Use of Antenatal Corticosteroids in the Management of Preterm Delivery

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Abstract

Objective This narrative review of the literature explores the current evidence and recommendations in favor of antenatal corticosteroids use during impending preterm deliveries as well as related issues and concerns.

Study Design Synthesis of findings from published medical literature on antenatal corticosteroids and prematurity, retrieved from searches of computerized databases and authoritative texts.

Results It is now recognized that an intramuscular course of betamethasone or dexamethasone given to a woman expected to deliver preterm not only accelerates pulmonary epithelial development but also matures other organ systems, significantly decreasing the chances of neonatal morbidities and increasing chances of survival.

Conclusion There remain uncertainties over the efficacy of the established protocol in populations such as the very early preterm, the late preterm, and multiple gestations. Alternative regimens remain controversial because of fear of adverse effects and doubts regarding whether benefits outweigh risks.

Keywords
- antenatal corticosteroids
- prematurity
- betamethasone
- dexamethasone

Preterm birth, or birth at less than 37 completed weeks of gestation, is a main determinant of postnatal and long-term morbidity and mortality.[1] Around 12% of the United States births are preterm and mortality among these infants constitutes two-thirds of all infant deaths.[2] While its rates have recently been witnessing a strong decline within the United States,[2] preterm birth rates have been increasing worldwide, spawning a public health burden with significant social and economic ramifications.[3] Aside from the risk factors—namely, social stress and race, infection and inflammation, and genetics—that contribute to preterm birth, the mechanisms involved in the initiation of labor have not been identified yet, and it is not possible to predict with precision the timing of birth in humans.[4] The efficacy of antenatal corticosteroids (ACSs) in promoting the survival of preterm infants is unprecedented. Moreover, they were demonstrated to have no adverse effects into adulthood[5] and their action, not only reduces the risks of respiratory distress syndrome (RDS), a major contributor to preterm death and disability,[6] but also lowers incidence and severity of other important risk factors associated with prematurity such as intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and systemic infections.[5] Many studies are currently aiming to optimize ACS therapy by exploring its use in different situations.

Use and Action of Antenatal Corticosteroids

Glucocorticoids promote the maturation of many vital fetal organs through the action of cortisol that binds to the glucocorticoid receptors (GR) of target cells.[7] They are indispensable for the proper development and maturation of fetal lungs and subsequent postnatal survival.[8,9] Glucocorticoids stimulate the development of lung tissue structure, thus increasing lung volume and enhancing pulmonary surfactant synthesis and secretion, resulting in effective clearance of lung fluids and improved respiratory function.[7,10,11]

The two ACS betamethasone and dexamethasone are effective in promoting the development of fetal organs and in increasing the effectiveness of surfactant therapy.[5,12] These synthetic fluorinated steroid molecules with a very high

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affinity to GR are isomers with similar ideal pharmacological properties.[7] Both have no mineralocorticoid activity, weak immunosuppressive effects and can easily cross the placental barrier without being metabolized.[7,12] The betamethasone solution is composed of an equal mixture of betamethasone sodium phosphate and betamethasone acetate.[13,14] The former has a short half-life, and is rapidly absorbed after dephosphorylation unlike the latter which has a longer half-life providing long-lasting activity.[7] It is administered as two intramuscular (IM) injections of 12 mg, 24 hours apart.[12] The dexamethasone solution is composed of dexamethasone sodium phosphate, which is metabolized and absorbed faster than betamethasone. It is administered as four IM injections of 6 mg, 12 hours apart.[12] Hydrocortisone has at times been considered an alternative ACS, however a very high dose is needed to overcome its rapid metabolism.[15] Studies exploring hydrocortisone use are limited and do not confirm efficacy.[15–17]

