Past and Present: A Review of Antenatal Corticosteroids and Recommendations for Late Preterm Birth Steroids

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Abstract

Keywords

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Since 1972, the beneficial neonatal effects of antenatal corticosteroids (ACSs) have been repeatedly demonstrated in pregnancies at risk of preterm birth before 34 weeks' gestation. While ACS utilization before 34 weeks has been high since the 1990s, knowledge gaps regarding the risks and benefits of ACS continue to exist. Recent evidence has been published regarding the benefit of ACS in the late preterm period. This review addresses the evidence and knowledge gaps for ACS use before and after 34 weeks' gestation. We also provide recommendations for ACS use in the late preterm period.

Review of Steroids before 34 Weeks

Forty-five years ago, Liggins and Howie demonstrated that antenatal corticosteroid (ACS) use could significantly decrease respiratory distress syndrome (RDS) in live born infants less than 32 weeks' gestation.[1] Follow-up studies confirmed the beneficial effect of ACS on RDS[2–4] and subsequently, several articles were published detailing the additional beneficial effects of ACS on other neonatal outcomes. In 1990, Crowley et al performed a systematic review and meta-analysis of 12 trials demonstrating a significant decrease in RDS, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and neonatal death in neonates exposed to corticosteroids.[5] In 1994, based on these and other results, a National Institutes of Health (NIH) consensus development panel published recommendations for treatment of all fetuses between 24 and 34 weeks' gestation at risk of preterm delivery.[3]

Knowledge gaps at the time that needed to be addressed in future research included repeat ACS and long-term cognitive, behavioral, psychological, and physical development outcomes.[3] These recommendations were reaffirmed by the NIH and received support from the American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice in May, 2002.[6] At that time, the evidence regarding the use of ACS after 34 weeks' gestation was considered inadequate to recommend for or against its use; it was only to be used if there was evidence of fetal pulmonary immaturity. For many years now, a single course of ACS for fetuses between 24 and 34 weeks' gestation at risk of preterm birth has been a mainstay in obstetrical practice. The most recent Cochrane review and meta-analysis of 30 studies (7,774 women and 8,158 infants) found a reduction in perinatal death, neonatal death, RDS, IVH, NEC, need for mechanical ventilation, and systemic infections in those treated with ACS.[7]

Remaining Knowledge Gaps for Steroids before 34 Weeks

Periviable Birth

While the use of ACS between 24 and 34 weeks' gestation has been steadfast, there has been some controversy surrounding other aspects of ACS administration. Periviable birth has recently been defined as delivery occurring from $20^{0/7}$ to $25^{6/7}$ weeks' gestation.[8] While long-term morbidity of surviving periviable infants is very high, the survival rates vary based on institutional practices regarding initiation of resuscitation. Survival is as high as 27% for births at 23 weeks and 59% for births at 24 weeks.[8,9] Recently, a study compared survival and neurodevelopmental outcomes of 4,274 infants born at 22 to 24 weeks' gestation, across three consecutive birth-year epochs (2000–2003, 2004–2007, and 2008–2011). They determined that the rate of survival with neurodevelopmental impairment compared with death (adjusted relative risk [aRR]: 1.27, 95% confidence interval [CI]: 1.01–1.59) and the rate of survival without neurodevelopmental impairment compared with death (aRR: 1.59, 95% CI: 1.28–1.99), increased over time. In this study, the rate of ACS use increased with time, however, this variable was left out of the analysis, so the temporal effect would not be obscured. When analysis was restricted to infants who received active treatment, the study outcomes were unchanged, making it unlikely that the increased rate of survival was due to the increase in ACS use.[10] In a 2011 cohort study, ACS was found to reduce death, IVH, periventricular leukomalacia, NEC, and neurodevelopmental impairment at 18 to 22 months for those exposed to ACS at 23 to 25 weeks' gestation.[11] These associations have been confirmed in additional studies.[12–15] None of these studies, however, were randomized trials. Due to the relatively low volume and complexity of periviable deliveries, randomized trials are highly unlikely. In 2014, a joint workshop among Society for Maternal-Fetal Medicine (SMFM), ACOG, National Institute of Child Health and Human Development (NICHD), and American Academy of Pediatrics (AAP) provided recommendations for periviable birth. For threatened or imminent periviable birth, they recommended to consider ACS for women at risk of delivery between $22^{0/7}$ and $22^{6/7}$ weeks' gestation, and recommended the use of corticosteroids for all women at risk of preterm birth $\geq$ 23 weeks' gestation.[16] This recommendation has since been amended by ACOG and SMFM to consider ACS at $23^{0/7}$ to $23^{6/7}$ weeks, and recommend its use for all births $\geq$ 24 weeks' gestation.[8] To assist in the counseling of patients regarding possible outcomes of periviable birth, the NICHD provides an online calculator that estimates survival, survival without neurodevelopmental impairment, and death.[17]

