Published online: 2020-10-14

A Growing Dilemma: Antenatal Corticosteroids and Long-Term Consequences

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Am J Perinatol 2022;39:592–600.

Abstract

Objective A single course of synthetic antenatal corticosteroids is standard care for women considered to be at risk for preterm birth before 34 weeks of gestation. While the intended target is the fetal lung, the fetal brain contains remarkably high levels of glucocorticoid receptors in structures critical in the regulation of behavior and endocrine function. Negative programming signals may occur which can lead to permanent maladaptive changes and predispose the infant/child to an increased risk in physical, mental, and developmental disorders.

Methods Framed around these areas of concerns for physical, mental, and developmental disorders, this narrative review drew on studies (animal and clinical), evaluating the long-term effects of antenatal corticosteroids to present the case that a more targeted approach to the use of antenatal corticosteroids for the betterment of the fetus urgently needed.

Results Studies raised concerns about the potential negative long-term consequences, especially for the exposed fetus who was born beyond the period of the greatest benefit from antenatal corticosteroids. The long-term consequences are more subtle in nature and usually manifest later in life, often beyond the scope of most clinical trials.

Conclusion Continued research is needed to identify sufficient safety data, both short term and long term. Caution in the use of antenatal corticosteroids should be exercised while additional work is undertaken to optimize dosing strategies and better identify women at risk of preterm birth prior to administration of antenatal corticosteroids.

Keywords

- antenatal corticosteroids
- neurodevelopmental outcomes
- long-term outcomes
- term infant
- preterm infant

Key Points

- A single-course ACS is a remarkable therapy with substantial benefits.
- There is a potential of long-term neurodevelopmental consequences in the ACS-exposed fetus.
- There is a need to improve dosing strategies and identification of appropriate at risk women.

received
June 7, 2020
accepted
September 7, 2020
published online
October 14, 2020

Thieme Medical Publishers, Inc.,
333 Seventh Avenue, 18th Floor,
New York, NY 10001, USA

DOI https://doi.org/10.1055/s-0040-1718573.
ISSN 0735-1631.

A single course of synthetic antenatal corticosteroids (ACS) is standard care for women who are considered at risk for a preterm birth before 34 weeks of gestation.[1–4] The benefits of reduced mortality and significant morbidity, particularly respiratory, of fetuses at risk of preterm birth in high- and many middle-income countries are striking.[5] While the intended target is the fetal lung, the fetal brain contains high levels of glucocorticoid receptors particularly in structures critical in the regulation of behavior and endocrine function. Fetal exposure to ACS may contribute to negative programming signals.[6] These negative signals can lead to permanent maladaptive changes after birth and predispose the infant/child to an increased risk in physical, mental and developmental disorders.[7–17] These disorders may outweigh any potential benefits for the infant/child from ACS. Framed around these areas of concerns of physical, mental, and developmental disorders, this narrative review will draw on studies (animal and clinical) which have the long-term effects of ACS to support the case that a more targeted long-term approach to the use of ACS for the betterment of the fetus is urgently needed.

Materials and Methods

A narrative review of the literature was performed pertaining to the long-term effects of corticosteroids. This review was framed around areas of long-term physical, mental, and developmental challenges for the fetus/infant/child. Emphasis was placed on the evidence of not only the benefits but the risks of ACS specifically, as follows: (1) current use of ACS in at risk pregnancies (preterm, near term, and term); (2) animal studies outlining effects of ACS, both positive and negative, on fetal lung function and brain development; and (3) human studies that describe and support the manifestations of findings in animal studies and the concerns associated with ACS treatment.