While several studies have attempted to understand the peculiarities of each of betamethasone and dexamethasone, the data available till date has not clearly shown which ACS is more beneficial and offers fewer risks. Indirect comparisons of trials involving ACS versus placebo or no treatment included in the Cochrane review revealed that betamethasone exhibited a greater reduction in RDS and lower risk of sepsis.[5] Moreover, betamethasone has been shown in some comparative retrospective studies to have a greater reduction in neonatal mortality,[18] reduced risk of impaired neurodevelopmental status and hearing impairment,[19] bronchopulmonary dysplasia (BPD),[20] and lower risk of periventricular leukomalacia (PVL).[21] Dexamethasone still has wider availability and lower cost[22] and was proven to be as equally effective as betamethasone in reducing neonatal morbidities and mortalities.[5,14] The Cochrane systematic review that included trials directly comparing outcomes of betamethasone versus dexamethasone has shown that dexamethasone significantly decreases the risk of IVH (risk ratio [RR] 0.44, 95% confidence interval [CI]: 0.21–0.92; four trials, 549 infants).[14] With the exception of lower fetal heart rates (FHR) and higher breathing times at day 2,[23] as well as increased fetal movements in dexamethasone-exposed fetuses,[24] it is not clear which steroid improves the biophysical profile.[14] Nonetheless, dexamethasone has powerful nongenomic effects on cellular functioning,[25] requires four injections (compared with two for betamethasone), and lacks long-term assessment.[5] It is prudent to note that many of the above-cited studies must be interpreted cautiously due to inherent biases resulting from their small sample size or retrospective nature. A large multicenter, randomized, placebo-controlled trial currently being conducted is expected to determine which corticosteroid is more beneficial.[26]

Benefits of a Single Antenatal Corticosteroid Dose

Essentially based on Liggins and Howie's trial,[13] designed to achieve optimal duration and occupancy of GR sites,[7] the most studied and validated protocol for ACS therapy has been to provide either two 12-mg doses of betamethasone every 24 hours or four 6-mg doses of dexamethasone every 12 hours.[12] This regimen raises occupancy levels of GR sites to a maximum of 75%, providing near-maximal induction of associated genes in fetal tissues.[7] Limited data exist on the benefits of the administration of one dose of ACS in humans. Retrospective studies evaluating the effectiveness of an incomplete course in preterm neonates born before being given a second dose have shown inconsistent results.[27–32] In some studies, ACS reduced neonatal death after exposure to a single dose,[5] and was found to be associated with significant reductions in morbidities.[27,29] Other studies could not find such a benefit.[32] When compared with infants exposed to a complete course, those exposed to a single dose had similar outcomes,[30,31] except for a higher neonatal death rate at 24 to 27 weeks gestational age (GA).[28] In one randomized trial, infants at 34 to 36 weeks GA exposed to a single dose had lower rates of RDS compared with unexposed.[33] While animal studies suggest that a single dose may be sufficient,[33–35] results have not been translated clinically due to inadequate study designs, evaluating the unintended administration of a dose that was barely given enough time to act.

Timing of Antenatal Corticosteroid Therapy

Studies attempting to estimate an ideal time to begin ACS therapy have found that 40 to 60% of women deliver within 7 days after first injection.[36–38] Women exposed to a complete course had an average GA of $28^{6/7}$ weeks at intake and delivered at 32 weeks.[37] The median time interval between an ACS injection and delivery was around 11 days and reached up to 25 and 41 days in women with spontaneous preterm labor (PTL) and vaginal bleeding, respectively.[37] Moreover, women were more likely to last more than 7 days when treated before 28 weeks GA compared with those treated later.[39] Infants exposed to ACS within a week before birth (48 hours–7 days) fared better than those born within 2 weeks (7–14 days)[5,13,36,40–42] or those who were remotely exposed ($>$ 14 days).[12,43] Most importantly, corticosteroids were not shown to decrease rates of RDS after 1 week of exposure.[36]

Administration of repeat ACS courses remains controversial. While some studies in animals and humans did not find differences,[44–47] others have found proportionately higher occurrences of decreased birth weight, decreased head circumference, decreased growth, and brain development delay, cerebral palsy, NEC, death, and increased sepsis.[48–58] Two randomized trials have been terminated after demonstrating lack of benefits or evidence of decreased birth weight in the treatment group.[45,49] The Cochrane systematic review on repeat ACS therapy concluded that the practice has short-term benefits in reducing the incidence of RDS (RR: 0.83, 95% CI: 0.75–0.91, eight trials, 3,206 infants, number needed to treat [NNT] 17, 95% CI: 11–32) and other serious composite morbidities (RR: 0.84, 95% CI: 0.75–0.94, seven trials, 5,094 infants, NNT: 30, 95% CI: 19–79) such as BPD, IVH grade 3 or 4, NEC, sepsis, PVL, and or retinopathy of prematurity.[59] The review did not find statistically significant reductions in birth

weight after adjusting for GA, but it did not assess whether there was an increased risk of harm with increasing doses either. Studies on long-term outcomes are limited and there is currently no evidence regarding benefits or risks. The Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study (MACS) trial found smaller anthropomorphic measures for repeatedly exposed infants[48] however a follow-up study on those children at age 5 found no increased risks of death[60] but increased risk of neurodevelopmental/neurosensory disability[61] for those born at $\geq$ 37 weeks.

