Title Page

Title: Trends in Receipt of Single and Repeat Courses of Antenatal Corticosteroid Administration Among Preterm and Term Births: A Retrospective Cohort Study

Short Running Title: Trends in Antenatal Corticosteroid Administration

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Abstract

Aim: To investigate trends in receipt and timing of antenatal corticosteroid (ACS) administration over a 10-year interval.

Methods: Retrospective cohort study of all live births from 2006 to 2015 occurring at a Tertiary level teaching hospital in Adelaide, Australia. We analysed temporal trends in the receipt of single courses and repeat doses of ACSs, according to administration timing prior to birth. The main outcome measures were receipt of a single course of ACS and whether administration was 'Optimal' (≥24 hours to <7 days) or 'Suboptimal' (<24 hours OR ≥7 days) according to timing prior to birth, as well as administration of repeat doses.

Results: Among 47,105 live births, 4,191 (8.9%) received any ACS, while 1,009 (2.1%) received at least one repeat dose. From 2006/7 to 2014/15, receipt of a single course (RR 1.33; 95%CI 1.21, 1.47) or repeat dose of ACS (RR 1.24; 95%CI 1.01, 1.55) increased. Among women giving birth between 23 to 34 weeks' gestation, receipt of any ACS increased from 75% to 84%, while an optimally timed single course of ACS increased from 20.4% to 31.0% (RR 1.40; 95%CI 1.24, 1.87). From 2006/7 to 2014/15, the greatest increase in ACS administration was evident among infants born 35-36 and ≥37 weeks' gestation by caesarean section (RR 1.94; 95%CI 1.48, 2.55 and RR 2.55; 95%CI 1.86, 3.50, respectively).

Conclusions: While frequently used, less than half of ACS administration prior to preterm birth was optimally timed. The impact of suboptimal ACS timing on neonatal outcomes requires further investigation.

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Introduction

Administration of antenatal corticosteroids (ACS) to women at risk of preterm birth has been demonstrated to significantly reduce the risk of perinatal morbidities such as respiratory distress syndrome, intraventricular haemorrhage, and necrotising enterocolitis, as well as perinatal mortality.[1, 2] Despite these benefits, significant challenges exist with respect to the optimal timing of administration of ACS prior to preterm birth. While the optimal ACS-to-birth interval remains unclear, a notable reduction in efficacy is evident when the interval exceeds 7 days.[2-4] However, only half the women who present with symptoms of preterm labour give birth within the subsequent 7 days.[5-7] Conversely, some women will unexpectedly give birth in less than 24 hours, with administration of ACS in this setting still considered advantageous.[8] Recent studies have demonstrated that while a large proportion of women receive ACS prior to preterm birth, suboptimal timing (administration <24 hours or ≥7 days prior to delivery) of such administration occurs in a majority.[9, 10] Such difficulties in optimal timing of administration have led to investigations around the role of repeat ACS, for women who remain at risk of preterm birth 7-days or more following their initial course.[11] While evidence has accumulated around the benefits of a repeat dose or doses of ACS on reducing the risk of respiratory distress syndrome and combined serious neonatal morbidity compared with a single course for women who remain at ongoing risk of preterm birth, uncertainty surrounds the potential long-term effects in both childhood and later life.[11]

More recently, interest has grown in the potential benefits of ACS in reducing neonatal respiratory complications when administered to women at risk for later preterm birth[12], as well as prior to elective caesarean section at term[13]. Despite such interest in the purported

benefits, few attempts have been made to quantify patterns of ACS administration over time and according to factors such as timing, type of labour onset, and gestational age at delivery. Insight and understanding of these patterns are a first step towards optimal implementation of ACS in clinical practice. Therefore, we carried out a retrospective cohort study to investigate trends in receipt and timing of ACS administration over a 10-year interval in an Australian setting.

