Antenatal corticosteroid prophylaxis at late preterm gestation: Clinical guidelines vs clinical practice

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September 14, 2022

Abstract

Objective: To investigate whether the Antenatal Late Preterm Steroids (ALPS) trial, has been translated into clinical practice in Canada and the United States. Temporal trends in optimal and suboptimal antenatal corticosteroid (ACS) use among late preterm deliveries were also assessed. Design: A retrospective cohort study. Setting: USA and Canada, 2007 to 2020. Population: All live births in the US (n= 32,476,039) and Nova Scotia, Canada (n= 116,575). Methods and Main outcome measured: Using data from the Natality database and the Nova Scotia Atlee Perinatal Database, ACS administration within specific categories of gestational age was assessed by calculating rates per 100 live births. Temporal trends in optimal, and suboptimal ACS use were also assessed. Results: In Nova Scotia, the rate of any ACS administration increased significantly among women delivering at 35-36 weeks, from 15.2% in 2007-2016 to 19.6% in 2017-2020 (OR 1.36, 95%CI 1.14, 1.62). In the U.S., among live births at 35-36 weeks' gestation, any ACS use increased from 4.1% in 2007–2016 to 18.5% in 2017–2020 (OR 5.33, 95% CI 5.28–5.38). Among infants between 24 and 34 weeks' gestation in Nova Scotia, 32% received optimally timed ACS, while 47% received ACS with suboptimal timing. Of the women who received ACS in 2020, 34% in Canada and 20% in the United States delivered at [?]37 weeks. Conclusion: Publication of the ALPS trial resulted in increased ACS administration at late preterm gestation in Nova Scotia, Canada and the U.S.. However, a significant fraction of women receiving ACS prophylaxis delivered at term gestation.

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Running title: Antenatal corticosteroid at late preterm gestation

Conflict of interest: The authors report no conflict of interest.

Financial disclosure: The authors have no financial relationships relevant to this article to disclose.

Abstract

Objective: To investigate whether the Antenatal Late Preterm Steroids (ALPS) trial, has been translated into clinical practice in Canada and the United States. Temporal trends in optimal and suboptimal antenatal corticosteroid (ACS) use among late preterm deliveries were also assessed.

Design: A retrospective cohort study.

Setting: USA and Canada, 2007 to 2020.

Population: All live births in the US (n= 32,476,039) and Nova Scotia, Canada (n= 116,575).

Methods and Main outcome measured: Using data from the Natality database and the Nova Scotia Atlee Perinatal Database, ACS administration within specific categories of gestational age was assessed by calculating rates per 100 live births. Temporal trends in optimal, and suboptimal ACS use were also assessed.

Results: In Nova Scotia, the rate of any ACS administration increased significantly among women delivering at 35-36 weeks, from 15.2% in 2007-2016 to 19.6% in 2017-2020 (OR 1.36, 95%CI 1.14, 1.62). In the U.S., among live births at 35-36 weeks' gestation, any ACS use increased from 4.1% in 2007–2016 to 18.5% in 2017–2020 (OR 5.33, 95% CI 5.28–5.38). Among infants between 24 and 34 weeks' gestation in Nova Scotia, 32% received optimally timed ACS, while 47% received ACS with suboptimal timing. Of the women who received ACS in 2020, 34% in Canada and 20% in the United States delivered at [?]37 weeks.

Conclusion: Publication of the ALPS trial resulted in increased ACS administration at late preterm gestation in Nova Scotia, Canada and the U.S.. However, a significant fraction of women receiving ACS prophylaxis delivered at term gestation.

Funding: This study was funded by the Canadian Institutes of Health Research (grant number PJT-173329). NR is supported by a grant from the Swedish Research Council for Health, Working Life and Welfare (grant number 4-2702/2019). KSJ is supported by an Investigator award from the BC Children's Hospital Research Institute.