Studies assessing a single rescue course in pregnancies still at high risk of imminent delivery within the following week have shown an increase in respiratory compliance[62] and a reduction in rates of RDS, composite neonatal morbidity, and days on ventilator support.[63,64] Administering one extra booster dose after an initial course of corticosteroids in another trial showed that more infants in the treatment group required surfactant therapy and those who were delivered within 24 hours of the dose had increased risks of developing RDS compared with placebo.[65] The American Congress of Obstetricians and Gynecologists (ACOG) recommends administering a single additional course of ACS in pregnancies below $32^{6/7}$ weeks GA after 2 weeks from the initial course.[12]

All women presenting with threatened preterm delivery are considered as primary candidates for immediate ACS therapy. Obstetricians must be able to precisely predict the time of delivery so that therapy could be administered early enough for maximum effect. In cases of PTL or vaginal bleeding with intact membranes, fetal fibronectin (fFN) tests may be useful to estimate if delivery might happen within the following 7 to 10 days.[66–68]

Assessment of the cervicovaginal fFN assay, fetal breathing movements (FBM), and sonographic measurement of cervical length (CL) with various cutoff values have been used in identifying which women who present with signs and symptoms of PTL will benefit from admission to the hospital for corticosteroid, tocolytic therapy, and/or transfer to a facility which can provide a more advanced level of perinatal care. Conversely, these tests can detect women with signs and symptoms of PTL who can safely avoid potentially harmful treatments such as repeat courses of steroids. A recent study concluded that CL when combined with fFN testing in case of CL between 15 and 30 mm, improves identification of women with a low risk to deliver spontaneously within 7 days.[68] Another recent metaanalysis,[69] has calculated a positive likelihood ratio for predicting preterm delivery within 48 hours and 7 days of 3.3 (2.1–5.0) and 3.6 (3.1–4.3) for fFN, 10.4 (2.8–38.4) and 31.6 (4.1–244) for FBM, and 6.4 (4.7–8.7) and 6.8 (5.1–9.2) for CL (1.5 cm), respectively. The negative likelihood ratio was 0.47 (0.29–0.76) and 0.31 (0.25–0.39) for fFN, 0.27 (0.15–0.49) and 0.34 (0.18–0.64) for FBM, 0.26 (0.12–0.58) and 0.29 (0.17–0.49) for CL. The authors concluded that absence of FBM appears to afford the highest diagnostic accuracy. Studies addressing the combination of two or more of these tests are limited and no published studies have assessed whether combining fFN and/or transvaginal ultrasonography with FBM might improve the short-term prediction of preterm birth in symptomatic women. Furthermore, a recent study evaluated a quantitative fFN test for spontaneous preterm birth in symptomatic women and reported that quantitative information has added value over the currently used qualitative fFN test.[70] Increasing the fFN threshold could perhaps enhance its value in predicting preterm birth in symptomatic women.

Antenatal Corticosteroid in Early Preterm

Studies examining ACS administration in extremely low-birth-weight ($<$ 1,000 g) and extremely preterm infants ($<$ 25 weeks GA) are limited. Neonates born at that age are extremely fragile. Their chances of survival to 28 days are very low and they may suffer from severe respiratory and neurodevelopmental disabilities that have lifelong sequelae.[71,72] Before the advent of assisted ventilation, few neonates born before 28 weeks GA were able to survive. Most clinical trials included in the original Crowley et al report[73] excluded neonates $<$ 28 weeks GA, and as data was insufficient and prognosis grim, decision to resuscitate, and treat intensively was less likely with lower GA.[74] Regardless of the time of exposure to ACS, most infants below 28 weeks GA are intubated.[12] Moreover, physiologically, the induction of lung maturation relies on the presence of cells that are sensitive to corticosteroids. Fetuses below 25 weeks GA, in the canalicular stage of lung development, lack sufficient amounts of surfactant-producing type II pneumocytes and gas-exchanging type I pneumocytes, and do not have properly functioning alveolar structures.[75] Thus, it was thought that such early use of ACSs is unnecessary. The ACOG does not recommend administration of corticosteroids before viability[12] due to lack of supporting data and systematic reviews have not found enough evidence to confirm the effectiveness of ACS at ages below 26 weeks GA.[5,76] With the advancement that perinatal care has witnessed lately, the decision to resuscitate, intensively care for, and accordingly administer ACS to extremely preterm babies has become frequent. Studies exploring the action of corticosteroids on the extremely preterm lung have observed larger alveoli, thinner alveolar walls, increased capillary supply, increased maturation and differentiation of epithelial cells, as well as emergence of lamellar bodies.[8,75] These changes in lung structure are likely to enhance lung function, improve postnatal surfactant treatment outcomes, and increase chances of survival.