Issues of Preterm Birth

Every year, it is estimated that 15 million infants are born preterm, that is, before 37 completed weeks of gestation, with this number rising.[18] Approximately, 1 million children die each year due to complications of preterm birth; many of those who survive can face lifetime disability of varying degrees.[19–21] Morbidity and mortality associated with preterm birth increases with lower gestational age and are the highest in infants born less than 28 weeks of completed gestation.[22–24] Preterm birth is associated with a significant cost to health care systems, as well as adding considerable psychological and financial hardship, to families.[25–27] Despite many factors being associated with the incidence of preterm birth, the cause, particularly for spontaneous preterm birth, remains unclear.[28]

Current Approaches in Use of Antenatal Corticosteroids

It has been almost 50 years since the initial publication of the landmark study by Liggins and Howie that evaluated the effects of a single-course ACS. A single-course ACS reduced the incidence of respiratory distress syndrome (RDS) in preterm infants from 25.8 to 9% and mortality from 15 to 3.2%.[29] Influential meta-analyses initially done by Crowley in 1990,[30] followed by Roberts and Dalziel in 2006[31] and Roberts et al in 2017[32] have provided the base for the use of ACS in women at risk for preterm birth, particularly under 34 weeks of gestation. The most recent Cochrane review done in 2017 included 30 studies of 7,774 women and 8,158 infants.[32] Treatment with a single-course ACS is associated with a reduction in the most serious adverse outcomes related to prematurity including perinatal and neonatal mortality, RDS, intraventricular hemorrhage, necrotizing enterocolitis, the need for aggressive mechanical ventilation, and systemic infections in the first 48 hours of life. Not all outcomes were measured, some of the trials were under powered to detect some changes in outcomes, particularly mortality, and some of the studies were of low-to-moderate quality. In addition, many of the trials were conducted with an extremely small number of pregnancies <28 weeks of gestation, thus fewer infants in the early gestation to evaluate. For these pregnancies, large epidemiological research studies have been used to evaluate the benefits of ACS. These studies used mortality and neurodevelopmental outcomes to evaluate the benefits for these fetuses and infants and the benefits are striking.[33–36] ACS-managed pregnancies, where infants born at <28 weeks of gestation, were likely to have a lower risk of mortality and adverse neurodevelopmental outcomes but not prevent the complications of extreme prematurity. Consequently, as many as 85% and more of these at-risk pregnancies at <28 weeks are now managed with ACS prior to delivery.[5,37]

The benefits seen for preterm infants have led individuals to evaluate the use of ACS in other clinical settings where infants may be at risk of serious respiratory morbidities; these include later preterm (34–36 weeks of gestation) and elective cesarean births for term pregnancies. The antenatal late preterm steroids (ALPS) trial was a multicentre, randomized trial of 2,800 women deemed at high risk of a late preterm birth, with a composite outcome of stillbirth, neonatal death, and the need for respiratory support in the first 72 hours after birth.[38] With no stillbirths or neonatal death, the major benefit of ACS was a reduction in transient tachypnea of the newborn and the need for some oxygen for the first 28 days of life. There was no difference in severe neonatal morbidity (RDS, necrotizing enterocolitis, and intraventricular hemorrhage), 5.7 versus 6.4%. This short-term gain in respiratory morbidity came at an increase in neonatal hypoglycemia (24 vs. 15%); this clinical entity itself is viewed as a major factor for developmental delay in the late preterm infant at a preschool age.[39] Despite this concerning finding, the results from the ALPS trial related to the reduction in minor respiratory morbidity, and further supported by a systematic review in 2016,[40] have led to an endorsement by the American College of Obstetricians and Gynecologists (ACOG) for the use of ACS in later term singleton pregnancies at risk for preterm birth.[41]

The antenatal steroids for term elective caesarean section (ASTECS) trial randomized 998 women at ≥37 weeks of gestation, who were giving birth by an elective cesarean section.[42] The primary outcome was admission to higher level neonatal care with respiratory distress. The incidence of admission with respiratory distress was 0.051 in the control

group and 0.024 in the treatment group (relative risk [RR] = 0.46, 95% confidence interval [CI]: 0.23–0.93). The incidence of transient tachypnoea of the newborn was 0.040 in the control group and 0.021 in the treatment group (RR = 0.54, 95% CI: 0.26–1.12). The incidence of RDS was 0.011 in the control group and 0.002 in the treatment group (RR = 0.21, 95% CI: 0.03–1.32). ACS was found to be beneficial at all gestational ages and admission to higher levels of care fell with increasing gestational age. A Cochrane review which included this trial and three others concluded that ACS was associated with a reduced risk of RDS; however, the overall risk of RDS was small (1.7%) and the quality of evidence was low.[43] Currently, there remains no consensus regarding the use of ACS for planned term cesarean deliveries.[4,44]