Keyword: antenatal corticosteroid, preterm birth, Antenatal Late Preterm Steroids

Introduction

First introduced by Liggins and Howie in 1972,[1]administration of a single course of antenatal corticosteroids (ACS) to women at risk of preterm birth between 24 and 34 weeks gestation, has been shown to significantly reduce infant morbidity and mortality.[2 3] Nevertheless, translation of this knowledge into clinical practice has been less than ideal: population-based studies show that rates of any ACS use ranged from 65% among deliveries at 24-27 weeks, to 79% among deliveries at 28-32 weeks and 50% of deliveries at 33-34 weeks' gestation in Canadian settings in 2008-12.[4 5] Rates of optimal ACS prophylaxis were significantly lower, and these rates reflect the challenges associated with accurate prediction of preterm delivery, differences in international guidelines, and inconsistencies in clinical practice.[6] An added concern is the significant rate of ACS administration among women who go on to deliver at term gestation.[4]

In recent years there has been a re-evaluation of the upper gestational age limit for ACS prophylaxis following the Maternal Fetal Medicine Units Network Antenatal Late Preterm Steroids trial (ALPS) in 2016.[7] The ALPS study, which was a double-blind, placebo-controlled, randomized trial published in April 2016, showed that administration of ACS to women at risk for delivery at late preterm gestation (i.e., 34+0 to 36+6 weeks)

significantly reduces the rate of neonatal respiratory complications.[7] In response, the American College of Obstetricians and Gynecologists (ACOG)[8] and the Society for Maternal-Fetal Medicine (SMFM)[9] altered their guidance regarding ACS administration to include women at risk of late preterm delivery. However, the higher rates of hypoglycemia following ACS therapy at late preterm gestation,[7] (potentially leading to longer-term risks of developmental delay),[10] and the paucity of rigorous follow-up studies regarding the long-term effects of ACS exposure in late-preterm infants,[10] led several experts[11 12] to advise against ACS administration in the late preterm period. The 2018 Canadian guideline from the Society of Obstetricians and Gynaecologists of Canada (SOGC) also did not support initiation of ACS therapy at 35 and 36 weeks gestation.[13]

Given the existing evidence and conflicting guidelines, it is unclear how clinical practice has changed with regard to ACS prophylaxis for women at risk of late preterm delivery. We carried out a study to investigate how the ALPS trial findings, and the recent ACOG, SMFM and SOGC guidelines, have been translated into clinical practice in Canada and the United States. We also assessed rates of optimal and suboptimal trends in ACS use.

Methods

All live births in Nova Scotia, Canada, and the United States from 2007 to 2020 were included in the study. Data on live births in Canada were obtained from the Nova Scotia Atlee Perinatal Database. This population-based, clinically-focused database, contains information on maternal characteristics, delivery events and neonatal information for all births (with a birth weight of at least 500 gram or gestational age of 20 weeks or more) in the province. Information in the database is routinely abstracted from antenatal and medical charts by trained personnel using standardized forms.[14] Data for births in the United States were obtained from the natality files of the National Center for Health Statistics, which includes information on all live birth registrations in the United States.[15]

ACS use in the Natality database of the United States was defined as "ACS for fetal lung maturation received by the mother before delivery" and available for all live births. The gestational age at ACS administration was unknown in both Canada and the United States. However, in Nova Scotia, information on ACS use in the Nova Scotia Atlee Perinatal Database included the timing of the first dose administered in relation to delivery (viz., first dose received <24 hours prior to delivery, first dose received between 24 hours and 48 hours prior to delivery, first dose received between 48 hours and 7 days prior to delivery, and first dose received >7 days prior to delivery) and this enabled us to distinguish between receipt of a partial course (one dose) versus a complete course (two doses of betamethasone) of ACS. Thus, women who received ACS <24 hours prior to delivery were deemed to have received suboptimal ACS as this represented insufficient time for receipt of a complete single course.[16-18] Women who received ACS prophylaxis more than 7 days before preterm delivery at 24 to 34 weeks were also considered to have received less than optimal therapy since the efficacy of ACS in reducing respiratory distress syndrome does not extend beyond 7 days.[16-18] We, therefore, categorized ACS use as follows: i) any administration of ACS in the period before delivery; ii) optimal ACS administration i.e., ACS administration between 24 hours to 7 days before delivery to women who delivered a live birth between 24 to 34 weeks of gestation; and iii) suboptimal ACS administration i.e., ACS administration <24 hours or >7 days prior to delivery to women who delivered a live birth between 24 and 34 weeks of gestation. In Nova Scotia, gestational age was based on the following hierarchy: the date of early second trimester ultrasound or the date of the last menstrual period, or a postnatal assessment, and in the United States it was based on the clinical (obstetric) estimate of gestation.