Methods

We performed a retrospective cohort study relating to all live births at the Women's and Children's Hospital in Adelaide, South Australia, Australia, between January 2006 and December 2015. The WCH is a specialist metropolitan tertiary level teaching hospital and South Australia's largest maternity and obstetric service, with over 4,000 births each year. Data were obtained from the WCH Perinatal Statistics Collection (PSC), which includes information on maternal characteristics and prenatal, labour, delivery, and neonatal events for all live births, stillbirths and terminations of pregnancy of at least 400g birthweight or 20 weeks' gestation occurring at the hospital. Data are collected from each woman's medical records after delivery by a specially trained research midwife utilising a standardised data collection form. In the case of women transferred from other hospitals, their corresponding medical history is also transferred and included in the review. A more detailed description of the electronic data collected can be found elsewhere.[14, 15] Information stored within the PSC has previously been validated and shown to be reliable when compared with hospital case records[16].

Information collected on receipt of ACS included the timing of the first dose administered in relation to birth (none, < 24 hours, ≥ 24 hours to < 7 days, & ≥ 7 days), and the number of

repeat doses administered. In accordance with guidelines in place at the hospital during the study period, a course of ACS consisted of 2 doses of 11.4mg betamethasone administered 24 hours apart. Receipt of ACS were categorised as: 1) any administration of ACS prior to birth, irrespective of timing, 2), any administration of a repeat course of ACS prior to birth, irrespective of timing, 3) optimal administration of ACS (between 24 hours and 7 days prior to delivery), 3) suboptimal administration of ACS (less than 24 hours OR more than or equal to 7 days before birth). Gestational age at birth was taken from the perinatal record, which reflects the best clinical estimates according to information combined from last menstrual period and early ultrasonography.

The prevalence of any and repeat ACS administration was evaluated according to various maternal and obstetric characteristics and compared using a generalised linear model (Poisson distribution) with robust variance estimates (and resulting relative risks (RR) and 95% confidence intervals). The prevalence of any and repeat ACS administration was also evaluated according to each calendar time period, timing of ACS administration, individual categories of gestational age (<24, 24-27, 28-32, 33-34, 35-36, ≥37 weeks' gestation), and type of labour onset (spontaneous labour, induction of labour, and LSCS without labour). Temporal trends of ACS administration over time were plotted using 3-year moving averages (2-year averages for the extremes). Statistical significance was defined as a 2-sided p <0.05. All statistical analyses were undertaken using STATA 11 (Stata, College Station, Texas).

Ethics and governance approval was obtained from the Women's and Children's Health Network (HREC/14/WCHN/080).

Results

Among 47,105 women who had a live births between 2006 and 2015, 4,191 (8.9%) received any ACS, while 1,009 (2.1%) received at least one repeat dose.

Temporal trends from 2006 to 2015 in the frequency of receipt of any ACS (single or repeat) and repeat ACS administration are displayed in **Figures 1A and 1B**. Rates of ACS administration increased significantly between 2006/7 and 2014/15, from 7.2/100 to 9.6/100 (RR 1.33; 95%CI 1.21, 1.47). Similarly, the rate of women receiving any repeat dose of ACS increased from 1.5/100 to a peak of 2.9/100 (RR 1.87; 95%CI 1.53, 2.29) in 2012/13, before dropping to 1.9/100 (RR 1.24; 95%CI 1.01, 1.55) in 2014/15. The proportion of women receiving multiple repeat doses increased substantially from 2006 to 2013, before dropping back to the rates reported in 2006/7 (16%, 2006/7; 30%, 2008/9; 48%, 2010/11; 51%, 2012/13; 19%, 2014/15). When examined according to gestational age at birth, significant increases in any ACS administration were only evident among infants born ≥33 weeks' gestation (**Figure 1A**). Administration of ACS to women delivering beyond 35 week's gestation accounted for 35% and 50% of overall ACS use in 2006/7 and 2014/15 respectively.

