Antenatal Corticosteroid Prophylaxis at Late Preterm Gestation: Clinical Guidelines Versus Clinical Practice

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ABSTRACT

Objective: We investigated how the Antenatal Late Preterm Steroids (ALPS) trial findings have been translated into clinical practice in Canada and the United States (U.S.).

Methods: The study included all live births in Nova Scotia, Canada, and the U.S. from 2007 to 2020. Antenatal corticosteroids (ACS) administration within specific categories of gestational age was assessed by calculating rates per 100 live births, and temporal changes were quantified using odds ratio (OR) and 95% confidence intervals (CI). 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 35^0 to 36^6 weeks, from 15.2% in 2007–2016 to 19.6% in 2017–2020 (OR 1.36, 95% CI 1.14–1.62). Overall, the U.S. rates were lower than the rates in Nova Scotia. In the U.S., rates of any ACS administration increased significantly across all gestational age categories: among live births at 35^0 to 36^6 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 24^0 and 34^6 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 U.S. 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.

Keywords: antenatal corticosteroid; preterm birth; Antenatal Late Preterm Steroids

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RÉSUMÉ

Objectif : Les auteurs ont étudié la manière dont les résultats de l'essai Antenatal Late Preterm Steroids (ALPS) ont été transposés dans la pratique clinique au Canada et aux États-Unis (É.-U.).

Méthodologie : L'étude portait sur toutes les naissances vivantes enregistrées en Nouvelle-Écosse, au Canada et aux États-Unis entre 2007 et 2020. L'administration d'une corticothérapie prénatale (CTP) dans des catégories précises d'âge gestationnel a été évaluée par le calcul du taux par 100 naissances vivantes, et les changements temporels ont été quantifiés au moyen du rapport de cotes (RC) et d'un intervalle de confiance (IC) à 95 %. L'étude a également évalué les tendances temporelles pour l'utilisation optimale et sous-optimale de la CTP.

Résultats : En Nouvelle-Écosse, le taux d'administration de toute CTP a considérablement augmenté chez les femmes ayant accouché entre 35 semaines d'aménorrhée (SA) + 0 j et 36 SA + 6 j, passant de 15.2 % entre 2007 et 2016 à 19.6 % entre 2017 et 2020 (RC : 1.36; IC à 95 % : 1.14-1.62). En général, les taux étaient plus faibles aux États-Unis qu'en Nouvelle-Écosse. Aux États-Unis, le taux d'administration de toute CTP a considérablement augmenté dans toutes les catégories d'âge gestationnel. Dans le groupe de naissances vivantes entre 35 SA + 0 j et 36 SA + 6 j, l'utilisation de toute CTP a augmenté de 4.1 % entre 2007 et 2016 à 18.5 % dans la période de 2017 à 2020 (RC : 5.33; IC à 95 % : 5.28-5.38). Dans le groupe des naissances vivantes entre 24 SA + 0 j et 34 SA + 6 j en Nouvelle-Écosse, 32 % des patientes ont reçu une CTP au moment optimal, alors que 47 % ont reçu la CTP à un moment sous-optimal. Au final, 34 % (Canada) et 20 % (É.-U.) des femmes ayant reçu une CTP en 2020 ont accouché à 37 SA ou plus.

Conclusion : La publication de l'essai ALPS a entraîné une augmentation de l'administration d'une CTP en période de

prématurité tardive en Nouvelle-Écosse, au Canada et aux États-Unis. Néanmoins, une proportion importante des femmes ayant reçu une CTP en prophylaxie ont accouché à terme.

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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] 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 2008–2012.[3,4] Rates of optimal ACS prophylaxis were significantly lower, and these rates reflect the challenges associated with an accurate prediction of preterm delivery, differences in international guidelines, and inconsistencies in clinical practice.[5] An added concern is the significant rate of ACS administration among women who go on to deliver at term gestation.[3]

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.[6] 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., 34^0–36^6 weeks) significantly reduces the rate of neonatal respiratory complications.[6] In response, the American College of Obstetricians and Gynecologists (ACOG)[7] and the Society for Maternal-Fetal Medicine (SMFM)[8] 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,[6] (potentially leading to longer-term risks of developmental delay),[9] and the paucity of rigorous follow-up studies regarding the long-term effects of ACS exposure in late preterm infants,[9] led several experts[10,11] 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 35^0–36^6 weeks gestation.[12]