The effect of ACS lasts at least 7 days[31,32]; approximately 50% of women remain pregnant 7 to 14 days after an initial course of ACS[45] which has led to the question of continuing ACS weekly or biweekly to optimize continuing the benefits for the fetus or providing an extra dose or course in the form of a rescue approach. Several trials evaluated repeated courses and their pooled results show that infants had reduced risks of respiratory morbidities.[46] However, no benefit was seen for chronic lung disease, intraventricular hemorrhage, or mortality (fetal and neonatal). There was a negative effect on head circumference at birth when adjusted for gestational age at birth. The trials' varying approaches questioned the generalizability of the findings for clinical management and there still remains a lack of consensus for this approach in practice.[4,44,47]

In addition to the consideration of repeated courses of ACS should women remain pregnant 14 days after the initial course, a modified rescue approach to the repeat dosing concept was considered. In 2009, a trial enrolled over 400 women who had received an initial course of ACS and had remained pregnant 14 days later.[48] These women were randomized to receive no further course or a repeat single course; 55% of the women enrolled delivered <34 weeks of gestation. There was a significant reduction in the primary outcome of composite neonatal morbidity <34 weeks in the rescue steroid group versus placebo (43.9 vs. 63.6%; odds ratio [OR] = 0.45; 95% CI: 0.27–0.75; $p = 0.002$) and significantly decreased RDS, ventilator support, and surfactant use. Perinatal mortality and other morbidities were similar in each group. Including all neonates in the analysis (regardless of gestational age at delivery) still demonstrated a significant reduction in composite morbidity in the rescue course group (32.1 vs. 42.6%, OR = 0.65; 95% CI: 0.44–0.97; $p = 0.0034$) and improvement in respiratory morbidities. These findings supported a move to endorse a rescue approach in a woman who had received a single course and was actively at risk of a preterm birth <34 weeks of gestation 14 days after the initial administration od ACS.[4,44]

Effects of Antenatal Glucocorticoids on the Developing Fetus

Following the landmark trial by Liggins and Howie in 1972, there have been numerous animal studies undertaken to determine how and why ACS acts in the vulnerable fetus at risk for preterm birth. Animal studies have shown that ACS plays a pivotal role in optimizing lung function in the preterm infant and its transition to life outside the womb, regardless of gestation age. These include the following: (1) increasing surfactant production, (2) increasing lung compliance and volume, (3) reducing vascular permeability, (4) promoting maturity of the lung parenchyma, (5) increasing clearance of lung water, and (6) increasing response to exogenous surfactant treatment.[49–53]

While animal studies have outlined the improvement in postnatal lung function, an equal number, if not more, has found evidence of increased risk of adverse outcomes targeting brain structures and the cardiometabolic systems.[54–58] Glucocorticoids are known to affect growth by inhibiting hormones critical for fetal growth, such as insulin-like growth factors I and II and placental lactogen.[59] They have been shown to cause decreased cortical surface area and dendritic complexity in the prefrontal cortex and the hippocampus.[60–62] Additional animal studies have shown impaired myelination and impaired neurologic development, altered hypothalamic–pituitary–adrenal (HPA) axis function, decreased hippocampal weight and neuron number, impaired retinal maturation, impaired axonal myelination of optic and auditory nerves, abnormal auditory function, and altered behaviors.[63–70]

Studies in various animal models have shown that maternal administration of ACS during pregnancy has profound acute and long-term effects on the developing HPA axis. The fetal brain contains high levels of glucocorticoid receptors (the primary target for synthetic glucocorticoids) in the second and third trimesters, with highest levels in the limbic system (which includes prefrontal cortex, hippocampus, and amygdala), the hypothalamic paraventricular nucleus, and the anterior pituitary.[63–70] Exposure of these structures to high levels of glucocorticoid can lead to permanent programming of function via modification of both glucocorticoid receptors and mineralocorticoid receptors levels in the hippocampus, hypothalamus, and pituitary gland and involves epigenetic processes.[71–74] Changes in glucocorticoid receptor and mineralocorticoid receptor expression in these structures result in altered negative feedback sensitivity and altered set points for HPA function. Long-term changes in the regulation of HPA function can predispose to chronic cardiometabolic and neurological disorders. An imbalance of glucocorticoid and mineralocorticoid receptors in the limbic system can have profound effects on behavior, learning, and memory.[75,76]