Temporal trends from 2006 to 2015 in the timing of receipt of ACS prior to birth are displayed in **Figures 2A and 2B**. Regardless of gestation at birth, administration of a single course of ACS with optimal timing prior to birth significantly increased over the 10-year period. Among infants born 23-34 weeks' gestation, receipt of any ACS increased from 75% to 84% (RR 1.12; 95%CI 1.05, 1.18) between 2006/7 and 2014/15, while those receiving optimally timed ACS increased from 20% to 31% after single course (RR 1. 50; 95%CI 1.24, 1.87). If extended to include any ACS administration that occurred from 0 to 7 days prior to

birth, this increased from 44% to 51% (RR 1.16; 95%CI 1.02, 1.31) between 2006/7 and 2014/15.

Temporal trends from 2006 to 2015 in timing of ACS administration according to labour onset are displayed in **Figure 3A**. According to onset of labour, administration of any ACS increased between 2006/7 and 2014/15 among mothers delivering following spontaneous onset labour (72% vs. 79%; RR 1.10; 95%CI 1.01, 1.21), LSCS (no labour) (80% vs. 90%; RR 1.13: 95%CI 1.04, 1.21), and induction of labour (77% vs. 85%; RR 1.10: 95%CI 0.91, 1.34). From 2006 to 2015, approximately half of the women who received an initial course of ACS more than 7 days prior to birth, but still ended up delivering prior to 35 weeks, ended up receiving a repeat dose (58%). Among these women, when separated according to type of labour onset, the proportion of women receiving a repeat dose of ACS was 57%, 47%, and 63% according to spontaneous labour onset, induction of labour, and LSCS respectively.

Among infants born 35 to 36 weeks' gestation, receipt of any ACS increased from 19.3% to 34.6% between 2006/7 and 2014/15. Of the group receiving ACS, optimal timing of a single course increased from 22.7% to 45.6% (RR 2.01, 95%CI 1.35, 2.99). According to onset of labour, any administration of ACS significantly increased among women delivering following LSCS (no labour) (39% vs 76%; RR 1.94, 95%CI 1.48, 2.55), but not following spontaneous onset labour (13.8% vs 16.2%; RR 1.17, 95%CI 0.78, 1.75) or induction of labour (17.6% vs 26.1%; RR 1.49, 95%CI 0.95, 2.32) (**Figure 3B**).

From 2006/7 to 2014/15, a significant increase in ACS administration was evident among infants born ≥37 weeks' gestation by LSCS (without labour) (4.9% vs. 12.5%; RR 2.55, 95%CI 1.86, 3.50). No such differences were evident among those who delivered following

spontaneous onset labour (0.9% vs. 1.0%; RR 1.01, 95%CI 0.66, 1.56) or induction of labour (1.8% vs. 1.5%; RR 0.80, 95%CI 0.53, 1.21).

Administration of any ACS was significantly higher among women who were of low socioeconomic status, advanced maternal age (35 years or greater), smokers (including those who quit smoking during pregnancy), multiparous, and overweight or obese (**Supplemental Table 1**). Obstetric characteristics such as previous obstetric history of preterm birth, preterm pre-labour rupture of membranes, plurality, pre-existing diabetes, cervical suture, threatened preterm labour, and antepartum haemorrhage were all associated with more than a 2-fold increased risk of receiving at least a single course of ACS during pregnancy (**Supplemental Table 2**).

When restricted to births occurring less than 35 weeks' gestation, despite high rates of overall ACS use, the presence of obstetric characteristics such as gestational diabetes, threatened miscarriage, or threatened preterm labour were all associated with a 21-39% less likelihood of optimally timed ACS administration (**Table 1**). In contrast, pre-eclampsia, suspected IUGR, iatrogenic preterm birth, induction of labour, and increasing calendar year were all associated with 37-67% increased likelihoods of optimally timed ACS administration. Non-medical maternal characteristics were not associated with optimally timed ACS administration (**Supplemental Table 3**).