The time span of the study was divided into two periods, 2007-2016 (i.e., the period before and including the year of publication of the ALPS trial) vs 2017-2020 (i.e. the period after the publication of the ALPS trial), with the earlier period used as the reference. Rates of ACS use were also examined by year. The frequency of ACS administration within specific categories of gestational age (<24, 24-27, 28-32, 33-34, 35-36, [?]37 weeks) was assessed by calculating rates per 100 live births within each gestational age category in both Canada and the United States. Odds ratios (OR) were used to quantify temporal changes in ACS use by gestational age.

In Nova Scotia, Canada, we estimated the frequency of ACS administration within categories of maternal and clinical characteristics including mode of delivery. Mode of delivery was categorized as spontaneous vaginal delivery, instrumental vaginal delivery, cesarean delivery in labour, and planned cesarean delivery. Temporal trends were assessed by plotting the frequency of optimal and suboptimal ACS administration using 2-year moving averages over the study period. The rate denominators for optimal and suboptimal administration were the number of live births between 24 and 34 weeks' gestation. The statistical significance of a linear pattern in annual rates was assessed using the Cochran-Armitage chi-square test for linear trend, and also visually to identify non-linear patterns. The statistical significance of differences was assessed using two-sided P-values and a P-value <0.05 was considered statistically significant. Analyses were performed using SAS software Version 9.2 of the SAS System for Windows ©. The Reproductive Care Program of Nova Scotia and the Research Ethics Board of the IWK Health Centre provided data access and ethics approval, respectively.

RESULTS

The United States study population included 32,476,039 live births between 2007 and 2020, of which 1.5% received any antenatal corticosteroid prophylaxis. In Nova Scotia, among 116,575 live births between 2007 and 2020, 3.4% received any antenatal corticosteroid prophylaxis. Characteristics of the Nova Scotia cohort stratified by ACS use are shown in Table S1.

In Nova Scotia, rates of any ACS administration did not change significantly between 2007-2016 and 2017-2020 among all deliveries, with rates declining slightly from 3.4% to 3.3% (Table 1). However, the temporal patterns varied by gestational age. For instance, the rate of any ACS administration for women delivering at 28-32 weeks of gestation decreased from 83.1% in 2007-2016 to 74.3% in 2017-2020 (OR 0.59, 95% CI 0.42-0.84; Table 1). On the other hand, the rate of any ACS administration increased significantly among women delivering at 35-36 weeks, from 15.2% in 2007-2016 to 19.6% in 2017-2020 (OR 1.36, 95% CI 1.14, 1.62). Figure 1 shows temporal patterns in any ACS administration by year in each gestational age category. In 2020, 80% of live births at 28-32 weeks gestation received ACS, whereas only 75% of all live births at 33+0 to 33+6 weeks' gestation and 60% of live births at 34+0 to 34+ 6 weeks' gestation received any ACS prophylaxis. The rate of any ACS use for women who delivered at 35 weeks increased steadily from 27% in 2017 to 32% in 2019 (Figure 1), while there was no change in ACS rates for infants born at 36 weeks. The proportion of infants at [?]37 weeks gestation who had received ACS was 1.9% in 2016 and this proportion decreased to 1.1% in 2020.

