gestation.
- A rescue course of antenatal corticosteroids before 34^{+0} weeks can be considered if 14 days have elapsed since an initial course and the woman is judged to have a risk of preterm birth within the next seven days.

Research Directions

- The current “one-size fits all” dosing of antenatal corticosteroids does not provide the same benefit to all women and newborns. Individualized therapy needs to be investigated to understand these disparities.
- Biomarkers of response to antenatal corticosteroids are needed. Alternative dosing strategies may be needed for optimal response and should be investigated.
- Well-powered trials in special populations and gestational ages beyond the current recommendations are needed, as are long-term infant follow-up studies.

1. Introduction

Corticosteroid administration before anticipated preterm birth is one of the most important antenatal therapies available to improve newborn outcomes [1,2]. For women at risk of preterm delivery within seven days, a single course of antenatal corticosteroids (ACS) is recommended between 24^{+0} weeks and 33^{+6} weeks' gestation. Consideration is now extended toward the therapy for women starting at 23^{+0} weeks and for those between 34^{+0} weeks and 36^{+7} weeks of gestation at risk of preterm delivery within seven days [1]. This therapy is truly a success of translational research.

Beginning with observations from studies in preterm lambs, Liggins and Howie performed a landmark trial in the 1970s that demonstrated improved neonatal outcomes in humans born preterm and exposed to ACS [3,4]. In an initial publication that reported on the first 282 women enrolled in this trial, a reduction in the rate of respiratory distress syndrome (RDS) and early neonatal death was seen in the group of infants exposed to betamethasone compared to those exposed to placebo (3.2% vs. 14.1%, p = 0.02 for early neonatal deaths). This finding was confirmed in multiple subsequent trials and finally synthesized in the Cochrane review by Patricia Crowley in 1996, subsequently updated [5]. In summary, treatment with ACS, compared with placebo or no treatment, is associated with a reduction in perinatal death (risk ratio [RR] 0.72, 95% confidence interval [CI] 0.58, 0.89), RDS (RR 0.66, 95% CI 0.56, 0.77), intraventricular hemorrhage (IVH, RR 0.55, 95% CI 0.40, 0.76), and necrotizing enterocolitis (NEC, RR 0.50, 95% CI 0.32, 0.78). There have not been identified increased maternal or long-term infant adverse effects of ACS, at least in well-resourced settings [5]. Based on animal models and observations in humans, it is suggested that ACS mature a number of organ systems in addition to the

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lungs [6,7]. For these reasons, ACS are now a staple of modern obstetric practice.

However, practice changes throughout the years have revealed that ACS may still cause controversy and there are many research questions that are yet to be answered. For instance, not all infants receive the same benefit from ACS and further work is needed to understand the contributors to this outcome disparity [8]. For a time, it was routine to give ACS therapy weekly to women at risk of preterm delivery. However, in some studies this was found to be associated with increased rates of fetal growth restriction [9]. Additionally, while antenatal corticosteroids initially were recommended for gestational ages between 24^{+0} and 33^{+7} weeks, many felt there may be benefit at earlier or later gestational ages. Moreover, the dose and type of betamethasone most commonly given today is the same as that used in Liggins and Howie's original trial [4]. Should the dose be changed based on gestational age or body composition of the woman? Thus, even though ACS are used daily on labor units around the world, there are still many controversies in practice and research, as we mature in our understanding of this pivotal therapy. This article will summarize several of the common controversies and changes with ACS, explore the evidence existing, and identify any recommendations and future areas for research.

2. Choice of corticosteroid

Two corticosteroids, betamethasone and dexamethasone, have been found efficacious in promoting fetal lung development. Betamethasone and dexamethasone are optical isomers that differ in the orientation of a methyl substituent at position 16 (Fig. 1). These drugs are synthetic fluorinated steroids with high affinity towards the glucocorticoid receptor, but minimal mineralocorticoid activity [10]. Both drugs easily cross the placenta.