Discussion

Despite significant improvements in the overall use of ACS over the 10-year period, optimal timing of a single course prior to preterm birth does not occur in the majority of cases. Use of repeat ACS administration has increased over time among women delivering prior to 35

weeks' gestation, with a shift away from multiple repeat ACS doses towards a single repeat ACS dose as required.

Previous studies have reported variable ACS administration rates of among live births below 35 weeks' gestation of between 35% to 93%.[7, 17-19] While not always clear as to whether such administration relates to a partial or complete single course of ACS as evaluated in this study, studies reporting optimal administration have uniformly demonstrated low rates of 25% to 50% of livebirths,[9, 10, 20] More recently, interest has grown in determining what defines optimal ACS administration. While often regarded and studied as administration occurring more than 24 hours but less than 7 days following the first dose, there is still evidence that ACS use reduces neonatal death even when birth occurs within 24 hours of the first dose.[2, 4] Therefore, whether anticipated or not, there is advantage in ACS administration within the first 24 hours, albeit full benefits with respect to prevention of neonatal respiratory complications do not become evident until beyond the 24 hour ACS-to-birth interval.[8] However, even if ACS administration less than 24 hour prior to birth was considered optimal, overall optimal timing of ACS administration remained less than 50% in this cohort.

The prevalence of optimal timing of ACS administration differed substantially according to maternal obstetric history, being lowest among women with a history of threatened miscarriage, threatened preterm labour, and gestational diabetes, while highest among women with suspected IUGR and pre-clampsia. These differences may reflect clinical heterogeneity related to different indicated and spontaneous preterm birth pathways. It is positive that iatrogenic preterm birth was associated with the highest rates of optimal ACS timing, but this still achieved in less than half of women. Such findings are in agreement with previous studies,[9] but raise questions as to what degree optimal administration rates can be improved.

The unpredictable occurrence and varying clinical courses with regard to when delivery occurs spontaneously or is medically indicated across various obstetric complications make optimal ACS administration a challenge, with future investigations needed to better determine optimal steroid administration strategies.

Despite the noted benefits of administration between 34 to 35 weeks' gestation, we identified a much lower rate of ACS administration at this gestation compared with less than 34 weeks' gestation (88% vs. 70%, respectively). This finding is consistent with that of other studies where the absolute difference in ACS rates at these gestations differed by 20-40%.[10, 19], and highlights a key area for improving clinical practice and the continued promotion of clinical practice guidelines.

Limited studies have examined trends in the administration of repeat doses of ACS. Similar to our findings, Levin et al. demonstrated an increase in the use of repeat doses from 2006 to 2011,[9] however, in contrast to their findings of a consistent increase in use over time, our findings demonstrated a decline in use in more recent years. We also observed a decline in the number of total repeat doses administered. Independently of repeat doses we saw significant increases in the optimal administration of ACS. Among women who received a course of ACS more than 7 days prior to birth, but still ended up delivering prior to 35 weeks, 53% of them ended up receiving a repeat ACS dose, compared to rates of 60% and 70% in two recent studies.[9, 21] Notably, a recent study demonstrated no difference in the optimal timing of ACS prior to birth following the introduction of a rescue course (i.e. repeat ACS dose) protocol[20], so there remains a need for improvement with respect to the prediction of preterm birth and subsequent timing of ACS administration.

Despite scant literature on the usage pattern of ACS beyond 35 weeks' gestation, our identified rates of ACS administration among women delivering between 35-36 weeks' gestation (34.6%) and more than 37 weeks' gestation (2.9%) are much higher than that reported in a recent population based study from Canada (11% and 1.2% respectively).[10] While Razaz et al.[10] did not stratify usage patterns according to method of delivery, we observed a significant increase in ACS prior to elective caesarean section, occurring between 37 and 38 weeks' gestation, from 8.8% in 2006/7 to 21.8% in 2014/15. Such an increase mirrors the updated publication of clinical guidelines by the Royal College of Obstetricians and Gynaecologists (RCOG) in 2010 strongly recommending use of ACS prior to planned elective caesarean section.[22]

A strength of this study lies in the large sample size and the rich and validated data capture on a large range of maternal and obstetric characteristics. An additional strength lies in the presence of data on receipt of a repeat dose of ACS, which has been missing in a number of previous studies,[10] and the stratification of outcomes according to type of labour onset.