In the United States, rates of any ACS use were lower at each gestational age compared with the same rates in Nova Scotia. However, rates of ACS administration increased significantly and to a much larger extent in the United States between 2007-2016 and 2017-2020 across all gestational age categories (Table 2). For instance, the rate of any ACS administration for women delivering at 33-34 weeks of gestation increased substantially from 18.8% in 2007–2016 to 39.9% in 2017–2020 (OR 2.85, 95% CI 2.85–2.90); among live births at 35-36 weeks of gestation, receipt of any ACS increased from 4.1% in 2007–2016 to 18.5% in 2017–2020 (OR 5.33, 95% CI 5.28–5.38; Table 2). The rate of any ACS use for women who delivered at 35 weeks increased sharply from 14% in 2016 to 27% in 2020, while rates among infants born at 36 weeks' gestation increased from 7% in 2016 to 16% in 2020 (Figure 1). Among live births at [?]37 weeks gestation, the rate of ACS administration increased from 0.5% in 2016 to 0.8% in 2020.

In Nova Scotia, in 2020, approximately 34% of infants whose mothers received ACS were born at 37 weeks of gestation or greater, while the corresponding rate in the United States was 20%. Rates of ACS use by mode of delivery in Nova Scotia are shown in Table 3; rates were highest among women who delivered by cesarean delivery, in particular those with planned cesarean delivery. Among women who delivered at 35-36 weeks' gestation by planned cesarean delivery, rates of ACS use increased from 17.6% in 2007-2016 to 23.8% in 2017-2020 (OR 1.46, 95% CI 1.08-1.98; Table 3), while rates of ACS use decreased substantially in women who delivered at 28-32 weeks by cesarean delivery. The latter decrease was observed among both the planned and the in-labour cesarean delivery subtypes. The rate of any ACS use among women who had a spontaneous vaginal delivery at 33-34 weeks of gestation significant increased from 45.4% in 2007-2016 to

54.9% in 2017-2020 (OR 1.46, 95% CI 1.04-2.05).

Temporal trends in the frequency of optimal and suboptimal antenatal corticosteroid use between 2007 and 2020 in Nova Scotia are displayed in Figure 2. Rates of optimal ACS use (live births delivered between 24 and 34 weeks whose mothers received ACS between 24 hours to 7 days before delivery expressed as a proportion of all live births delivered between 24 to 34 weeks) increased from 28% in 2007 to 32% in 2020 (the linear trend was not significant). Rates of suboptimal administration of ACS also increased slightly from 44% in 2007 to 47% in 2020 (linear trend was not significant).

DISCUSSION

Main findings:

Our population-based study demonstrated that publication of APLS trial in 2016 resulted in a significant rise in the rates of any ACS administration among infants delivered at 35-36 weeks of gestation between 2017 and 2020 in both Nova Scotia, Canada and the United States. Although rates of any ACS administration in each gestational age category were lower in the United States compared with Nova Scotia, there was a substantial temporal increase in the rates of ACS administration from 2007 to 2020 in the United States. Among live births delivered between 24 and 34 weeks' gestation in Nova Scotia in 2020, 32% received the optimal dose and appropriately timed ACS, while 47% received ACS with suboptimal timing. There was a significant reduction in the proportion of infants born at [?]37 weeks' gestation who received any ACS in Nova Scotia between 2016 and 2020, while in the United States, there was an increase in any ACS use in infants born at [?]37 weeks gestation. Approximately, 34% of infants born in Canada and 20% in the United States, whose mothers received ACS in 2020 were born at term gestation.

Strength and limitations:

The strengths of our study include the use of the previously validated and clinically-focused Nova Scotia database that included detailed information on ACS administration[14]. The population-based nature of our study, with less than 2% missing information on gestational age, is also a significant strength, and this increases the likelihood that our findings are generalizable to a wide range of settings. Limitations of our study include the lack of data on the indication for steroids use and the dosage of antenatal corticosteroid administered. Also, our data source only captured the timing of the earliest dose of the first course of ACS administered in relation to delivery.