Betamethasone is usually administered intramuscularly as two 12 mg doses given 24 h apart. The formulation is comprised of equal mixtures of betamethasone phosphate and betamethasone acetate [11]. The half-life of betamethasone following intramuscular administration is dictated by absorption rate. The phosphate salt is rapidly dephosphorylated and absorbed while the hydrophobic acetate salt acts as a depot and releases drug slowly. Dexamethasone sodium phosphate is administered as four 6 mg intramuscular injections given 12 h apart. It is more rapidly absorbed than the betamethasone phosphate and acetate mixture. In one trial, intramuscular administration of dexamethasone was found to be superior to oral administration and thus ACS are currently given intramuscularly [12].

There is conflicting evidence comparing the clinical efficacy of betamethasone and dexamethasone for fetal lung maturation. Both steroids exhibit similar biological activity, with high glucocorticoid receptor binding activity but minimal, if any, mineralocorticoid activity and weak immunosuppressive activity [13]. Only a few small clinical studies have directly compared antenatal betamethasone and dexamethasone [14–18]. A Cochrane review of studies comparing antenatal betamethasone and dexamethasone evaluated results from 10 trials that recruited 1159 women and 1213 infants [19]. Dexamethasone exhibited an increased risk of IVH compared to betamethasone (RR 0.04, 95% CI 0.21, 0.92). However, there were no differences with respect to risk of neonatal death, RDS, neonatal intensive care unit (NICU) admissions, vasopressor requirement, bronchopulmonary dysplasia, periventricular leukomalacia, NEC, retinopathy of prematurity, or patent ductus arteriosus. The meta-analysis also indirectly compared studies of either betamethasone or dexamethasone versus placebo. This indirect comparison identified a higher rate of RDS in infants exposed to dexamethasone (RR 1.4, 95% CI 1.09, 1.9, $p = 0.03$). It also identified a higher rate of chorioamnionitis in women who received antenatal dexamethasone (RR 1.9, 95% CI 1.1, 3.28, $p = 0.02$) [19]. A more recent Cochrane review also conducted an