Fetal Growth Restriction

Concerns regarding the effect of ACS on growth-restricted fetuses arose when Liggins and Howie found an increase in fetal death in a subgroup of women with severe hypertension, proteinuria, fetal growth restriction and low urinary estrogen.[1] Since, studies evaluating the outcomes of growth-restricted fetuses treated with ACS versus no intervention yielded conflicting results. A recent study found no difference in RDS, IVH, NEC, and neonatal mortality.[18] Another found a decreased neonatal mortality and overall neonatal morbidity.[19] In a 2009 review of the literature, Torrance et al concluded that the effect of ACS on neonatal outcomes of intrauterine growth restricted (IUGR) fetuses remains inconclusive, and IUGR fetuses with abnormal umbilical artery Doppler studies treated with ACS did not have a significant alteration in the incidence of RDS, IVH, NEC, or neonatal mortality.[20] In IUGR fetuses with abnormal umbilical artery Doppler blood flow, some studies have demonstrated a transient improvement in the umbilical artery Doppler blood flow,[21–24] while others have not.[25,26] This divergence in effect has caused some to hypothesize that IUGR fetuses without a transient improvement in umbilical artery Doppler flow may be at a higher risk for perinatal complications and hemodynamic decompensation after ACS administration.[23,24] IUGR fetuses are exposed to more endogenous steroids due to a reduced expression of 11 β-hydroxysteroid dehydrogenase type-2, which prevents maternal steroids from crossing the placenta. This physiologic change may reduce the effect of exogenous steroids on an IUGR fetus.[20] With a lack of randomized controlled trials (RCTs) addressing this population, others have expressed desire to conduct a definitive trial.[27] The current recommendations for ACS use do not differentiate between IUGR and non-IUGR fetuses.

Multifetal Gestations

Similarly, the effect of ACS in multifetal gestations remains understudied. While multiple gestations were included in the ACS trials, there is no trial that definitively addresses this group of patients. A subgroup analysis in the 2006 Cochrane review on ACS revealed no differences in RDS, cerebroventricular hemorrhage, and neonatal death in multifetal gestations treated with ACS compared with those untreated.[28] Of note, the direction and magnitude of the relative risks for these outcomes in multifetal gestation were similar to the analysis in the overall groups; however, the number of patients with multifetal gestation was small and mostly from two studies.[28] A subsequent Cochrane review confirmed these findings and also found no evidence that ACS work differently in singleton versus multifetal gestation.[7] A pharmacokinetic study suggests the half-life of betamethasone is significantly shorter in twin pregnancies and the volume of distribution is unchanged when comparing twin and singleton gestations; however, clinical outcomes were not assessed.[29] Maternal and umbilical cord blood concentrations of betamethasone were similar in singleton and twin pregnancies.[30] Studies on the effect of corticosteroids on multifetal gestations would need to be adequately powered to demonstrate a difference. Although lacking evidence, expert opinion recommends ACS for multiple gestations at risk of preterm birth between 24 and 34 weeks' gestation.[31]

Maternal Obesity

Pre-pregnancy obesity continues to rise in the United States, increasing from 18% in 2003 to 26% in 2014.[32,33] In obese patients, there is a theoretical concern that intramuscular

medications are less effective because of altered body weight distribution, decreased lean muscle mass, alterations of pharmacokinetics, and the inadequate length of standard needles to reach the intramuscular space.[34,35] Studies that have addressed betamethasone efficacy in this population have reported no difference in rates of RDS or umbilical cord blood concentrations of betamethasone in these patients.[30,36] These studies were secondary analyses of existing data and were limited by the number of patients enrolled in the parent trials and further studies are needed to validate these findings.