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 U.S. from 2007 to 2020 were included in the study. Data on live births in Nova Scotia 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 grams 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.[13] Data for births in the U.S. were obtained from the natality files of the National Center for Health Statistics, which includes information on all live birth registrations in the U.S.[14]

ACS use in the natality database of the U.S. 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 U.S. 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 (namely, 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 (1 dose) versus a complete course (2 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.[15] Women who received ACS prophylaxis more than 7 days before preterm delivery at 24^0 to 34^6 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.[15] We, therefore, categorized ACS use as follows: (1) any administration of ACS in the period before delivery; (2) optimal ACS administration that is, ACS administration between 24 hours to 7 days before delivery to women who delivered a live birth between 24^0 and 34^6 weeks gestation; and (3) suboptimal ACS administration, that is, ACS administration <24 hours or >7 days prior to delivery to women who delivered a live birth between 24^0 and 34^0 weeks 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 U.S. it was based on the clinical (obstetric) estimate of gestation.

The time span of the study was divided into 2 periods, 2007–2016 (i.e., the period before and including the year of publication of the ALPS trial) versus 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 in completed weeks (<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 Nova Scotia, Canada, and the U.S. Odds ratios (ORs) were used to quantify temporal changes in ACS use by gestational age.

In Nova Scotia, 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 24^0 and 34^6 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 nonlinear patterns. The statistical significance of differences was assessed using 2-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 U.S. study population included 32,476,039 live births between 2007 and 2020, of which 1.5% received any ACS prophylaxis. In Nova Scotia, among 116,575 live births between 2007 and 2020, 3.4% received any ACS prophylaxis. Characteristics of the Nova Scotia cohort stratified by ACS use are shown in Table S1; online Appendix.

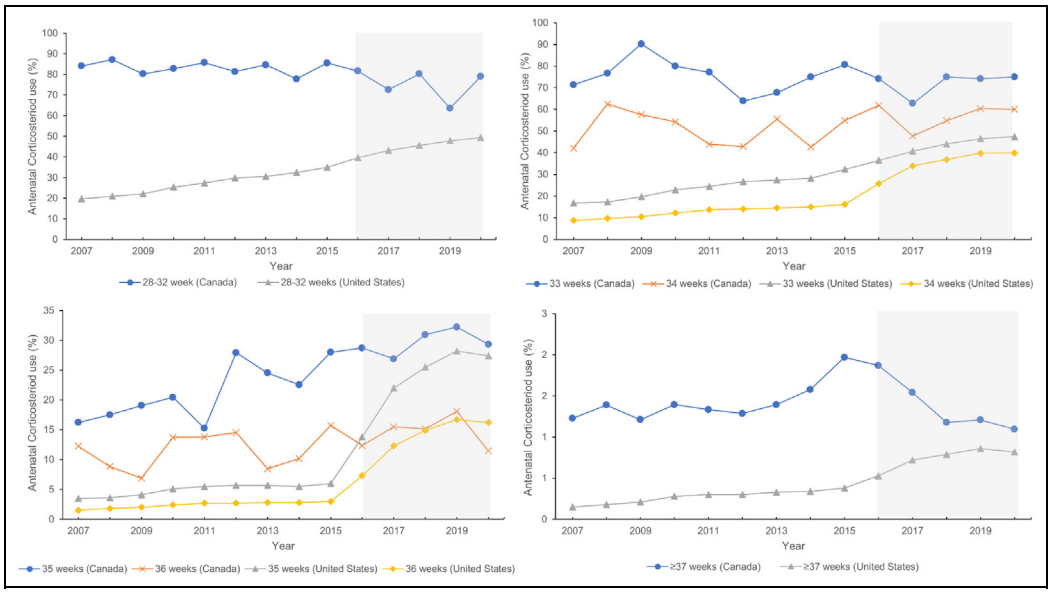
In Nova Scotia, rates of any ACS administration did not change significantly between 2007–2016 and 2017–2020 among all deliveries, with rates declining slightly from 3.4% to 3.3% (Table 1). However, the temporal patterns varied by gestational age. For instance, the rate of any ACS administration for women delivering at 28^0–32^6 weeks 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). In contrast, the rate of any ACS administration increased significantly among women delivering at 35 to 36^6 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 28^0–32^6 weeks gestation received ACS, whereas only 75% of all live births at 33 to 33^6 weeks gestation and 60% of live births at 34^0–34^6 weeks gestation received any ACS prophylaxis. The rate of any ACS use for women who delivered at 35 to 35^6 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 36^0–36^6 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 U.S., 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 U.S. between 2007 to 2016 and 2017 to 2020 across all gestational age categories (Table 2). For instance, the rate of any ACS administration for women delivering at 33^0–34^6 weeks gestation increased substantially from 18.8% in 2007–2016 to 39.9% in 2017–2020 (OR 2.85, 95% CI 2.85–2.90; Table 2). The rate of any ACS use for women who delivered at 35^0–35^6 weeks increased sharply from 14% in 2016 to 27% in 2020, while rates among infants born at 36^0–36^6 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.