Limitations include the lack of data on the exact gestational age of administration of ACS, rather just timing of administration. In addition, timing of administration relates to timing of birth following the first course, rather than timing of birth following any repeat doses. The exact type of ACS administered is not recorded and could either be betamethasone or dexamethasone, although betamethasone was listed as the preferred option in hospital clinical guidelines and is likely to represent the vast majority of use. Further, no data were available on indication for ACS use.

In conclusion, although there were significant improvements in the use of ACS over the 10-year period, optimal timing of a single course prior to preterm birth occurred in less than 50% of cases. Despite an initial increase in the use of repeat doses of ACS, there has been a decline in both the administration of a repeat dose and the number of repeat doses in more recent years, potentially relating to concerns about long-term effects on child development. The greatest increases in optimally timed ACS use were evident among planned deliveries occurring between 35 and 36 weeks' gestation and beyond 37 weeks' gestation, now accounting for 50% of overall ACS use.

Contribution to authorship

LEG conceptualised and designed the study, carried out the initial analyses, and drafted the initial manuscript. RMG and BWM helped design the study, assisted in the interpretation of results, and reviewed and revised the initial manuscript. All authors approved the final article for publication.

Details of ethics approval

This project was approved by the Human Research Ethics Committees of the Children, Youth, Women's Health Service and the University of Adelaide, in South Australia, Australia (HREC/14/WCHN/080; 06 May 2015) and received governance approval from the Research Governance Unit, Women's and Children's Health Network (SSA/14/WCHN/089).

Conflict of Interest: The authors have no conflicts of interests to disclose

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Table 1. Receipt of a single course of optimally timed antenatal corticosteroids according to obstetric characteristics among 2,926 live births occurring between 23 and 34 weeks' gestation, 2006-2015

Figure 1. Temporal trends in the administration of any antenatal corticosteroids (A) or a repeat dose of antenatal corticosteroids (B) according to gestational age at delivery, Adelaide, 2006-2015.

Figure 2. Temporal trends in the timing of a single course of ACS and a repeat dose of ACS among deliveries occurring between 23 and 34 weeks gestation (A) and between 35 and 36 weeks' gestation (B), Adelaide, 2006-2015. Data points are cumulative percentages and represent 3-year moving averages (2-year averages for the extremes).

Figure 3. Temporal trends in the optimal and suboptimal timing of a single course of ACS according to labour onset among deliveries occurring between 23 and 34 weeks' gestation (A) and between 35 and 36 weeks' gestation (B), Adelaide, 2006-2015.

Supplemental Table 1. Number of Live Births and Rate of Any and Repeat Antenatal Corticosteroid Administration by Maternal Characteristics Among 47,105 Live Births Between 2006 and 2015

Supplemental Table 2. Rate of Any and Repeat Antenatal Corticosteroid Administration by Obstetric Characteristics Among 47,105 Live Births Between 2006 and 2015

Supplemental Table 3. Receipt of a single course of optimally timed antenatal corticosteroids according to maternal characteristics among 2,926 live births occurring between 23 and 34 weeks' gestation, 2006-2015

Table 1. Receipt of a single course of optimally timed antenatal corticosteroids according to obstetric characteristics among 2,926 live births occurring between 23 and 34 weeks' gestation, 2006-2015