Preterm Premature Rupture of Membranes

ACS has not been adequately or specifically evaluated in the setting of preterm premature rupture of membranes (PPROM). However, systematic reviews have demonstrated a reduction in fetal and neonatal death, RDS, IVH, and NEC in this subgroup.[7,28] Initially, there was concern for the risk of maternal and neonatal infection in those treated with ACS, a concern which was not confirmed in the systematic reviews.[7,28] A recent study found that even a second ACS is not associated with higher rates of neonatal sepsis.[37] As further evidence of safety, in the setting of histologic chorioamnionitis, treatment with ACS decreases the incidence of RDS, IVH, neonatal mortality, and adverse neurologic outcomes without increasing neonatal sepsis.[38,39] Overall consensus opinion is to administer corticosteroids for threatened delivery in the setting of PPROM before 34 weeks' gestation.[40]

Type of Corticosteroid

The ideal choice of ACS continues to be debated. Betamethasone and dexamethasone are both fluorinated steroids with nearly identical structures.[41] The recommended regimens of two doses of 12 mg of betamethasone intramuscularly every 24 hours or four doses of 6 mg of dexamethasone every 12 hours has not changed since the original recommendations by the NIH consensus development panel.[3] While both regimens provide demonstrable benefits, there are studies reflecting differences between the two types. Lee et al and Feldman et al found betamethasone to be associated with a reduced risk of neonatal death and lower rate of pulmonary complications in very low birth weight infants, respectively.[42,43] A RCT by Elimian et al found similar effects of betamethasone and dexamethasone; however, dexamethasone was more effective in reducing the rate of IVH.[44] A 2013 Cochrane review examined 12 RCTs comparing dexamethasone and betamethasone. Dexamethasone was found to be associated with a reduced risk of IVH and a shorter length of neonatal intensive care unit (NICU) admission. The author concluded that there is no clear advantage of one over the other and urged additional trials comparing the two corticosteroids.[45]

Timing of Antenatal Corticosteroid

The timing of ACS has been extensively studied. While the benefit of ACS is greatest 24 hours after administration and lasts for at least 7 days, even one 12 mg dose of betamethasone is associated with decreased rates of IVH and neonatal death.[46] Multiple studies and systematic reviews have also demonstrated a lack of efficacy of ACS after 7 days.[47,48] In a

retrospective cohort, delivery between 8 and 14 days was not found to be associated with increased perinatal morbidity when compared with delivery 1 to 7 days after ACS.[49] Another retrospective cohort study found that delivery >14 days after ACS was associated with increased severity of neonatal respiratory illness compared with delivery 2 to 14 days after ACS.[50]

Repeat Courses of Antenatal Corticosteroid

The initial response to the lack of demonstrated efficacy after 7 to 14 days was to repeat the ACS courses weekly. However, there were concerns regarding the risks of repeat corticosteroids without solid evidence from RCTs of a neonatal benefit. Legitimate concerns of potential harm focused on growth restriction, decreased head circumference, and delayed psychomotor development associated with repeat corticosteroids. Since then, multiple RCTs have been performed to evaluate repeated ACS courses; the largest of which by Crowther et al (Australasian Collaborative Trial of Repeat Doses of Steroids [ACTORDS]), Guinn et al, McEvoy et al, Murphy et al (Multiple courses of antenatal corticosteroids for preterm birth [MACS]), and Wapner et al (NICHD), evaluated weekly or every 2 weeks administration.[51–55] Results of the studies differed as some found no improvement in their primary neonatal outcome,[52–55] while one found reduced neonatal morbidity.[51] In the Guinn et al and Wapner et al trials, even though the primary composite outcome did not differ between the groups, some neonatal respiratory outcomes such as severe RDS were significantly lower in the repeat corticosteroid group.[52,55] In regard to adverse outcomes, Crowther et al found a decrease in weight and head circumference at birth but no difference in mean weight, length, and head circumference at the time of hospital discharge.[51] A subsequent secondary analysis revealed a rapid acceleration of postnatal growth 3 to 5 weeks after birth in those exposed to repeat corticosteroids.[56] Murphy et al found that those exposed to repeat corticosteroids weighed less were shorter and had smaller head circumferences at birth. The relationship between corticosteroids and decreased fetal growth was later found to be dependent on the number of ACS courses.[57] Wapner et al found that repeat corticosteroids ≥4 courses significantly reduced birth weight.[55]