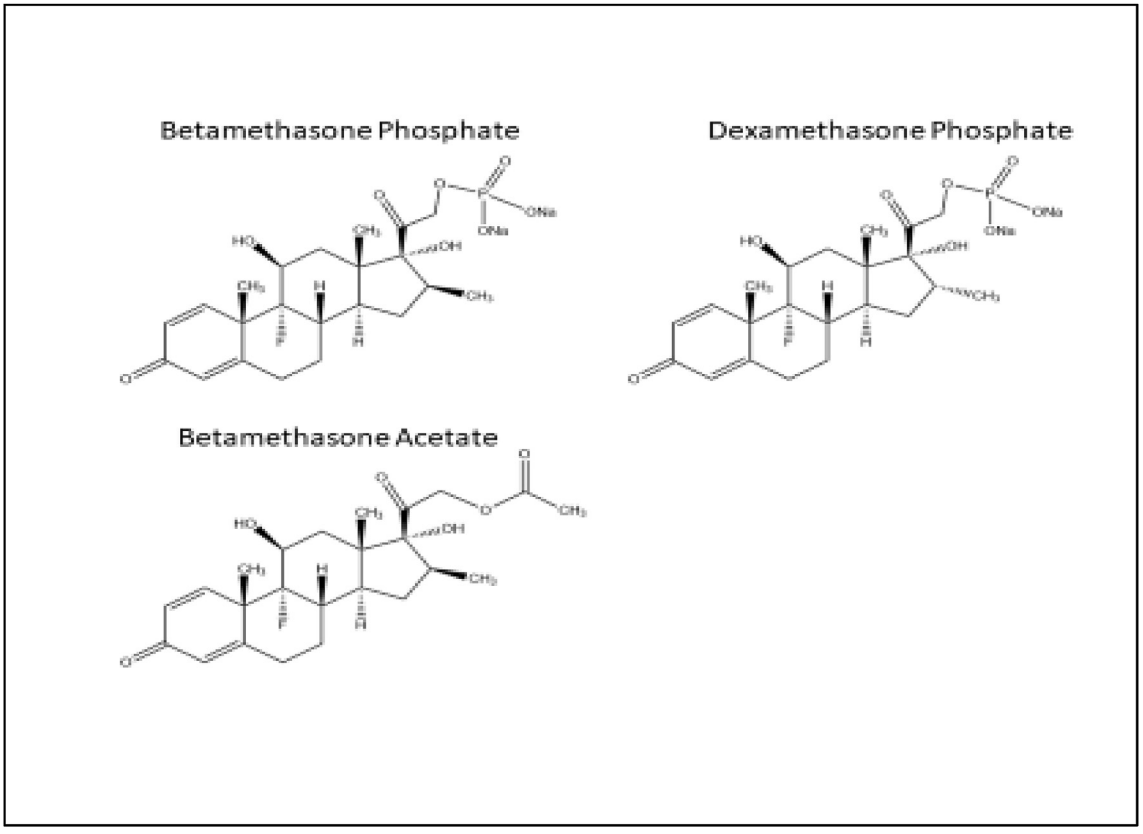

Fig. 1. Antenatal corticosteroid chemical structures. Chemical structures of betamethasone phosphate, betamethasone acetate, and dexamethasone phosphate. Note stereo-center at C16 differs between betamethasone and dexamethasone.

indirect comparison of antenatal betamethasone and dexamethasone [5]. In agreement with Brownfoot et al. this analysis found evidence of lower risk of maternal chorioamnionitis in women treated with betamethasone (RR 0.67, 95% CI 0.50, 0.90) than with dexamethasone (RR 1.35, 95% CI 0.89, 2.05) [20]. However, there was no evidence of a differential effect on the risk of perinatal, neonatal or fetal death, RDS, IVH, moderate/severe RDS or bronchopulmonary dysplasia, or birth weight, with betamethasone or dexamethasone.

Based on current data, betamethasone and dexamethasone exhibit similar efficacy and safety profiles. However, large, well-controlled clinical trials are needed to confirm these observations. The A*STEROID trial randomized over 1500 women at risk of preterm birth at less than 34 weeks' gestation to treatment with either two 11.4 mg doses of betamethasone (Celestone Chronodose, 7.8 mg betamethasone phosphate and 6 mg betamethasone acetate) 24 h apart or two 12 mg doses of dexamethasone (as dexamethasone phosphate) [21]. The primary outcome is death or any neurosensory disability in children at two years of age. Until results from this study are released, choice of ACS use can continue to be based on provider preference, ease of administration, cost, and availability.

3. Use in cases of extreme prematurity

Original recommendations for the lowest gestation at which ACS should be used was 24^{+0} weeks [22]. The 1995 recommendation from the National Institutes of Health (NIH) consensus panel did not comment on therapy at less than 24 weeks' gestation. This was likely because survival was felt to be rare at those gestational ages and those women were excluded from the randomized trials. However, an observational cohort from the NIH Neonatal Research Network revealed a reduction in death and neurodevelopmental impairment at 18–22 months for infants who had been exposed to ACS and were born at 23^{+0} to 23^{+6} weeks' gestation (Fig. 2) [23]. Coupled with advances in neonatal care for extremely premature infants, the use of ACS for periviable pregnancies has increased. The data demonstrate that for infants with planned resuscitation, outcomes can be improved with ACS. This led the American College of Obstetricians and Gynecologists (ACOG) to state in the most recent Committee Opinion update that ACS "may also be considered for pregnant women starting at 23^{+0} weeks of gestation" at risk of preterm delivery within seven days [1].

Recent trends, however, push the limit of viability even lower despite the uncertainty regarding the physiologic receptivity of fetal development at these earlier gestational ages [24]. Modern reports document survival rates of approximately 25–35% for infants born at 22 weeks' gestation, dramatically higher than rates only a decade earlier which were less than 10% [25]. Discussions about resuscitation of extremely premature newborns are more common today and ACS are being offered at earlier gestations. Carlo et al. found a lower rate of death or neurodevelopmental impairment at 18–22 months of age in infants exposed to ACS with no effect if given at 22 weeks [23]. The recommendations by ACOG reflect this evidence but it is undeniable that there has been significant improvement in the outcome of the fetus delivered in the periviable period. As the limit of viability continues to reduce, the role and rationale for ACS may also change.