	All Live Births		Optimal Timing‡ of ACS Administration		
Obstetric Characteristic	**n**	**%**	**n**	**Rate/100**	**RR (95% CI)**
Plurality					
Singleton	2369	81.0	656	27.7	Reference
Twins	518	17.7	128	24.7	0.89 (0.76, 1.05)
Triplets or more	39	1.3	11	28.2	1.02 (0.61, 1.70)
Previous Obstetric History of Preterm Birth					
No	1128	38.6	313	27.8	Reference
Yes	433	14.8	101	23.3	0.84 (0.69, 1.02)
Not Applicable	1365	46.7	-	-	-
Gestational Diabetes					
No	2655	90.7	736	27.7	Reference
Yes	271	9.3	59	21.8	0.79 (0.62, 0.99)
Hypertensive Disorders of Pregnancy					
None	2406	82.2	596	24.8	Reference
Gestational Hypertension	36	1.2	10	27.8	1.12 (0.66. 1.91)
Pre-Eclampsia	484	16.5	189	39.1	1.58 (1.38, 1.80)
Cervical Suture					
No	2817	96.3	771	27.4	Reference
Yes	109	3.7	24	22.0	0.80 (0.56, 1.16)
Threatened Miscarriage					
No	2843	97.2	781	27.5	Reference
Yes	82	2.8	14	16.9	0.61 (0.38, 0.99)
Threatened Preterm Labour					
No	1223	41.8	414	33.9	Reference
Yes	1703	58.2	381	22.4	0.66 (0.59, 0.74)
Antepartum Haemorrhage					
No	2424	82.8	663	27.4	Reference
Yes	502	17.2	132	26.3	0.96 (0.82, 1.13)
Suspected IUGR					

No	2359	80.6	598	25.4	Reference
Yes	567	19.4	197	34.7	1.37 (1.20, 1.57)
Preterm Pre-labour Rupture of Membranes					
No	1678	57.4	467	27.8	Reference
Yes	1248	42.7	328	26.3	0.94 (0.84, 1.07)
Delivery					
Spontaneous Vaginal	1273	43.5	313	24.6	Reference
LSCS, in labour	621	21.2	146	23.5	0.96 (0.80, 1.14)
LSCS, no labour	1032	35.3	336	32.6	1.32 (1.16, 1.51)
Labour Onset					
Spontaneous	1618	55.3	357	22.1	Reference
No Labour (Elective LSCS)	1032	35.3	336	32.6	1.48 (1.30, 1.68)
Induction	276	9.4	102	37.0	1.67 (1.40, 2.00)
Type of preterm birth					
Spontaneous	1618	55.3	357	22.1	Reference
Medically Indicated	1308	44.7	438	33.5	1.52 (1.35, 1.71)
Year of Delivery					
2006-2007	570	19.5	116	20.4	Reference
2008-2009	587	20.1	150	25.6	1.26 (1.01, 1.55)
2010-2011	588	20.1	179	30.4	1.50 (1.22, 1.83)
2012-2013	652	22.3	186	28.5	1.40 (1.15, 1.72)
2014-2015	529	18.1	164	31.0	1.52 (1.24, 1.87)

Abbreviations: ACS, antenatal corticosteroid; RR, relative risk; CI, confidence interval; LSCS, lower segment caesarean section

‡ Optimal ACS administration defined as administration of the first single course of ACS >24 hours but <7 days prior to delivery