Just as with the short-term outcomes in the original studies, long-term outcomes differed between the studies that followed the children. The 18 to 24 months and 5 years follow-up of children from the MACS trial found no difference in risk of death or disability.[58,59] However, after stratifying by gestational age at the time of birth, children born ≥ 37 weeks and were exposed to multiple ACS therapy were at increased risk of neurodevelopment/neurosensory impairment by 5 years of age.[60] Children in the NICHD trial followed up at 2 to 3 years of age had no differences in physical or neurocognitive measures; however, a higher rate of cerebral palsy was noted among children who had been exposed to repeat corticosteroids, but the difference was not statistically significant.[61]

Given these findings, investigators began to consider evaluating a single repeat ("rescue") course of ACS for women who remain at risk of preterm birth before 34 weeks. In 2001, a prospective, nonrandomized study demonstrated reduced RDS

in neonates who received rescue steroids before delivery between 28 and 34 weeks' gestation.[62] Peltoniemi et al found that a repeat course of betamethasone >7 days after a single course did not increase the rate of intact survival without RDS or severe IVH. They also noted that those who received a rescue course required more surfactant therapy for RDS.[63] In 2010, McEvoy et al reported an increase in respiratory compliance of newborns treated with a single repeat course of ACS ≥ 14 days after the initial course.[64] The definitive study of "rescue steroids" was published by Garite et al and found a significant reduction in composite neonatal morbidity for those treated with a single repeat course of steroids ≥ 14 days after the initial course if they remained at risk for preterm birth before 33 weeks' gestation.[65] No adverse growth outcomes were found in any of these three studies and a 2-year follow-up by Peltoniemi et al found no adverse effects on growth or neurodevelopmental outcomes in those treated with rescue steroids.[66]

Over the years, multiple systematic reviews have focused on the efficacy and safety of repeat corticosteroids.[67–69] The most recent Cochrane review found that repeat corticosteroids 7 days or more after the initial course reduce the risk of RDS and serious adverse infant outcome. While repeat doses of corticosteroids were associated with a reduction in mean birth weight, the adjusted birth weight for gestational age was not different between the groups. Early childhood follow-up also did not demonstrate any differences between the groups.[67]

At present, ACOG recommends to consider a single repeat course of ACS in pregnant women less than 34[0/7] weeks' gestation who are at risk of preterm delivery within the next 7 days, have intact membranes, and whose prior course of ACS was administered more than 14 days previously. They also acknowledge that rescue steroids could be provided as early as 7 days from the prior dose, and there is not enough evidence to recommend for or against rescue ACS in the setting of PPROM.[31]

Review of Steroids after 34 Weeks

Late preterm birth, delivery between 34[0/7] and 36[6/7] weeks' gestation, accounts for 71% of preterm births and 8.7% of all live births. These infants have longer hospital stays, higher hospital costs, and higher risk of other morbidities (hypoglycemia, hypothermia, feeding difficulty, and sudden infant death syndrome),[70] as well as a threefold increase in neo-

natal mortality when compared with term infants.[71,72] More than one-third of these infants will be admitted to the NICU, most frequently for respiratory indications, and will constitute 33% of all NICU admissions.[73,74]

When compared with infants born from 39 to 40 weeks' gestation, infants born at 34 weeks were at higher risk of respiratory complications, including RDS/hyaline membrane disease (odds ratio [OR]: 40.1, 95% CI: 32.0–50.3), transient tachypnea of the newborn (OR: 14.7, 95% CI: 11.7–18.4), pneumonia (OR: 7.6, 95% CI: 5.2–11.2), respiratory failure (OR: 10.5, 95% CI: 6.9–16.1), and need for ventilator support (OR: 13.9, 95% CI: 11.0–17.6).[73] The risk of pulmonary morbidity decreased with advancing gestational age.