4. Use in cases of late preterm birth

Despite 8% of births occurring in the late preterm period, the role of ACS between 34^{+0} weeks and 36^{+6} weeks remains controversial [26]. The NIH consensus conference in 1994 originally extended recommendations for corticosteroid use only to 34 weeks, both due to a lack of evidence of benefit beyond 34 weeks as well as the belief that survival of late preterm infants was within 1% of those at term [22]. Since that time, awareness has increased of higher rates of both acute respiratory complications and chronic lung disease among infants born in the late preterm period [27,28].

The Antenatal Late Preterm Steroids (ALPS) trial established that ACS in patients expected to deliver between 34^{+0} weeks and 36^{+6} weeks can be beneficial [29]. In this multicenter double-blind placebo-controlled randomized trial, maternal betamethasone administration was associated with decreased rate of neonatal composite respiratory treatment, stillbirth, or neonatal death within 72 h after delivery (11.6% [165/1427] vs 14.4% [202/1400], RR 0.80, 95% CI 0.66, 0.97, $p < 0.001$). Neonatal hypoglycemia rates were higher in the betamethasone group (24.0% [343/1427] vs 15.0% [210/1400], RR 1.60, 95% CI 1.37, 1.87). Rates of other neonatal complications and length of hospital stay did not differ between groups. Betamethasone was not associated with increased rates of either maternal or neonatal infection.

In this study, benefit was found despite the fact that only 60% of enrolled women received the full course of two doses of betamethasone prior to delivery [29]. Tocolysis was not routinely administered and delivery was not delayed to allow for corticosteroid administration. Notably, women with pre-gestational diabetes, multiple gestations, or who had received previous ACS were excluded. Thus, ACS have not adequately been studied for all women with threatened late preterm birth.

Although smaller randomized trials have not demonstrated a benefit for ACS in the late preterm period, a recent meta-analysis of three trials, including ALPS, had similar conclusions to the ALPS trial [30]. The analysis included three studies, including the ALPS trial, and a total of 3200 women at risk of late preterm birth. ACS were associated with lower risk of severe RDS, transient tachypnea of the newborn, and use of surfactant. The meta-analysis again demonstrated higher rates of hypoglycemia among infants whose mothers received ACS. No differences were found in overall rates of RDS, need for mechanical ventilation, NICU admission rates, APGAR scores, or neonatal mortality.

The World Health Organization's (WHO) guidelines on interventions to improve preterm birth outcomes were last updated in 2015, before the publication of the ALPS trial [2]. In that document, WHO does not recommend ACS after 34 weeks. The Royal College of Obstetricians and Gynaecologists' (RCOG) Green-top Guideline on ACS was published in 2010 and does not recommend, late preterm ACS [31]. Updated in 2017, the current ACOG guidelines state that "a single course of betamethasone is recommended for pregnant women between 34^{+0} weeks and 36^{+6} weeks of gestation at risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids." [1] In alignment with exclusion criteria of the ALPS trial, ACOG recommends against use of late preterm ACS in women with chorioamnionitis, and states that tocolysis should not be used to delay delivery in order to administer ACS.

Although the overall incidence of severe respiratory complications is relatively low in late preterm infants compared to those born before 34 weeks, large adequately powered trials have demonstrated benefits of ACS administration in the late preterm period. Further study is needed in women who previously received a course of ACS, women with pregestational diabetes, multiple gestations, and women who receive ACS due to threatened late preterm delivery but ultimately deliver at term.

5. Use at term with cesarean deliveries

Compared to infants born via vaginal delivery, infants born via cesarean section have higher incidences of RDS, transient tachypnea of the newborn (TTN), and NICU admission [32,33]. These risks are even higher for infants born via planned cesarean section, prior to the onset of labor [32]. ACS have been shown to reduce these risks in preterm infants, but indications for steroids at term remain less clear.