ACS was shown to be the strongest factor that affected survival of the extremely preterm.[28,77–80] ACS-treated infants born at 23 to 25 weeks GA had more chances of survival and less neurodevelopmental impairment at 18 to 22 months while 22-week infants had lower mortality and suffered less NEC.[81] Retrospective analyses detected significant increases in survival to discharge of ACS-treated infants at GA ranging between 22 and 27 weeks.[82] RDS, oxygen use duration, and surfactant use were decreased at ages above 24 weeks and ACS use was extremely effective in reducing IVH and severe IVH. Studies that have examined the effect of ACS in early preterm infants are summarized in ►**Table 1**.

Table 1 Summary of studies on the effect of ACS in early preterm infants

Authors	Design	Objective	Participants	Main findings
Onland et al[76]	Systematic review	ACS effect at < 26 wk GA	1,118 infants (nine randomized trials)	No evidence of beneficial effects of ACS treatment at < 26 wk GA
Carlo et al[81]	Prospective cohort study	ACS effect at 22–23 wk GA	10,541 infants born at 22–25 wk	Exposure was associated with lower rate of death or neurodevelopmental impairment at 18–22 mo
Foix-L'Helias et al[28]	Retrospective cohort study	ACS effect on mortality and morbidity in infants born at 24–27 and 28–32 wk GA	2,323 infants born at 22–32 wk	Increase in survival of the extremely preterm 24–27 wk: no decrease in adverse long-term outcomes 28–32 wk: lower risk of white matter disease
Hayes et al[78]	Retrospective cohort study	ACS effect in decreasing rate of death at 23 wk GA	181 infants born at 23 wk	A complete course at 23 wk GA resulted in reduction in odds of death
Abbasi et al[80]	Retrospective cohort study	ACS effect at < 24 wk GA	117 infants born at 23–25 wk	Exposure < 24 wk GA was associated with reduction in risk for severe IVH and neonatal mortality
Mori et al[82]	Retrospective cohort study	ACS effect at < 24 wk GA	11,607 infants born at 22–33 wk	Exposure improved survival and decreased acute respiratory and neurological morbidity and decreased IVH and severe IVH at 24–29 but not at < 24 wk GA
Manktelow et al[83]	Prospective cohort study	ACS effect at different GAs	13,406 infants born at < 32 wk	Exposure improved 24–29 wk infant survival with no effect on length of hospital stay and chronic lung disease incidence

Abbreviations: ACS, antenatal corticosteroids; GA, gestational age.

The decision to treat an extremely preterm infant must be approached with extreme caution and carefully discussed with obstetricians, neonatologists, and parents. Though studies have shown less mortality, morbidity is substantial.[83] The abnormal adaptations that happen in the lungs and brains allowing survival push the fetus's developmental plasticity to its extremes and increase disability.[84] It is also important to take into account, in case delivery did not occur, the risks and benefits of a potential repeat dose.

Antenatal Corticosteroid in Late Preterm and Term Infants

Late preterm (LP) infants (34–36 weeks GA) constitute 74% of all preterm births[85] and have fewer adverse outcomes than infants born earlier. Incorrectly assumed to be as physiologically and metabolically developed as term infants,[86] LP infants generate a considerable burden on the health system as they constitute 73% of neonatal intensive care unit (NICU) admissions[79,85,87] and suffer from higher rates of mortality and neonatal morbidities compared with term infants.[2,87–92]

Fetal lungs in the LP period attain a relatively advanced level of structural and physiological maturity. Surfactant secretion is maintained while rapid alveolarization, vascularization, and thinning of interstitial tissue take place to allow for efficient gas exchange and to prevent the collapse of the alveoli.[75] Glucocorticoids are directly involved in the regulation of fetal lung fluid secretion and resorption through promoting the expression of epithelial sodium channels and aquaporin-1 water channels.[93] Underdeveloped lung epithelial ion and fluid transport mechanisms affect the transition to air breathing resulting in an increased risk of transient tachypnea of the newborn (TTN) and RDS.[93]