In the 1994 NIH consensus statement, ACS was not recommended beyond 34 weeks because of the low risk of neonatal mortality, RDS, and IVH in this age group.[3] A meta-analysis of RCTs published between 1972 and 1994 showed similar risk of RDS in the late preterm period when compared with infants delivered after 37 weeks (OR: 0.62, 95% CI: 0.29–1.30).[48] However, the pulmonary system may not be structurally or functionally mature in the late preterm period.[75] While the literature supports increased risk of short-term respiratory morbidities of prematurity, the long-term outcomes are less clear. Some studies have shown an association between late preterm birth and childhood respiratory conditions, such as asthma and bronchitis; however, this has not been a consistent finding in the literature.[76–78]

Modern literature suggests a benefit for ACS for infants delivered in the late preterm period. Retrospective studies have reported that exposure to ACS before 34 weeks was beneficial to infants born in the late preterm period, and was associated with a significant reduction in respiratory morbidity, including RDS and need for ventilation.[79,80]

Though ACS administered in the late preterm period have shown improvement of fetal lung maturity testing,[81] few studies have evaluated the clinical outcomes (►Table 1). Retrospective observational studies of immature fetal lung maturity testing and subsequent ACS administration have been inconsistent. Some reported benefit with decreased need for respiratory support, while other studies have reported no benefit and increased risk of hypoglycemia and presumed sepsis.[82,83] Porto et al conducted a small RCT administering one course of betamethasone for women

Table 1 Summary of randomized controlled trials of antenatal corticosteroid administration in the late preterm period

Study	Study design	TTN	BPD	RDS	Mechanical ventilation	NICU admission
Balci et al (2010)	100 patients Betamethasone 12 mg × 1	NA	NA	0.21 (0.04–1.08)	0.34 (0.12–0.93)	NA
Porto et al (2011)	273 patients Betamethasone 12 mg × 2	1.07 (0.69–1.65)	NA	1.82 (0.17–19.8)	1.82 (0.17–19.8)	0.99 (0.71–1.39)
Gyamfi-Bannerman et al (2016)	1,427 patients Betamethasone 12 mg × 2	0.68 (0.53–0.87)	0.22 (0.02–0.99)	0.87 (0.65–1.17)	0.78 (0.50–1.21)	0.93 (0.85–1.01)

Abbreviations: BPD, bronchopulmonary dysplasia; NA, not assessed; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; TTN, transient tachypnea of the newborn.
Note: Odds ratio or relative risk (95% confidence interval).

at high risk of delivering between $34^{0/7}$ and $36^{6/7}$ weeks' gestational age. They reported a decrease in neonatal jaundice requiring phototherapy, but no significant difference in the risk of respiratory morbidity, mechanical ventilation, RDS, or NICU admission, although the authors admitted the trial was underpowered for the primary outcome and had a 14% rate of loss to follow-up.[84] Balci et al reported that a single dose of betamethasone administered in the late preterm period was associated with a decrease in need for ventilation and resuscitation.[85] RDS is not a common finding at these gestational ages, and these studies were underpowered to evaluate this. The real benefit of ACS may be in the reduction of other morbidities, and a larger study was necessary prior to recommending the use of corticosteroids in the late preterm period.

Summary of the ALPS Trial

A recent study by Gyamfi-Bannerman et al, "Antenatal Betamethasone for Women at Risk for Late Preterm Delivery (ALPS)," addressed this question by performing the largest study to date addressing the utility of ACS in the late preterm period.[86] The Maternal-Fetal Medicine Units Network conducted a randomized, double-blind, placebo-controlled study at 17 academic centers of women with a singleton gestation at high risk for delivery in the late preterm period, including both indicated (hypertensive disease, ruptured membranes) or spontaneous delivery. These patients were randomized to receive two 12 mg doses of intramuscular betamethasone, every 24 hours. Women were excluded from the trial if they were diagnosed with chorioamnionitis, previously received ACS, did not have adequate dating, or if delivery was expected within 12 hours of enrollment. Spontaneous preterm deliveries were more common than indicated deliveries. Tocolysis was not used in the study protocol; however, oxytocin was deferred for 12 hours after the first dose of betamethasone for patients at higher risk for delivery (ruptured membranes, cervical dilation > 3 cm, or regular contractions). In both the study and control groups, 59 to 60% received the two doses of study medications. Follow-up of the infants was available until day of life 28.

The primary outcome, respiratory support requirement in the first 72 hours (defined as continuous positive airway pressure or high flow nasal cannula for > 2 hours) or severe respiratory morbidity (continuous positive airway pressure > 12 hours or a fraction of inspired oxygen of 30% or greater for > 24 hours) was less frequent in the betamethasone group than the placebo group (11.6 vs. 14.4%, RR: 0.80, 95% CI: 0.66–0.97). In addition, those in the betamethasone group required less surfactant use, were less likely to need resuscitation, develop bronchopulmonary dysplasia, develop transient tachypnea of the newborn, and stay in the intermediate nursery/NICU for more than 3 days (RR: 0.89, 95% CI: 0.80–0.98). There was no difference in the risk of RDS, apnea, or the need for mechanical ventilation. The ACS group had higher rates of neonatal hypoglycemia (24 vs. 15%, RR: 1.60, 95% CI: 1.37–1.87), but was not associated with longer hospitalization or adverse events.