The RCOG, United Kingdom currently recommends ACS for all women planning to deliver via cesarean section prior to 39^{+0} weeks [31], but ACOG does not recommend ACS for term births, regardless of planned mode of delivery [1]. The WHO recommendations on maternal health do not comment on ACS for term cesarean deliveries but

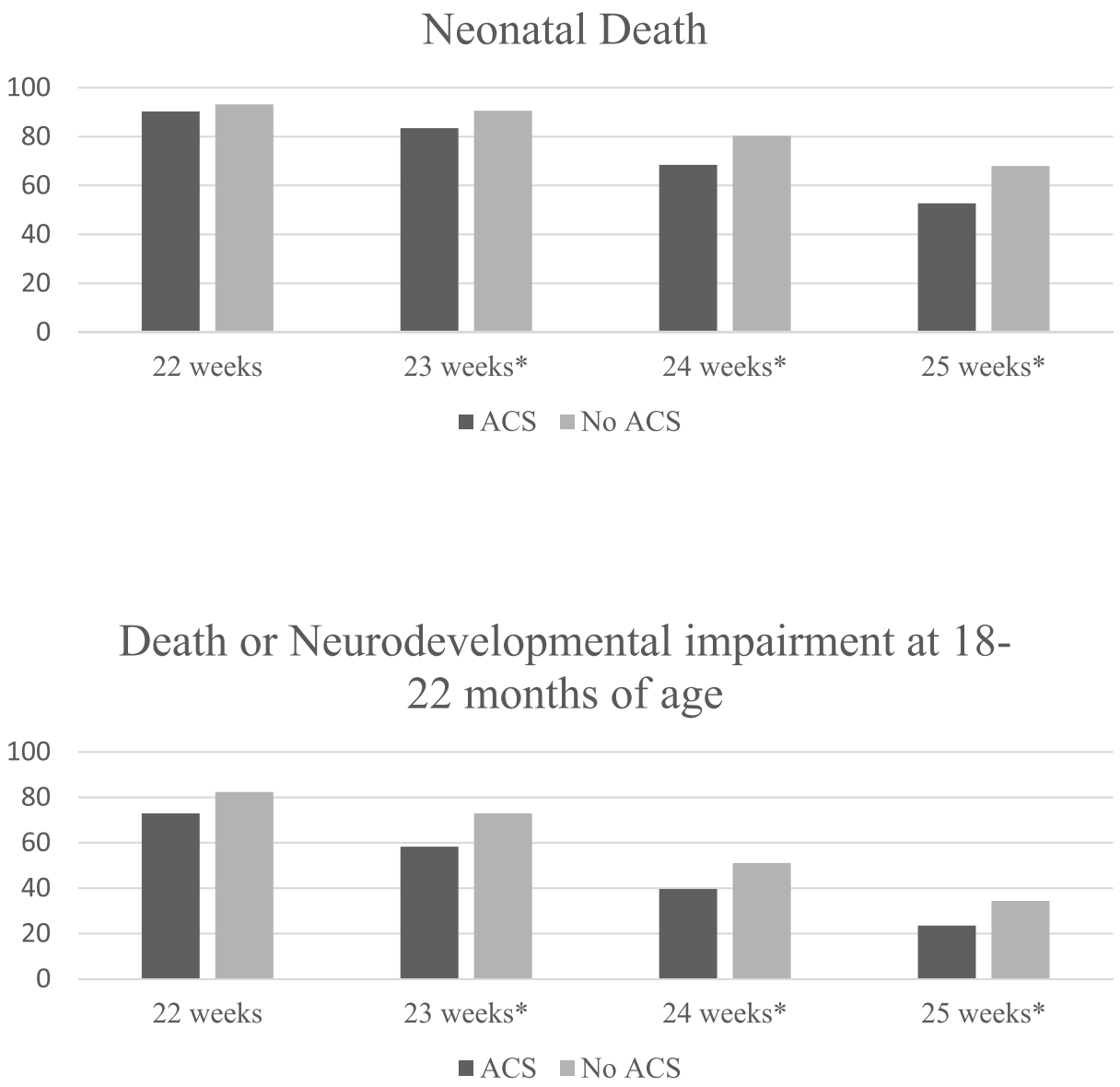

Fig. 2. Outcomes of periviable pregnancies impacted by antenatal corticosteroids. Outcomes (%) of pregnancies with and without exposure to antenatal corticosteroids (ACS). Top panel is the outcome of neonatal death. Bottom panel are outcomes of infant death or neurodevelopmental impairment at 18–22 months after delivery. * represents statistically significant differences between the ACS exposed infants and non-ACS exposed infants. Data from Carlo et al., *JAMA*, 2011 [20].