A Growing Dilemma

While animal studies have highlighted concerns related to ACS exposure, it is unclear whether the short-term benefits attained by ACS outweighs the longer term harms that ACS exposure may contribute to cognitive and other neurodevelopmental health outcomes in surviving children. Human evidence remains small in numbers but is slowly growing and showing some signal for concern.

There is an association between ACS exposure and reduced growth parameters at birth.[45,77,78] ACS exposure has been associated with reduced head circumferences (0.6 cm).[45,79] In late preterm pregnancies, ACS increased

the risk of hypoglycemia in the neonate[38] which is, in itself, associated with poor cognitive and motor function at 4.5 years of age.[80]

Due to the lack of precision in the clinical decision making, defining risks for preterm birth, many women may inappropriately receive ACS. In a recent Canadian population-based study, 52% of women who received ACS went on and delivered at 35 weeks of gestation or greater, thereby subjecting fetuses to an unnecessary exposure to ACS.[81] Up to one-third of women treated with ACS carry the pregnancy to term leading to many children being exposed to ACS without any benefit.[45] The longer exposure to ACS in utero, coupled with the natural cortisol surge in late gestation,[63] has the potential to contribute to negative programming within the developing brain, HPA axis, and cardiometabolic structures. Clinical trials evaluating ACS have been difficult to interpret due to the need to separate term from preterm-born children, particularly the small and very preterm children.

A long-term study, evaluating the 5-year outcome of children born to the women who participated in the multiple courses of antenatal corticosteroids for preterm birth study (MACS),[45,82] highlighted concerns regarding prolonged exposure to in utero ACS and outcomes. All the women received an initial course of ACS. If they remained at high risk of preterm birth, before 34 weeks of gestation, they were randomized to repeated courses of ACS or a placebo every 14 days. Of the original cohort, 1,728 (80.5%) children were available for follow-up at 5 years of (MACS-5). Overall, MACS-5 showed no long-term benefits or risks associated with either single or multiple courses of ACS. However, in single and multiple ACS-exposed children, over 13% demonstrated abnormalities in neurobehavioral function which is higher than reported for the general population.[82] This increase was seen irrespective of the gestational age at birth. Furthermore, children born at term gestation and received multiple courses of ACS exhibited negative effects with an increase in vision and hearing difficulties.[83] This increases in neurosensory difficulties that may reflect the impaired myelination that has been identified in the animal studies (sheep and rat) which evaluated optic and auditory nerve function following ACS expsoure.[64,65] The lack of a control unexposed to ACS, though limited the interpretation of these findings.

The ASTECS (demonstrated that ACS given prior to an elective cesarean delivery at term reduced short-term respiratory morbidity.[42] In the follow-up assessment for this trial, there were no differences in behavior and health for the patients at 8 to 15 years of age.[84] However, though not statistically significant, there was an increased incidence of being in the lowest quarter of academic ability in the ACS group compared with the controls (17.7 vs. 8.5%; number needed to harm [NNH] = 11). There are limitations to the interpretation of these results but the signal for concern for potential difficulties is there.

In a secondary analysis of the prediction and prevention of preeclampsia and intrauterine growth restriction (PREDO) study, the prevalence of any mental and behavioral, psychological development, emotional and behavioral, and comorbid disorders was higher in ACS-exposed, compared with nonexposed children (OR = 2.76 [95% CI: 1.76–4.32]; OR = 3.61 [95% CI: 2.19–5.95]; OR = 3.29 [95% CI: 1.86–5.82]; and OR = 6.04 [95% CI: 3.25–11.27], respectively].[85] These associations did not vary between preterm and term children.