There were no differences in chorioamnionitis/endometritis, cesarean delivery, or length of maternal hospitalization.

This study is the only RCT to assess bronchopulmonary dysplasia in former late preterm infants, which increases the risk of infection, rehospitalization, neurodevelopmental outcomes, cerebral palsy, and future pulmonary morbidity.[87] Follow-up studies are being planned for the infant cohort.

Long-Term Effects of Antenatal Corticosteroids

In the last 10 to 15 years, the concept of fetal programming in relation to prenatal corticosteroid administration has garnered a lot of attention. The hypothesis of fetal programming posits that fetal adaptations due to maternal and fetal environment alter physiologic function throughout life.[88] Several studies in animal models have found an association between ACS and long-term consequences such as hypertension, cardiac, metabolic, and vascular dysfunction,[89] although clinical follow-up studies have not shown similar findings.[90–92]

Several human studies found short- and long-term alterations in the hypothalamic–pituitary–adrenal (HPA) axis in infants exposed to ACS.[93–97] Changes in maternal and fetal leptin and adiponectin concentrations after betamethasone treatment have been described.[98] Antenatal betamethasone use is associated with neonatal hypoglycemia and hyperbilirubinemia.[99]

While there are definite biochemical changes in infants exposed to ACS, the extensive clinical experience with a single dose of corticosteroids supports its benefit over any potential long-term risk. The short-term safety of a single corticosteroid dose has been previously described in this article. Since the landmark article on ACS was published in 1972, there have been multiple long-term follow-up studies. In a 20-year follow-up study, Dessens et al found no differences in several of intellectual, medical, or psychological variables.[100] Alexander et al performed a follow-up study of children whose mothers were admitted for threatened preterm birth, but who ultimately delivered between 37 and 41 weeks' gestational age. The mothers who were admitted for threatened preterm labor had children who scored 6 to 7 points lower on IQ evaluations when compared with mothers who had uncomplicated pregnancies. When comparing the children who were and were not exposed to ACS prior to 34 weeks' gestation, there was no difference in IQ. The researchers concluded that the condition leading to preterm labor, not the single course of ACS, was associated with long-term cognitive changes.[101]

Several analyses by Dalziel et al found no effect of betamethasone on cardiovascular risk factors, lung function, cognitive functioning, or psychiatric morbidity 30 years after exposure.[90–92] One of the studies found an increased insulin resistance in adults exposed to corticosteroids, but there was no difference in blood pressure, fasting lipids, body size, and HPA function.[91] Another follow-up study found young adults exposed to in utero corticosteroids had increased aortic arch stiffness and altered glucose metabolism. The clinical implications of these findings has yet to be determined.[102] In regard to neurodevelopmental outcomes, a recent meta-analysis by Sotiriadis et al discovered that a single course

of ACS increased rates of intact survival, improved psycho-motor development index scores, and reduced rates of severe disability and cerebral palsy in those delivered before 34 weeks' gestation.[103] The most recent Cochrane reviews included long-term follow-up from four trials and found no reason to withhold ACS.[7,28]

Recommendations for Late Preterm Steroids

Based on the available literature, a single course of ACS is recommended for patients at high risk for late preterm birth to reduce the short-term respiratory morbidity of prematur-ity. This should be limited to patients who are unlikely to deliver within 12 hours of administration, as this may be insufficient time for corticosteroids to provide benefit. We recommend using the criteria of the ALPS trial to assess whether a patient is eligible for corticosteroids (►Fig. 1). Due to increased risk of hypoglycemia, blood glucose levels should be monitored in the neonatal period.