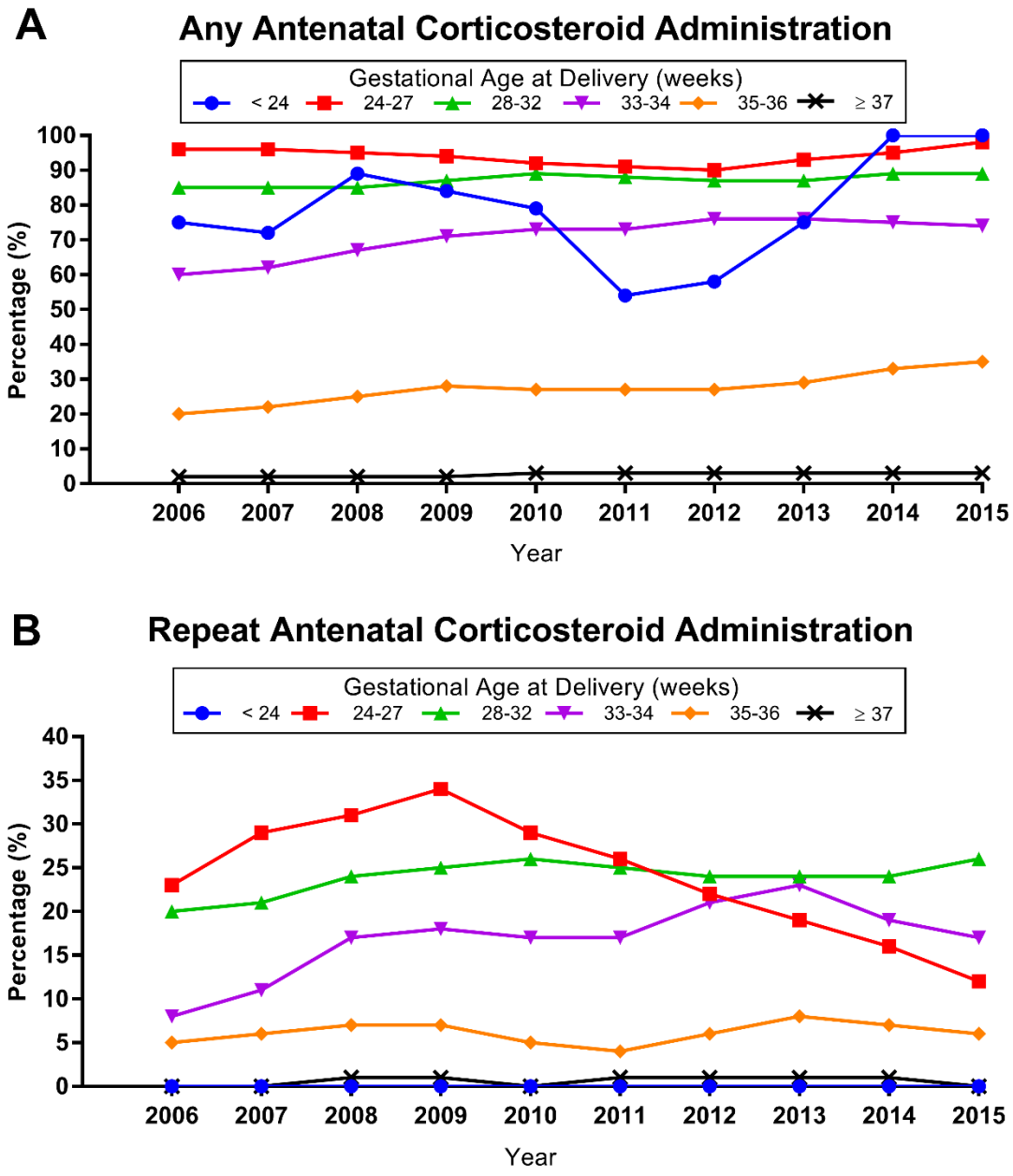

Figure 1. Temporal trends in the administration of any antenatal corticosteroids (A) or a repeat dose of antenatal corticosteroids (B) according to gestational age at delivery, Adelaide, 2006-2015.