Interpretation:

Our results show that publication of the ALPS trial in 2016 influenced clinical practice in Canada and the United States, despite conflicting recommendations regarding ACS use at late preterm gestation in the two countries. There was a steady increase in ACS use among infants born at 35 weeks' gestation in Nova Scotia and this increase was mainly observed among women who delivered by planned cesarean delivery. In line with our findings, a recent study from the United States reported that the publication of ALPS study was associated with an immediate increase in the rates of ACS administration in late preterm births across the United States.[19]

Consistent with our findings, Kearsey et al.[19]observed an increase in the proportion of babies born at term who had received ACS in the United States between 2016 and 2018, whereas in the Canadian setting, we observed a significant reduction in the administration of ACS in infants born at term gestation since 2016. Nevertheless, our study and previous research show that about 20-35% of infants whose mothers received ACS ultimately deliver at term gestation.[4 7 11] This highlights the challenge of accurately diagnosing preterm labour, an ongoing impediment to optimal ACS use.[20] Conversely, our findings and others have revealed that the opportunity for optimal ACS use, between 24 hours and less than 7 days prior to delivery, is missed in approximately 60% of preterm deliveries and nearly 50% of infants delivering preterm receive suboptimal ACS at <24 hours or >7 days prior to delivery.[4 11 21 22] The rate of optimal administration of ACS has not improved in the past 14 years in Nova Scotia and if labour is short, it is likely that ACS administration will be missed. Suboptimal administration of ACS is associated with reduced efficacy with regard to neonatal

respiratory complications and neonatal brain injury.[22 23] Nevertheless, ACS therapy is partially effective in reducing infant mortality even if it is given only hours before delivery.[23] With the potential for harm from unnecessary steroid therapy, and long term adverse impacts being increasingly recognized,[24 25] it is necessary to improve methods of preterm birth prediction, so that ACS can be administered within the ideal time frame.[12 26-28]

The current Canadian guideline recommends a single course of ACS for all pregnant women at risk of preterm delivery between "....24 and 34 weeks gestation", i.e., including women between 24 + 0 and 34 + 6 weeks gestation. However, rates of ACS administration have always been significantly higher among infants born at 33 weeks' gestation compared with those born at 34 weeks' gestation for various reasons.[6] In our study, 72% of live births at 33 weeks' gestation received ACS, whereas only 56% of live births at 34 weeks' gestation received ACS in Nova Scotia. Although the care of preterm infants has undergone significant changes since the introduction of ACS prophylaxis more than four decades ago, the magnitude of the reduction in neonatal mortality and severe neurological injury following ACS treatment among preterm infants has remained stable in the past few decades.[29] This highlights the critical and continuing role of ACS therapy in the current era of neonatal care.

The reduction in rate of ACS administration among live births delivered between 28 and 32 weeks' gestation in Nova Scotia was unexpected and may be due to recent concerns regarding the current double dose of ACS administration.[30] A few animal and human randomized trials have suggested that administration of a single dose of betamethasone might be equally beneficial in inducing fetal lung maturation compared with two doses at an interval of 24 hours.[31-34] Given the concerns about long-term effects of ACS, more definitive randomized controlled trials are urgently needed to determine the effect of lower doses of ACS in comparison to the standard double dose ACS.[35]

Conclusion:

In summary, our study showed that publication of the ALPS trial resulted in an increased rate of ACS administration among late preterm infants. ALPS trial findings influenced clinical practice in Canada and the United States, although in Canada the extent of the change in ACS use at late preterm gestation may have been moderated by the 2018 Canadian guideline which did not recommend routine ACS use at late preterm gestation. A significant proportion of the women receiving ACS delivered at [?]37 weeks gestation in both Canada and the United States. Future research should be directed at developing and validating prognostic models that accurately predict impending delivery among women at preterm gestation in order to optimize ACS use. Studies on the dose and long-term effects of ACS are also needed to address the long-term developmental effects of ACS and to resolve the existing conflict between clinical guidelines.