Remaining Knowledge Gaps for Late Preterm Steroids

Long-Term Effects
As discussed previously, a majority of follow-up studies support the safety of a single course of ACS in the preterm period. Late preterm and early-term exposure needs further study as this is a critical time for cerebellar development and cerebral myelination. Animal studies have shown evidence of HPA axis dysregulation and structural changes, such as hippocampal degeneration, when exposed to ACS.[88,104]

There are few human studies evaluating these neurodeve-lopmental outcomes of ACS in the late preterm period. Stutchfield et al evaluated children between 6 and 10 years of age who were exposed to a single course of ACS prior to delivery at term.[105] There were no differences in hyperac-tivity, emotional symptoms, conduct/peer problems, or level achievement in standardized testing; however, the children exposed to ACS were more likely to be perceived as being in the lower quartile of academic ability by the schools. This finding was a subjective outcome while all other objective behavioral and educational outcomes found no differences. As stated previously, a 30-year follow-up by Dalziel et al found no effect of betamethasone on cognitive functioning or psychiatric morbidity.[90] This was a follow-up of the original RCT by Liggins and Howie which included subjects up to 37 weeks' gestation.

Further investigation is needed to study the effect of ACS administered in the late preterm period. Long-term follow-up is planned to evaluate the effect of betamethasone on neurodevelopmental outcomes of subjects included in the ALPS trial.

Benefit of an Incomplete Course of Antenatal Corticosteroid
As described previously, there is limited evidence that an incomplete course of ACS improves neonatal outcomes. In the ALPS trial, only 60% of the patients received both doses of the study or placebo drug. However, no subgroup analysis was performed on those who only received a single dose of betamethasone. Further studies are needed to determine if a single dose of ACS is beneficial in the late preterm period.
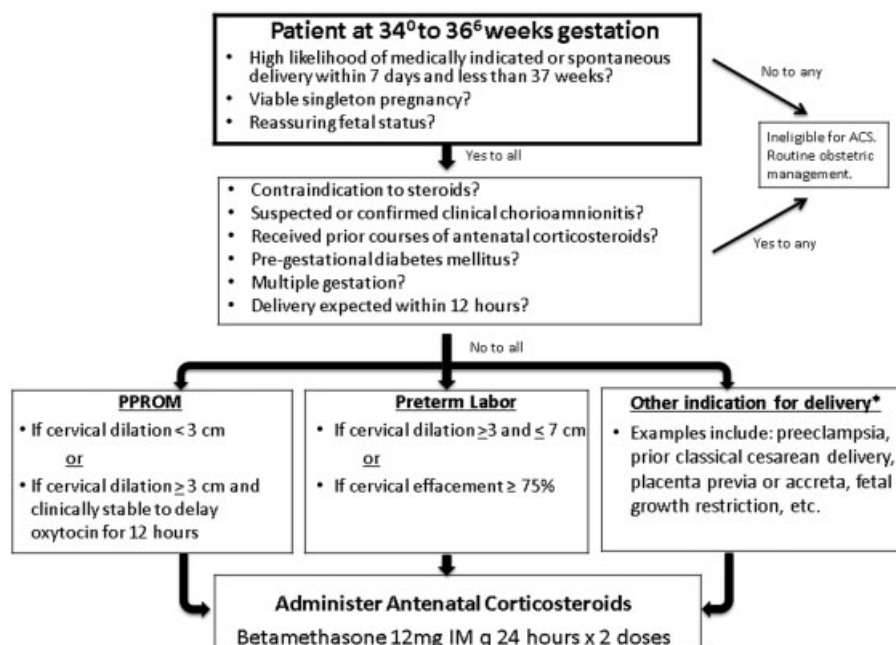
Fig. 1 Algorithm for eligibility for antenatal corticosteroids in the late preterm period. *Plan for first dose 2 to 7 days prior to anticipated cesarean delivery or induction of labor. ACS, antenatal corticosteroids; PPROM, preterm premature rupture of membranes; PTL, preterm labor. (Adapted from the Society for Maternal-Fetal Medicine preterm birth toolkit algorithm. Available at: https://www.smfm.org/publications/231-smfm-preterm-birth-toolkit. September, 2016.)

Benefit of Repeated Course of Antenatal Corticosteroid

For pregnant patients at high risk for delivery before 34 weeks' gestation, ACOG recommends the judicious use of a repeat course of corticosteroids.[106] None of the aforementioned trials of late preterm ACS enrolled patients who had a prior course of ACS. No study has evaluated the efficacy of a repeat course of ACS in the late preterm period. Further studies are needed to determine if there is benefit of a repeat course of ACS in the late preterm period.

Supplementary information of examples cases for ACS use in the late preterm period is available as ▶Supplementary Material (available in online version).

Conflict of Interest
None.

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