Table 1. Number of live births and rate of any antenatal corticosteroid prophylaxis by gestational age at delivery, Nova Scotia, Canada 2007–2020

	2007–2016			2017–2020			
	Live births	Antenatal corticosteroids		Live births	Antenatal corticosteroids		2017–2020 versus 2007–2016
Gestational age (wk)	n	n	Rate/100	n	n	Rate/100	Odds ratio (95% CI)
Less than 23^6	84	11	13.1	22	5	22.7	1.95 (0.6–6.36)
24^0 to 27^6	190	144	75.8	74	59	79.7	1.26 (0.65–2.43)
28^0 to 32^6	691	574	83.1	245	182	74.3	0.59 (0.42–0.84)
33^0 to 34^6	890	544	61.1	293	183	62.5	1.06 (0.81–1.39)
35^0 to 36^6	3028	459	15.2	1135	222	19.6	1.36 (1.14–1.62)
37^0 or greater	80,272	1171	1.5	29,449	371	1.3	0.86 (0.76–0.97)
Missing	183	12	6.6	19	0	0.0	
Total	85,338	2915	3.4	31,237	1022	3.3	0.96 (0.89–1.03)

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



In Nova Scotia, in 2020, approximately 34% of infants whose mothers received ACS were born at 37 weeks gestation or greater, while the corresponding rate in the U.S. 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 35^0–36^6 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 28^0–32^6 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 33^0–34^6 weeks gestation significantly increased.

Temporal trends in the frequency of optimal and sub-optimal ACS use between 2007 and 2020 in Nova Scotia are displayed in eFigure 1; online Appendix. Rates of optimal ACS use (live births delivered between 24^0 and 34^6 weeks whose mothers received ACS between 24 hours to 7 days before delivery expressed as a

Table 2. Number of live births and rate of any antenatal corticosteroid prophylaxis by gestational age at delivery, United States 2007–2020

	2007–2016			2017–2020			
	Live births	Antenatal corticosteroids		Live births	Antenatal corticosteroids		2017–2020 versus 2007–2016
Gestational week	n	n	Rate/100	n	n	Rate/100	Odds ratio (95% CI)
Less than 23^6	62,479	6528	10.5	27,151	5790	21.3	2.32 (2.23–2.41)
24^0 to 27^6	147,840	44,471	30.1	66,207	31,198	47.1	2.07 (2.03–2.11)
28^0 to 32^6	453,404	132,659	29.3	209,771	97,353	46.4	2.09 (2.07–2.12)
33^0 to 34^6	627,732	117,978	18.8	310,244	123,912	39.9	2.87 (2.85–2.90)
35^0 to 36^6	1,873,794	76,589	4.09	890,452	164,789	18.5	5.33 (5.28–5.38)
37^0 or greater	29,227,584	91,895	0.31	13,482,589	107,086	0.79	2.54 (2.52–2.56)
Missing	83,206	516	0.62	14,447	167	1.16	
Total	32,476,039	470,636	1.45	15,000,861	530,295	3.54	2.49 (2.48–2.50)

proportion of all live births delivered between 24^0 to 34^6 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 (the linear trend was not significant).