Acknowledgment: This study was funded by the Canadian Institutes of Health Research (grant number PJT-173329). NR is supported by a grant from the Swedish Research Council for Health, Working Life and Welfare (grant number 4-2702/2019). KSJ is supported by an Investigator award from the BC Children's Hospital Research Institute.

Conflict of interest: The authors report no conflict of interest.

Financial disclosure: The authors have no financial relationships relevant to this article to disclose.

Contribution to authorship:

Study concept and design: Razaz, Joseph, Fahey, Allen

Acquisition of data: Allen, Fahey

Drafting of the manuscript: Razaz

Critical revision of the manuscript for important intellectual content: Razaz, Joseph, Fahey, Allen

Statistical analysis: John

Obtained funding: Razaz, Joseph

Details of Ethics Approval: The Reproductive Care Program of Nova Scotia and the Research Ethics Board of the IWK Health Centre provided data access and ethics approval, respectively.

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Figure Legends:

Figure 1: Temporal trends in any antenatal corticosteroid prophylaxis by gestation age, Nova Scotia, Canada and United States, 2007-2020

Figure 2. Temporal trends in optimal, and suboptimal antenatal corticosteroid (ACS) prophylaxis, Nova Scotia, Canada 2007 to 2020. Data points represent 2-year moving averages

Optimal ACS: live births delivered between 24 and 34 weeks' gestation whose mothers received ACS between 24 hours to 7 days before delivery expressed as a proportion of all live births delivered between 24 to 34 weeks' gestation. *Suboptimal ACS:* live births delivered between 24 and 34 weeks' gestation whose mothers received ACS <24 hours or >7 days before delivery expressed as a proportion of all live births delivered between 24 to 34 weeks' gestation.

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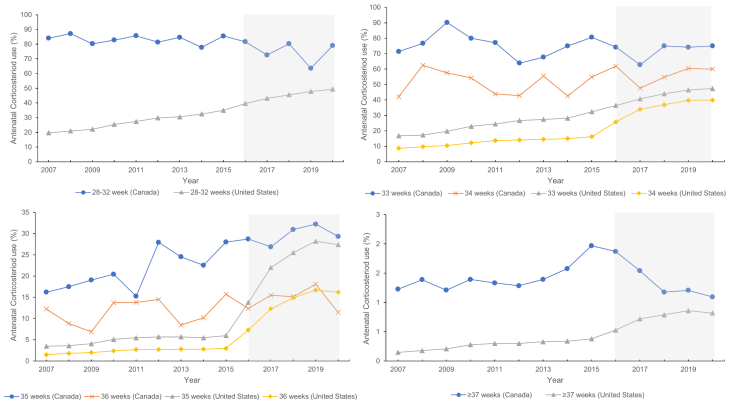
Figure 1: Temporal trends in any antenatal corticosteroid prophylaxis by gestation age at delivery, Nova Scotia, Canada and the United States, 2007-2020



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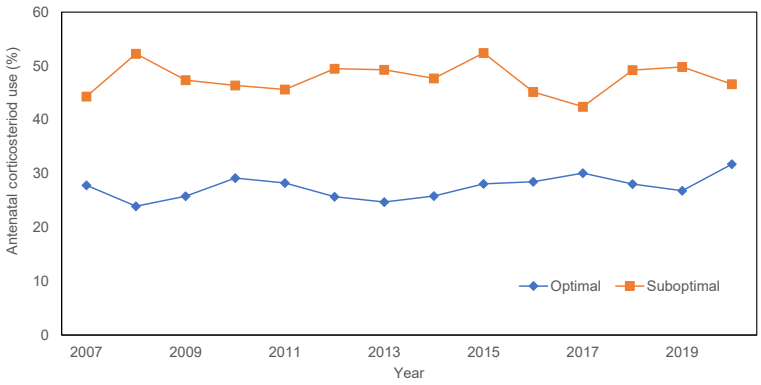

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