ACS have shown a nonsignificant protective effect against mortality in LP infants who have been admitted to NICU.[79] A cohort study observed reduced risks of RDS among LP infants who were previously exposed to ACS, however there were also increased risks of low Apgar score and a tendency for growth restriction.[94] A triple blind randomized clinical trial found that exposure to ACS at GA > 34 weeks did not result in a reduced risk of RDS and TTN but in lower rates of jaundice.[95] Another prospective case–control study found better Apgar scores and less RDS in ACS-treated LP infants.[33] Retrospective analyses also showed lower risks of respiratory disorders in infants exposed to ACS before 34 weeks and born after 34 weeks GA.[96]

Studies investigating whether providing ACS is beneficial after evidence of low TDx-fetal lung maturity (FLM)-II in LP infants have yielded unconventional results. One study found a significant increase in TDx-FLM-II values 1 week after ACS administration, suggesting an increase in FLM.[97] Another study however, found that, infants who tested immature and were managed expectantly had better respiratory outcomes and lower risks of hypoglycemia and sepsis than those who were ACS-treated.[98] The significance of FLM testing in the LP period is questionable as other studies have found higher rates of RDS among infants born after testing mature.[99–101] A summary of studies that evaluated the effect of ACS in late preterm infants is presented in ►**Table 2**.

As infants born by elective cesarean section (ECS) at term are still at higher risk compared with those vaginally delivered,[102] the usefulness of ACS at term ECS was assessed and exposed infants at 37 to 38 weeks GA were found to be at lower risk for RDS, TTN, or being admitted to special care.[103] ACS for ECS showed no differences in adverse behavioral, cognitive or developmental outcomes as well as reported medical problems in the long term.[104]

Prolonging gestation until term is ideally the best policy. Out of three threatened preterm pregnancies that are < 34 weeks, either one or two will be delivered later.[94] In high-risk cases such as preterm premature rupture of membranes, severe preeclampsia, or spontaneous labor however, more serious fetal/maternal morbidity or mortality could occur and delaying might not be an option. The baseline risk for developing RDS in LP infants is relatively low as it is estimated that 145 LP infants must be treated to avoid one case of RDS.[105] More studies are needed to confirm that the benefits of the prophylactic use of ACS in LP infants outweigh the possible risks. A large clinical trial on the effects of antenatal late preterm steroids, may give conclusive answers (http://clinicaltrials.gov/ct2/show/NCT01222247).

Antenatal Corticosteroid in Multiple Gestations

The evidence concerning efficacy of ACS in multiple gestations is limited and contradictory.[5] With assisted reproductive technology being increasingly accessible, there has been an upsurge in the occurrence of twins and multiples during the recent decades.[106–108] Preterm multiples are more likely to be given ACS[109] and more than 60% of multifetal gestation births are born preterm.[110] The same protocol for ACS therapy employed for singleton pregnancies is currently recommended for women with threatened preterm multifetal pregnancy.[111]

Many studies on twins have not been able to show a statistically significant reduction in the rates of death, or other morbidities following therapy,[112–114] however others have shown similar[109,115] or greater reduction.[116–118] It has been shown that ACS are most beneficial when delivery occurs 2 to 7 days after the first dose[119] and that its efficacy against RDS decreases when the fetal number increases,[118] and a complete course decreases the incidence of IVH regardless of the fetal number.[120] Repeat ACS courses in twins have shown no reduction in RDS and significantly lower birthweight[113,114,121] while an additional rescue course did not result in a reduction in RDS, but it improved neonatal outcomes without affecting growth.[122] ►**Table 3** summarizes studies that examined the effect of ACS in multiple gestation.

Explanation for such inconsistencies in the outcomes has led to a debate among researchers about whether the current dose and regimen are optimal in twins. A study found that the betamethasone half-life is significantly shorter in twin pregnancies and hypothesized that the presence of two fetoplacental units might lead to an increase in metabolism.[123] Conversely, another study found that betamethasone parameters were similar in singleton and multifetal pregnancies.[124]

Table 2 Summary of studies on the effect of ACS in late preterm infants

Authors	Design	Objective	Participants	Main findings
Eriksson et al[94]	Retrospective cohort study	Duration of effects and health consequences of earlier ACS exposure in late preterm or term infants	11,873 infants born at $>$ 34 wk	Reduction in risk of RDS and small head circumference. Term infants had increased risks of low Apgar scores
Porto et al.[95]	Randomized clinical study	Determine ACS effect in reducing respiratory disorders in 34–36 weeks GA infants	273 infants born at 34–36 weeks	No reduction in incidence of respiratory disorders
Balci et al[33]	Randomized clinical study	Determine effect of single ACS dose at 34–36 wk of pregnancy on lung maturation	100 34–36 wk pregnant women	Reduction in rate of RDS
Ventolini et al[96]	Retrospective cohort study	Determine effect of ACS on respiratory disorders incidence in infants born between 34 and 36 wk GA	1,078 infants born at 34–36 wk	Lower incidence of respiratory disorders in late preterm infants

Abbreviations: ACS, antenatal corticosteroids; GA, gestational age; RDS, respiratory distress syndrome.