DISCUSSION

Main Findings

Our population-based study demonstrated that the publication of the ALPS trial in 2016 resulted in a significant rise in the rates of any ACS administration among infants delivered at 35^0–36^6 weeks gestation between 2017 and 2020 in both Nova Scotia, Canada, and the U.S. Although rates of any ACS administration in each gestational age category were lower in the U.S. compared with Nova Scotia, there was a substantial temporal increase in the rates of ACS administration from 2007 to 2020 in the U.S. Among live births delivered between 24^0 and 34^6 weeks gestation in Nova Scotia in 2020, 32% received the optimal dose and appropriately timed ACS, while 47% received ACS with suboptimal timing. Approximately 34% of infants born in Canada and 20% in the U.S. 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.[13] 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 steroid use and the dosage of ACS administered. Also, our data source only captured the timing of the earliest dose of the first course of ACS administered in relation to delivery and repeated courses or rescue doses could not be ascertained.

Interpretation

Our results show that publication of the ALPS trial in 2016 influenced clinical practice in Canada and the U.S., despite conflicting recommendations regarding ACS use at late preterm gestation in the 2 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 U.S. reported that the publication of the ALPS study was associated with an immediate increase in the rates of ACS administration in late preterm births across the U.S.[16]

Consistent with our findings, Kearsey et al.[16] observed an increase in the proportion of babies born at term who had received ACS in the U.S. 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.[3,6,10] This highlights the challenge of accurately diagnosing preterm labour, an ongoing impediment to optimal ACS use.[17] 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.[3,10,18] The rate of

Table 3. Number of live births and rate of any antenatal corticosteroid prophylaxis by gestational age at delivery and mode of delivery, Nova Scotia, Canada 2007–2020

	2007–2016			2017–2020			
	Live Births	Antenatal corticosteroid		Live Births	Antenatal corticosteroid		2017–2020 versus 2007–2016
Onset of labour, gestational week	n	n	Rate/100	n	n	Rate/100	Odds ratio (95% CI)
Assisted vaginal delivery							
Less than 23^6	6	0	0.0	<5	0	0.0	-
24^0 to 27^6	9	5	55.6	<5	<5	-	0.8 (0.04–17.2)
28^0 to 32^6	29	17	58.6	8	<5	<62.5	-
33^0 to 34^6	66	27	40.9	20	8	40.0	0.96 (0.35–2.67)
35^0 to 36^6	321	42	13.1	124	18	14.5	1.13 (0.62–2.05)
37^0 to 43^6	7065	103	1.5	2827	34	1.2	0.82 (0.56–1.22)
$\geq 44^0$	7	0	0.0	0	0	0.0	-
Missing	15	<5	<33	<5	0	0.0	-
Cesarean delivery in labour							
Less than 23^6	<5	<5	-	<5	<5	-	-
24^0 to 27^6	35	22	62.9	12	10	83.3	2.95 (0.56–15.63)
28^0 to 32^6	141	117	83.0	59	36	61.0	0.32 (0.16–0.64)
33^0 to 34^6	176	97	55.1	57	28	49.1	0.79 (0.43–1.43)
35^0 to 36^6	476	49	10.3	218	30	13.8	1.39 (0.86–2.26)
37^0 to 43^6	9738	113	1.2	3864	31	0.8	0.69 (0.46–1.03)
$\geq 44^0$	5	0	0.0	<5	0	0.0	-
Missing	10	<5	<50	<5	0	0.0	-
Planned cesarean delivery							
Less than 23^6	6	<5	<83.3	<5	<5	-	-
24^0 to 27^6	76	64	84.2	32	28	87.5	1.31 (0.39–4.43)
28^0 to 32^6	274	239	87.2	115	90	78.3	0.53 (0.3–0.93)
33^0 to 34^6	304	170	55.9	95	59	62.1	1.29 (0.81–2.07)
35^0 to 36^6	841	148	17.6	357	85	23.8	1.46 (1.08–1.98)
37^0 to 43^6	10,835	178	1.6	4086	64	1.6	0.95 (0.71–1.27)
$\geq 44^0$	<5	<5	-	<5	0	0.0	-
Missing	30	5	16.7	<5	0	0.0	-
Spontaneous vaginal							
Less than 23^6	79	14	17.7	21	<5	<24	-
24^0 to 27^6	82	63	76.8	33	27	81.8	1.36 (0.49–3.77)
28^0 to 32^6	339	278	82.0	108	83	76.9	0.73 (0.43–1.23)
33^0 to 34^6	566	257	45.4	175	96	54.9	1.46 (1.04–2.05)
35^0 to 36^6	2370	227	9.6	863	89	10.3	1.09 (0.84–1.41)
37^0 to 43^6	51,275	667	1.3	18,135	196	1.1	0.83 (0.71–0.97)
$\geq 44^0$	25	<5	<20.0	0	0	0.0	-
Missing	130	5	3.8	14	0	0.0	-