More recently, population-based studies have been exploring whether an association exists among infants exposed and not exposed to ACS for adverse difficulties. In a Canadian population–based study, Melamed et al found an association among term infants between exposure to ACS during pregnancy and health care utilization during childhood related to suspected neurocognitive and neurosensory disorders.[86] The primary outcome was a composite of diagnostic or billing codes reflecting proven or suspected neurodevelopmental problems during childhood including audiometry testing, visual testing, or physician service claim with a diagnosis code related to a suspected neurocognitive disorder. At 5 years of age, the cumulative rate for the primary outcome was higher among infants exposed to ACS compared with nonexposed infants: 61.7% (3,346/5,423) versus 57.8% (302,520/523,782), respectively ($p < 0.001$; NNH = 25, 95% CI: 19–38; adjusted hazard ratio (aHR) = 1.12, 95% CI: 1.08–1.16). Similar findings were observed for each of the individual components of the primary outcome: 15.3 versus 12.7% for audiometry testing, 45.4 versus 43.5% for visual testing, and 25.8 versus 21.6% for suspected neurocognitive defects.

In a second study, Räikkönen et al noted that exposure to ACS during pregnancy was significantly associated with mental and behavioral disorders.[87] This study identified singleton infants, as well as consecutive maternal sib pairs born at term to determine if familial confounders could explain any associations that would be found. The primary outcome was any childhood mental and behavioral disorders diagnosed in public specialized medical settings. Among the 241,621 eligible term-born maternal sib pairs nested within this population, 4,128 (1.71%) pairs were discordant for treatment exposure. Treatment exposure, compared with nonexposure, was significantly associated with higher risk of any mental and behavioral disorder in the entire cohort of children (12.01 vs. 6.45%; absolute difference = 5.56% [95% CI: 5.04–6.19%]; aHR = 1.33 [95% CI: 1.26–1.41]), in term-born children (8.89 vs .6.31%; absolute difference = 2.58% [95% CI: 1.92–3.29%]; HR = 1.47 [95% CI: 1.36–1.69]), and when sib pairs discordant for treatment exposure were compared with sib pairs concordant for nonexposure (6.56 vs. 4.17% for within sib pair differences; absolute difference = 2.40% [95% CI: 1.67–3.21%]; HR = 1.38 [95% CI: 1.21–1.58]). In preterm-born children, the cumulative incidence rate of any mental and behavioral disorder was also significantly higher for the treatment exposed compared with the nonexposed children, but the HR was not significant (14.59 vs. 10.71%; absolute difference = 3.38% [95% CI: 2.95–4.87%]; HR = 1.00 [95% CI: 0.92–1.09]).

Animal studies have shown that high levels of glucocorticoids can lead to permanent altered programming of function in the limbic system (hippocampus and amygdala), hypothalamus and the pituitary gland; effects that involve epigenetic processes.[66–70,88,89] The hippocampus functions to support cognition, memory, and behavior. Early cohort studies show that the structural changes seen in animal studies regarding

decreased brain volume are present in preadolescent children exposed to ACS or higher levels of antenatal maternal cortisol and are associated with dysfunction.[90,91] Davis et al evaluated 54 children; those exposed to ACS had thinner cortex in the areas of the brain involved in affective disorders and demonstrated symptoms of affective disorders.[90] Buss et al was able to correlate amygdala and hippocampus volumes on MRI at 7 years of age, affective disorders in the child and maternal cortisol levels.[91] Although not specific to ACS, it suggests and reinforces the concerns that in utero exposure to high levels of circulating glucocorticoid, regardless of the source that has a negative long-lasting effect on brain structure in the fetus and child. Sex-associated differences have been noted. Animal studies suggest that increased fetal cortisol exposure during maternal stress in pregnancy results in long-term changes in the medial prefrontal cortex and the hippocampus, more so in males compared with females.[92]