specifically state the ACS before planned cesareans from 34 + 0 to 36 + 6 weeks are not recommended [2].

The pathophysiology of respiratory morbidity in term infants is usually different than that of preterm infants. Among term infants delivered via cesarean, respiratory complications are thought to be due primarily to increased fluid retention in the lungs [34] and lack of catecholamine surge that normally occurs with labor [35]. Additionally, labor activates sodium channels in lung epithelial cells that promote drainage of alveolar fluid [34,35]. In the absence of labor, glucocorticoids appear to increase activity of sodium channels, which represents a potential benefit of ACS for planned term cesarean deliveries [30,34,35].

A Cochrane review, updated in 2018, compared ACS (either betamethasone or dexamethasone) to placebo or control prior to planned cesarean delivery at term [36]. The review included a total of 3956 women and four trials, one study conducted in the United Kingdom and three in Egypt. The review concluded that ACS decrease the risk of RDS by approximately 50% (RR 0.48, 95% CI 0.27, 0.87) and TTN by approximately 60% (RR 0.43, 95% CI 0.29, 0.65) [36]. ACS were also associated with a 55% decrease in NICU admission rates for respiratory complications (RR 0.45, 95% CI 0.22 to 0.79). However, the quality of evidence for all of these outcomes was rated as low [36].

As the overall risk of respiratory morbidity at term is low, the clinical significance of these findings remains unclear in light of potential harms, known or unknown, from ACS. ACS are associated with increased risk of neonatal hypoglycemia in term infants (RR 1.61, 95% CI 1.38, 1.87) [30]. Neonatal hypoglycemia has been identified in some studies as an independent risk factor for developmental delay among preterm infants, raising concern about the risk-benefit balance of this intervention [37].

Only one study examined long term outcomes of infants receiving steroids prior to a planned cesarean birth at term. The Antenatal Steroids for Term Elective Cesarean Section (ASTECS-2) study examined outcomes at age 8–15 years of a cohort from the original ASTECS study [38], a large randomized controlled trial comparing betamethasone to standard care. Overall, no long-term adverse consequences from a single ACS course at term were found [39]. The only significant finding was that schools subjectively reported that a lower

proportion of children in the ACS group were perceived by their teachers to be in the top quartile of achievement (p = 0.03) [39]. However, no significant differences were found in any other outcomes between the groups, including objective assessments of achievement and test scores [39].

Overall, the benefits of ACS in reducing respiratory morbidity appear to diminish with increasing gestational age, including among infants delivered by cesarean section. When possible, cesarean delivery should be delayed until 39 weeks' gestation. For planned cesarean deliveries between 37^{+0} and 38^{+6} weeks, risks and benefits of a course of ACS should be considered. Recommendations for women in this gestational age range, however, are conflicting [1,31]. Larger randomized trials with longer follow up are needed before a definitive conclusion can be drawn.

6. Rescue dosing versus repeated dosing

ACS are proven to reduce the risk of RDS, NEC, IVH, and neonatal death when administered to women at risk for preterm birth before 34 weeks [5]. However studies suggest that the effects on fetal maturation dissipate if birth has not occurred within seven days of administration [40]. Given that less than 10% of women that present in preterm labor deliver within seven days [1,41], the ability to provide ACS closer to delivery proved to be an appealing idea. Clinicians began administering weekly courses of ACSin order to ensure that administration would occur within one week of delivery. Though studies demonstrated a possible benefit – especially decreasing the risk of RDS – this occurred at the expense of a decreased in birthweight [42,43]. A meta-analysis in 2015 of ten randomized controlled trials of over 4700 women and 5700 babies compared those that received a single course of ACS to those with multiple courses [44]. Their results demonstrated a decreased risk of RDS and severe lung disease with an increased risk of reduced birthweight. However, gestational age adjusted birthweights were not different for infants when multiple courses of ACS were administered.