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.[18,19] Nevertheless, ACS therapy is partially effective in reducing infant mortality even if it is given only hours before delivery.[19] With the potential for harm from unnecessary steroid therapy, and long-term adverse impacts being increasingly recognized,[20,21] it is necessary to improve methods of preterm birth prediction so that ACS can be administered within the ideal time frame.[11,22,23]

The 2022 Canadian guideline strongly recommends a single course of ACS for all pregnant women at risk of preterm delivery between 24^0 and 33^6 weeks gestation, and also recommends that ACS therapy be considered for pregnant individuals at risk of delivery between 34^0 to 36^6

weeks gestation on a risk-benefit basis.[24] 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.[5] The rates of any ACS administration at each gestational week, in particular those born prior to 34 weeks, were substantially lower in the U.S. compared with Nova Scotia, Canada. Although the care of preterm infants has undergone significant changes since the introduction of ACS prophylaxis more than 4 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.[25] 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^{0} and 32^{6} weeks gestation in Nova Scotia was unexpected and may be due to recent concerns regarding the current double dose of ACS administration.[26] 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 2 doses at an interval of 24 hours.[27-30] 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.[31]

CONCLUSION

In summary, the ALPS trial findings influenced clinical practice in Canada and the U.S., 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. Studies on the dose and long-term effects of ACS are needed to address the long-term developmental effects of ACS and to resolve the existing conflict between clinical guidelines.

SUPPLEMENTARY MATERIAL

Supplementary material related to this article can be found at https://doi.org/10.1016/j.jogc.2023.03.003.

REFERENCES

1. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972;50:515–25.
2. McGoldrick E, Stewart F, Parker R, et al. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2020;12:CD004454.
3. Razaz N, Skoll A, Fahey J, et al. Trends in optimal, suboptimal, and questionably appropriate receipt of antenatal corticosteroid prophylaxis. Obstet Gynecol 2015;125:288–96.
4. Joseph KS, Nette F, Scott H, et al. Prenatal corticosteroid prophylaxis for women delivering at late preterm gestation. Pediatrics 2009;124:e835–43.
5. Liauw J, Burrows J, Crane JM, et al. A common language: What exactly does 34 weeks gestation mean? J Obstet Gynaecol Can 2018;40:1623–6.
6. Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal betamethasone for women at risk for late preterm delivery. N Engl J Med 2016;374:1311–20.
7. American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. Society for Maternal– Fetal Medicine. Committee Opinion No.677: Antenatal Corticosteroid Therapy for Fetal Maturation. Obstet Gynecol 2016;128:e187–94.
8. Society for Maternal-Fetal Medicine (SMFM) Publications Committee. Implementation of the use of antenatal corticosteroids in the late preterm birth period in women at risk for preterm delivery. Am J Obstet Gynecol 2016;215:B13–5.
9. Kerstjens JM, Bocca-Tjeertes IF, de Winter AF, et al. Neonatal morbidities and developmental delay in moderately preterm-born children. Pediatrics 2012;130:e265–72.
10. Souter V, Kauffman E, Marshall AJ, et al. Assessing the potential impact of extending antenatal steroids to the late preterm period. Am J Obstet Gynecol 2017;217:461.e1–7.
11. Kamath-Rayne BD, Rozance PJ, Goldenberg RL, et al. Antenatal corticosteroids beyond 34 weeks gestation: what do we do now? Am J Obstet Gynecol 2016;215:423–30.
12. Committee on Obstetric Practice. Committee Opinion No. 713: Antenatal Corticosteroid Therapy for Fetal Maturation. Obstet Gynecol 2017;130:e102–9.
13. Fair M, Cyr M, Allen AC, et al. An assessment of the validity of a computer system for probabilistic record linkage of birth and infant death records in Canada. The Fetal and Infant Health Study Group. Chronic Dis Can 2000;21:8–13.
14. Centers for Disease Control and Prevention. Vital Statistics Online Data Portal. Available at: https://www.cdc.gov/nchs/data_access/vitalstatsonline.htm. Accessed on May 10, 2022.
15. Crane J, Armson A, Brunner M, et al. RETIRED: Antenatal corticosteroid therapy for fetal maturation. J Obstet Gynaecol Can 2003;25:45–52.
16. Kearsey EOR, Been JV, Souter VL, et al. The impact of the Antenatal Late Preterm Steroids trial on the administration of antenatal corticosteroids. Am J Obstet Gynecol 2022;227:280.e1–15.
17. Leviton LC, Baker S, Hassol A, et al. An exploration of opinion and practice patterns affecting low use of antenatal corticosteroids. Am J Obstet Gynecol 1995;173:312–6.
18. Frändberg J, Sandblom J, Bruschettini M, et al. Antenatal corticosteroids: a retrospective cohort study on timing, indications and neonatal outcome. Acta Obstet Gynecol Scand 2018;97:591–7.
19. Norman M, Piedvache A, Børch K, et al. Association of short antenatal corticosteroid administration-to-birth intervals with survival and morbidity among very preterm infants: results from the EPICE cohort. JAMA Pediatr 2017;171:678–86.
20. Asztalos EV, Murphy KE, Willan AR, et al. Multiple courses of antenatal corticosteroids for preterm birth study: outcomes in children at 5 years of age (MACS-5). JAMA Pediatr 2013;167:1102–10.
21. Räikkönen K, Gissler M, Kajantie E. Associations between maternal antenatal corticosteroid treatment and mental and behavioral disorders in children. JAMA 2020;323:1924–33.
22. DeFranco EA, Lewis DF, Odibo AO. Improving the screening accuracy for preterm labor: is the combination of fetal fibronectin and cervical length in