While many animal studies have investigated HPA function in juvenile and adult offspring after in utero exposure to ACS,[88,89] long-term effects on HPA function are slowly beginning to emerge in term-born children exposed to ACS.[93–96] Alexander et al evaluated 209 children, of which 81 were exposed to in utero ACS. Cortisol responses to a standardized laboratory stressor (trier social stress test for children) were assessed in term children (6–11 years of age) exposed to a single course of ACS in utero, and compared with control (non-ACS exposed). The ACS-exposed children showed significantly increased cortisol reactivity to acute psychosocial stress; this effect was more pronounced in females.[97] The children were assessed in adolescence (14–18 years of age); the findings persisted and reinforced concerns for increased vulnerability of developing stress-related disorders.[98] The long-term impact on cognitive skills in conjunction with functional brain correlates were assessed and a reduction in behavioral response consistency (indexed by lower reaction time variability) and brain correlate of conflict monitoring (the N2 event-related potential) in the ACS-exposed adolescents were noted particularly in the pre-frontal cortex.[99] Their findings suggest that ACS exposure yields lasting impacts on the development of frontoparietal brain functions, affecting multiple facets of adaptive cognitive and behavioral control.

No study has examined the impact of ACS on DNA methylation modifications in humans; however, recent studies in animal models have begun to examine epigenome-wide responses to exposure in various tissues.[100] These early studies are demonstrating altered DNA methylation in hundreds of gene promoters. Again, there is significant sex specificity with females being more sensitive than males to programming by synthetic glucocorticoids.[101]

Current Challenges

Given how beneficial ACS is in reducing the incidence of RDS, it is understandable that there is a "treat-all" approach to administer ACS to any and all women who have any sign of early labor or may be at risk of a preterm birth; this occurs despite the fact that more than 50% of pregnancies currently treated with ACS do not deliver within the therapeutic window of 7 days.[102] The signs and symptoms of preterm labor are nonspecific and false positives are common. In the population-based study by Razaz et al, more than half of women who received ACS went on to give birth well after 35 weeks of gestation.[81] The Finnish birth register study showed similar figures related to ACS exposure; in women exposed to ACS during pregnancy, the mean gestation at birth was over 35 weeks with 44% of the women delivering after 37 weeks.[78] The difficulty in predicting preterm labor and delivery leads to an unnecessary exposure to ACS for the pregnant woman and exposure to the negative aspects of steroid exposure to the developing fetus in preterm birth should be averted. Efforts at targeting preterm labor and delivery with more objective diagnostic tools and clinical data are needed to ensure that ACS is given in the most appropriate setting as possible. Utilization of biomarkers, such as placental α macroglobulin 1 (PAMG-1) and cervical measurements,[103] and other possible noninvasive maternal blood tests[104] may be of use in minimally symptomatic and asymptomatic women to better assess the woman truly at risk of a significant preterm birth.

The initial trial by Liggins and Howie utilized a 12-mg betamethasone mixture comprising of 6 mg of betamethasone phosphate (BetaP) and 6 mg of betamethasone acetate (BetaA) given initially at the sign of impending preterm delivery followed by a second 12-mg betamethasone mixture after 24 hours.[29] Since then, this formulation or varying formulations of BetaP/BetaA have been the treatment most studied in the trials evaluating ACS in the various clinical scenarios. An alternate treatment has been 6-mg dexamethasone phosphate (DexP) given in four doses 12 hours apart with similar results of effect in reducing RDS.[105] A recent trial comparing two injections of dexamethasone to two injections of betamethasone showed that the incidence of survival without neurosensory disability at 2 years of age did not differ between the two 12-hour drug approaches and may facilitate this formulation should betamethasone not be available.[106]

Dose-ranging trials have never been performed to evaluate efficacy or safety largely because the indication for use is off-label and the drugs are readily available and inexpensive.[5,105] Animal models have shown that these high-dose treatments may expose the fetus to significantly excessive amounts of steroids.[107–109] The phosphate forms of either betamethasone or dexamethasone are highly active yielding not only high-maternal concentrations but also high-fetal concentrations, which are likely and considerably greater than those required for fetal lung maturation. Animal studies evaluating pharmacokinetics of ACS suggest that dosing frequency and intervals are important in maintaining a concentration that is adequate for lung maturity in the fetus.[109,110] In addition, evaluating the differing components of betamethasone also suggests that BetaA is the critical component of the standard ACS treatment and has the capacity to maintain adequate fetal levels and achieve fetal lung maturity in sheep and primate models.[108–110]