Balancing the risk of imminent preterm birth with avoiding unnecessary additional courses of ACS is a difficult clinical challenge for obstetric providers. The distinction between recurrent contractions that will lead to delivery and threatened preterm labor is imprecise, and thus deciding when to give additional courses of ACS has been difficult to codify in protocols. On the one hand, ACS need to be administered early enough to provide benefit if the preterm birth is imminent; but on the other hand if labor does not progress, delaying treatment may avoid unnecessary ACS exposure. Providers must avoid “waiting too long” and missing the window where the ACS could provide benefits.

In 2009, a possible rescue course regimen was evaluated [45]. In this multicenter, randomized controlled trial, women $< 33^{+0}$ weeks who had received a course of ACS at least 14 days previously and were judged to have a recurring threat of preterm labor within the next seven days were administered one additional course, either two 12 mg doses of betamethasone 24 h apart or four 6 mg doses of dexamethasone 12 h apart. The authors found a decreased risk of RDS, ventilator support and surfactant use with repeat ACS. Importantly, there was no difference in birthweight, intrauterine growth restriction or head circumference in either group [45].

Though weekly courses of ACS are not recommended, the use of a single rescue course has been shown to have beneficial effects without the increased adverse risks of fetal growth restriction and cerebral palsy [44,46]. Childhood data in 5 year-old infants from the Multiple Courses of Antenatal Corticosteroids trial and the Australasian Collaborative Trial of Repeat Doses of Corticosteroids for the Prevention of Neonatal Respiratory Disease (6-8 years-old) are also reassuring without any increased risk of neurodevelopmental disability, cardiometabolic problems, or other serious outcome in those that received more than one course of ACS [44,47,48]. These reassuring findings include similar body size and composition during childhood for groups receiving multiple ACS courses compared to single courses. The WHO and other organizations have embraced this and recommend that a single repeat course of corticosteroids should be considered in women who are less than 34^{+0} weeks' gestation and judged to have a risk of preterm birth in seven days, and whose prior course of ACS was administered more than 7 or 14 days previously, (WHO or ACOG guidelines, respectively) [1,2]. However, there are still questions about whether multiple “rescue” courses of ACS are beneficial or if only one such course would be needed, even if delivery did not occur.

7. Special cases - multiple gestations, diabetes, premature rupture of membranes

The benefit of ACS to singleton gestations that deliver at less than 34 weeks is undeniable [5]. Other high-risk conditions that are associated with preterm delivery or increased morbidity would seem to warrant consideration for this therapy.

Women with multiple gestations are six times more likely to give birth preterm than women with singleton gestations [49]. Neonates from multiple pregnancies are also at an increased risk of the complications of prematurity, including IVH and periventricular leukomalacia [50]. Based on the improvement seen with singleton gestations, the WHO and other organizations recommend a course of ACS to women with multiple gestations at risk of preterm delivery within seven days at less than 34^{+0} weeks' gestation [1,2]. Data from a French cohort are reassuring that outcomes of ACS for twins between 24 and 31 weeks of gestation had no significant differences when comparing those who received repeated courses compared to a single complete course [51]. Though the completeness of data regarding repeated courses are not as robust for twins as singletons [5], multiple gestations at risk of preterm delivery can be candidates for rescue ACS. However, as the half-life of betamethasone is shorter in twin pregnancy than in singleton pregnancy, the optimal dose or course of repeated dosing may be different than for singletons [52].