symptomatic patients a useful predictor of preterm birth? A systematic review. Am J Obstet Gynecol 2013;208:233.e1–6.

23. Boots AB, Sanchez-Ramos L, Bowers DM, et al. The short-term prediction of preterm birth: a systematic review and diagnostic metaanalysis. Am J Obstet Gynecol 2014;210:54.e1–10.

24. Liauw J, Foggin H, Socha P, et al. Technical Update No. 439: antenatal corticosteroids at late preterm gestation. J Obstet Gynaecol Can 2022. https://doi.org/10.1016/j.jogc.2022.12.006.

25. Melamed N, Murphy K, Barrett J, et al. Benefit of antenatal corticosteroids by year of birth among preterm infants in Canada during 2003–2017: a population-based cohort study. BJOG 2021;128:521–31.

26. Jobe AH, Goldenberg RL. Antenatal corticosteroids: an assessment of anticipated benefits and potential risks. Am J Obstet Gynecol 2018;219:62–74.

27. Schmidt AF, Kemp MW, Rittenschober-Böhm J, et al. Low-dose betamethasone-acetate for fetal lung maturation in preterm sheep. Am J Obstet Gynecol 2018;218:132.e1–9.

28. Schmitz T, Doret M, Sentilhes L, et al. LB03 Dose reduction of antenatal betamethasone in women at risk of very preterm delivery (BETADOSE trial). Am J Obstet Gynecol 2021;224:S723–4.

29. Schmitz T, Alberti C, Ursino M, et al. Full versus half dose of antenatal betamethasone to prevent severe neonatal respiratory distress syndrome associated with preterm birth: study protocol for a randomised, multicenter, double blind, placebo-controlled, non-inferiority trial (BETADOSE). BMC Pregnancy Childbirth 2019;19:67.

30. Senat MV, Minoui S, Multon O, et al. Effect of dexamethasone and betamethasone on fetal heart rate variability in preterm labour: a randomised study. Br J Obstet Gynaecol 1998;105:749–55.

31. Ninan K, Morfaw F, Murphy KE, et al. Neonatal and maternal outcomes of Lower versus Standard doses of antenatal corticosteroids for women at risk of preterm delivery: a systematic review of randomized controlled trials. J Obstet Gynaecol Can 2021;43:74–81.