Due to concerns for potential harm and a lack of other formulations, namely, BetaA alone, to be considered for

Table 1 Incidence of outcome, Canadian Neonatal Network, annual report 2018[112]

	Gestational age (wk)					
Outcome	**≤25**	**26–28**	**29–30**	**31–32**	**33–36**	**≥37**
Survival	72	92	99			
RDS (%)	94.7	87.4	67.7	46.8	14.5	4.2
Surfactant at any time (%)	88.2	65.9	39.9	20.7	7.1	2.6
Late onset sepsis (%)	20		4	2	1	1

Abbreviation: RDS, respiratory distress syndrome.

human trials, attempts are underway to determine if less exposure with the current formulations can achieve a similar support to the fetus in the event of a preterm birth. A current trial (BETADOSE) is exploring whether a lower dose of betamethasone (one injection of 12-mg betamethasone) compared with the current dose (two injections of 12-mg betamethasone) is equally effective in reducing mortality and respiratory compromise.[111] The primary endpoint is severe RDS defined as the need for exogenous surfactant in the first 48 hours of life. The trial has recently completed recruitment and results should be available in 2021. Additional trials of similar design are currently being planned and will add important additional knowledge.

A final challenge is defining who best should receive ACS and at what gestational age in the pregnancy. No argument exists regarding the benefits seen in infants born <28 weeks of gestation whose mothers received ACS. Infants born between 29 and 32 weeks have morbidity but to a lesser degree and also can benefit from ACS administration. Beyond 32 weeks, the numbers are significantly reduced which brings to question whether ACS administration is helpful in these pregnancies. The Canadian Neonatal Network gathers data for all admissions admitted into any of the 26 NICUs contributing to the database.[112] Data from the network's 2018 Annual Report (►Table 1) outlines respiratory and other morbidities for infants ≤25 weeks to term gestation. Serious neonatal morbidities are lower in incidence beyond 32 weeks of gestation; chronic lung disease or bronchopulmonary dysplasia is not even captured in infants beyond 32 weeks because of its extremely low incidence. Trials that studied the use of ACS in pregnancies greater than 32 weeks, such as ASTECS and ALPS, evaluated outcomes which were not reflective of significant fetal lung immaturity. As clinicians, we need to question the administration of ACS to manage minor respiratory morbidity when much is not known about long-term consequences. The endorsement by ACOG for administration of ACS as suggested by the ALPS trial has been questioned and challenged by many but initially and most eloquently by Kaempf and Suresh.[113]

Conclusion

A single-course ACS is a remarkable therapy with substantial benefits for the preterm infant, particularly under 28 weeks, at risk for significant respiratory compromise. However, ACS has not gone through the same degree of rigor that many medications have undergone, as it relates to fetal wellbeing before being universally used. Studies, both animal and human, have raised concerns about the potential negative long-term consequences especially for the ACS exposed fetus who is born beyond the period of greatest benefit from ACS. These are important signals that should not be ignored nor put aside.

For any treatment to be effective, it is important to ensure that the effect achieved (benefit) outweighs the potential for harm (risk of harm). The potential of benefit has been widened to achieve not only the initial goal of ACS, namely, maturation of the fetal lung to reduce severe respiratory distress but also less serious outcomes such as transient tachypnea of the newborn and minimal ventilatory support and oxygen support. The latter can, and should, be managed most effectively in the neonatal arena. The long-term consequences associated with steroids are more subtle in nature and usually manifests later in life and often beyond the scope of most clinical trials. The clinical world (maternal fetal medicine, obstetrics, and neonatal) needs to use caution in its use of ACS as it balances the benefit to risk of this treatment. At the same time, additional studies are required to (1) better identify women at risk of impending preterm birth; (2) optimize dosing strategies to minimize exposure yet gain benefit for lung maturity; and (3) revisit dose, formulation, and regimen, and perhaps scale back who should and should not receive ACS.

Authors' Contributions

E.V.A., K.E.M., and S.G.M. conceptualized the study design. E.V.A. wrote and edited the manuscript. All authors critically revised the manuscript for important intellectual design.

Conflict of Interest

None declared.

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