Table 3 Summary of studies on the effect of ACS in multiple gestation

Authors	Design	Objective	Participants	Main findings
Hashimoto et al[109]	Retrospective cohort study	ACS effect in reducing death or major morbidity in very low-birth-weight multiple and singleton infants	2,357 infants (652 multiples) weighing 401–1,500 g	Similar risks on both singleton and multifetal infants
Turrentine et al[112]	Retrospective cohort study	ACS effect in reducing RDS in twins	168 infants born at 24–34 wk	No reduction in the incidence of RDS
Murphy et al[114]	Retrospective cohort study	ACS effect given prophylactically every 2 wk (24–32 wk GA) versus once at risk of preterm delivery	1,038 twin infants born at $\geq$ 24 wk	No reduction in the incidence of RDS
Battista et al[115]	Retrospective cohort study	ACS effect in preventing morbidity and mortality in preterm twins and singletons	60 twins and 60 singletons delivered at 24–34 wk	No differences in major morbidities or mortality
Blickstein et al[118]	Retrospective cohort study	ACS effect on incidence of RDS in very low-birth-weight singletons and multiples	8,120 multiples born at 24–32 wk	Efficacy of ACS against RDS decreased with increase in the fetal number
Blickstein et al[120]	Retrospective cohort study	ACS effect on severe IVH risk in very low-birth-weight preterm singletons and multiples	7,636 infants born at 24–32 wk	A complete course decreased incidence of IVH regardless of the fetal number
Kuk et al[119]	Retrospective cohort study	Effect of ACS time interval to delivery on RDS incidence in preterm twins	468 twins	A complete course decreased RDS rate when ACS-to-delivery interval was 2–7 d
Choi et al[113]	Retrospective cohort study	ACS effect on incidence of RDS in singletons and twins	450 singletons and 117 twins born at 24–34 wk	ACS exposure did not reduce RDS in twins
Waters et al[121]	Retrospective cohort study	ACS effect on anthropometric measurements in twins	178 twins born at $>$ 24 wk	Repeat ACS courses associated with decreased head circumference
Bibbo et al[122]	Retrospective cohort study	Efficacy of rescue ACS course in twin pregnancies	130 twins born at 24–34 wk	May be associated with improved neonatal outcomes
Quist-Therson et al[129]	Prospective cohort study	ACS effect on RDS incidence and surfactant use in low-birth-weight infants	946 infants weighing 501–1,500 g	No reduction in the incidence of RDS or surfactant use in multiple gestations of white race

Abbreviations: ACS, antenatal corticosteroids; GA, gestational age; RDS, respiratory distress syndrome.

Moreover, no significant difference was noted between twin and singleton blood levels in either singleton versus twin and singleton obese versus singleton nonobese gestations indicating that larger plasma volumes do not affect the distribution levels of the drug.[112,125] Variations in basal FHR, FHR variability, and body and breathing movements have also been found to be similar in twin and singleton fetuses after exposure to ACS.[126] These studies imply that when ACS is given in accordance with the current recommendations, the amount of steroid available for a preterm twin fetus could be sufficient, as it is comparable to that available to a singleton. Fetuses might be exhibiting lower responsiveness to therapy because the causes of PTL in multiple pregnancies do not exert enough "stress" for the fetus to respond to ACS.[127,128] There is evidence that in preterm twins a reduction in RDS after ACS occurs, but it might not be as evident as in preterm singletons. The main reason findings are still inconclusive in that regards, is that studies exploring twin gestations have all been retrospective with a relatively low sample size and multiple confounders, while it is practically impossible to design a cohort study with enough power to confirm a difference.

Conclusion

Antenatal administration of corticosteroids is perhaps one the most life-saving and cost-effective procedures in obstetrics. Many of the studies presented throughout this article may have limitations mainly because of the low power to detect differences. It is important to note that conducting randomized trials on such special populations is costly and difficult to design and execute. Nonetheless, research in this field is fast advancing and there is a great potential in the studies that are currently underway.

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