Women with diabetes have often been excluded from trials evaluating the benefits of ACS. However their exclusion from clinical trials should not prohibit them from being candidates for this therapy [53]. Clinicians should be aware of the resultant hyperglycemia that often occurs following ACS administration [54]. Maternal blood glucose rises shortly after initiation of treatment and can remain elevated for five days [55]. Blood sugars should be monitored during the time of ACS administration and likely for a few days afterwards until the blood glucose concentrations return to pre-ACS ranges. A proactive approach to diet and increases in insulin therapy during this period in diabetic women may be beneficial [56]. Women with diabetes may also be candidates for rescue ACS if clinically indicated [1,5].Non-diabetic pregnant women have not traditionally undergone routine glucose monitoring during ACS therapy.

ACS have also been shown to be beneficial in women with premature rupture of membranes at less than 34^{+0} weeks [5]. Decreased risks of RDS, periventricular hemorrhage, NEC, and neonatal death have been demonstrated with the administration of a single course of ACS, even with premature rupture of membranes (PPROM). Importantly there is no increased risk of maternal or neonatal infection when a single course is utilized. Though birth occurs within one week in at least one half of patients with PPROM [57], a large percentage will remain undelivered. With the recommendation that delivery occur at 34 weeks, the clinically stable patient with PPROM would seem to be a potential target for a repeat ACS [20]. Previous studies highlight the controversy in this approach.

While some studies of multiple courses of ACS demonstrated an increased risk of chorioamnionitis and neonatal sepsis when utilized, the Cochrane review, which included several trials that included women with PPROM did not find an overall increased risk of chorioamnionitis [58–60]. Two secondary analyses of one trial did not show an increased rate of neonatal sepsis when comparing patients that received a second course of ACS to those that received a single course

[61,62]. However the rate of neonatal sepsis was high in both groups (single course, 16.2% compared to two courses 17.2%, p 0.756) [61]. ACOG recognizes this controversy and states that there is insufficient evidence to make a recommendation for or against the use of rescue ACS in patients with PPROM [1]. The WHO states that ACS is appropriate for women with PPROM without clinical signs of infection [2].

8. Future directions and research

For the optimal use of ACS, there are several important areas of investigation that remain. The optimal dose and dose interval are still debated [63]. Some hypothesize that providers are giving too high a dose of ACS [64]. Better understanding how the concentration of ACS impact fetal development is important [65]. Alternative dosing intervals to administration every 24 h have scarcely been investigated [66]. One RCT of 12-h compared to 24-h dosing of betamethasone showed similar rates of respiratory and other outcomes, with the exception of an increased incidence of necrotizing enterocolitis in the 12-h group [67]. This may bear further study with larger trials. Pharmacokinetic and pharmacodynamic investigations are lacking for ACS. Additionally, the development of a measureable biomarker of fetal maturational response would be invaluable in determining appropriate dosing strategies.

Additionally, there may be potential for individualizing ACS therapy. Pharmacogenomics seeks to understand how genetic differences among individuals cause varied responses to the same drug and seeks to develop drug therapy strategies to compensate for these differences. Preliminary studies have found multiple genetic polymorphisms in drug metabolizing enzymes and steroid receptors that are associated with higher rates of neonatal RDS after ACS [68,69]. Further investigation is ongoing in this area. Just as in other areas of medicine, optimizing efficacy and minimizing adverse effects are the ultimate goals. For several therapeutics, the Clinical Pharmacology Implementation Guidelines (https://cpicpgx.org/guidelines) can help providers use pharmacogenomics to make treatment decisions. Perhaps utilizing genomic and phenotype markers, providers will be able to tailor ACS to individual patients in the future.

ACS are crucial therapies for women who will deliver preterm babies. For this reason dexamethasone is listed on the WHO's List of Essential Medicines [70]. As noted, however, there are still controversies related to ACS and active investigation into improving and individualizing this therapy is needed. As clinical practices change, providers often expand the indications for medication use before research has shown safety and efficacy. This includes extending use beyond populations included in trials. This creates some uncertainty and controversy for the use of ACS. However, the bottom line is that ACS reduce mortality and morbidity for preterm newborns and are one of the most important therapeutic advances of modern medicine used in everyday practice of obstetrics.

Conflicts of interest

The authors have no conflicts of interest.

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