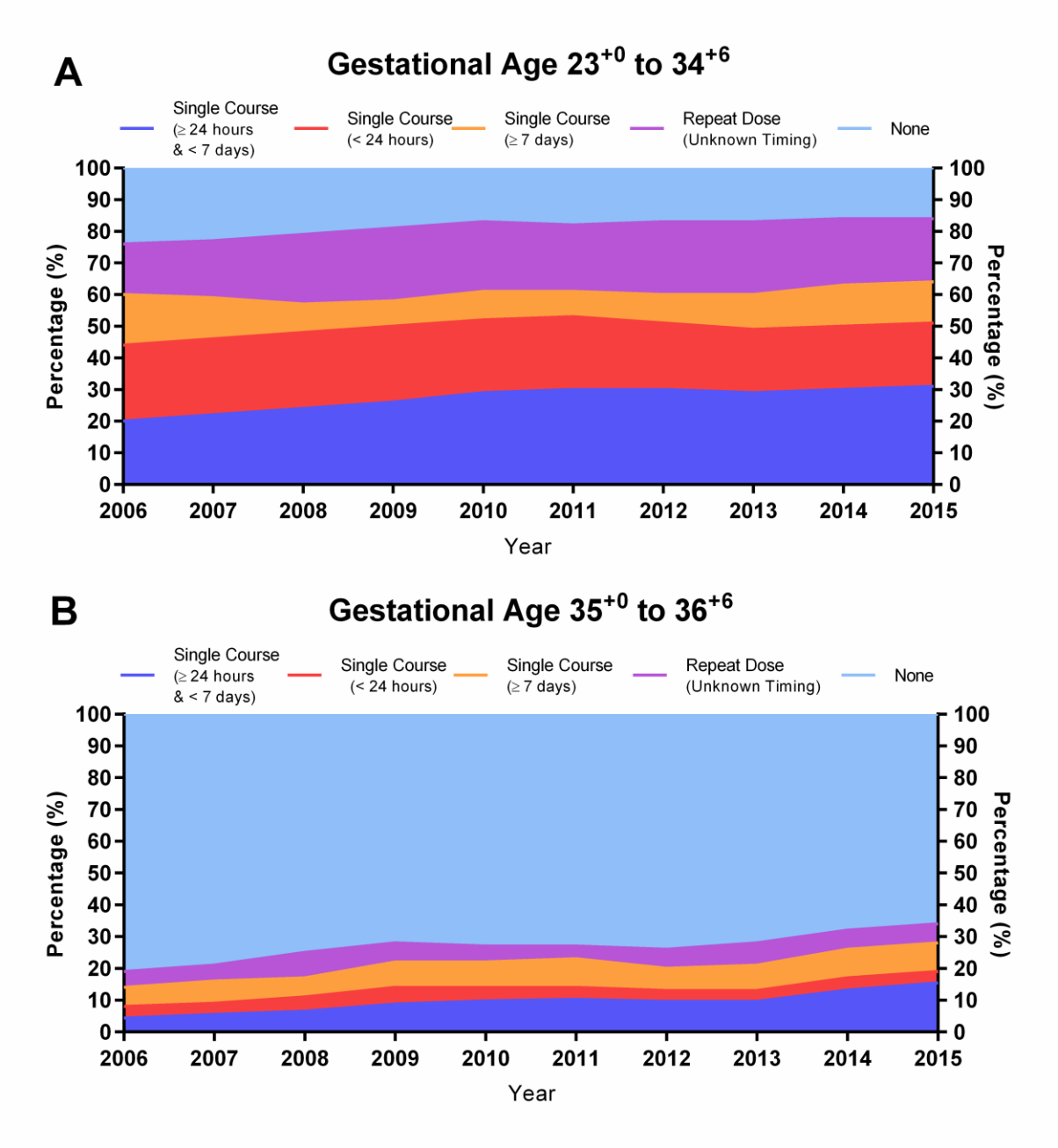

Figure 2. Temporal trends in the timing of a single course of ACS and a repeat dose of ACS among deliveries occurring between 23 and 34 weeks gestation (A) and between 35 and 36 weeks' gestation (B), Adelaide, 2006-2015. Data points are cumulative percentages and represent 3-year moving averages (2-year averages for the extremes).

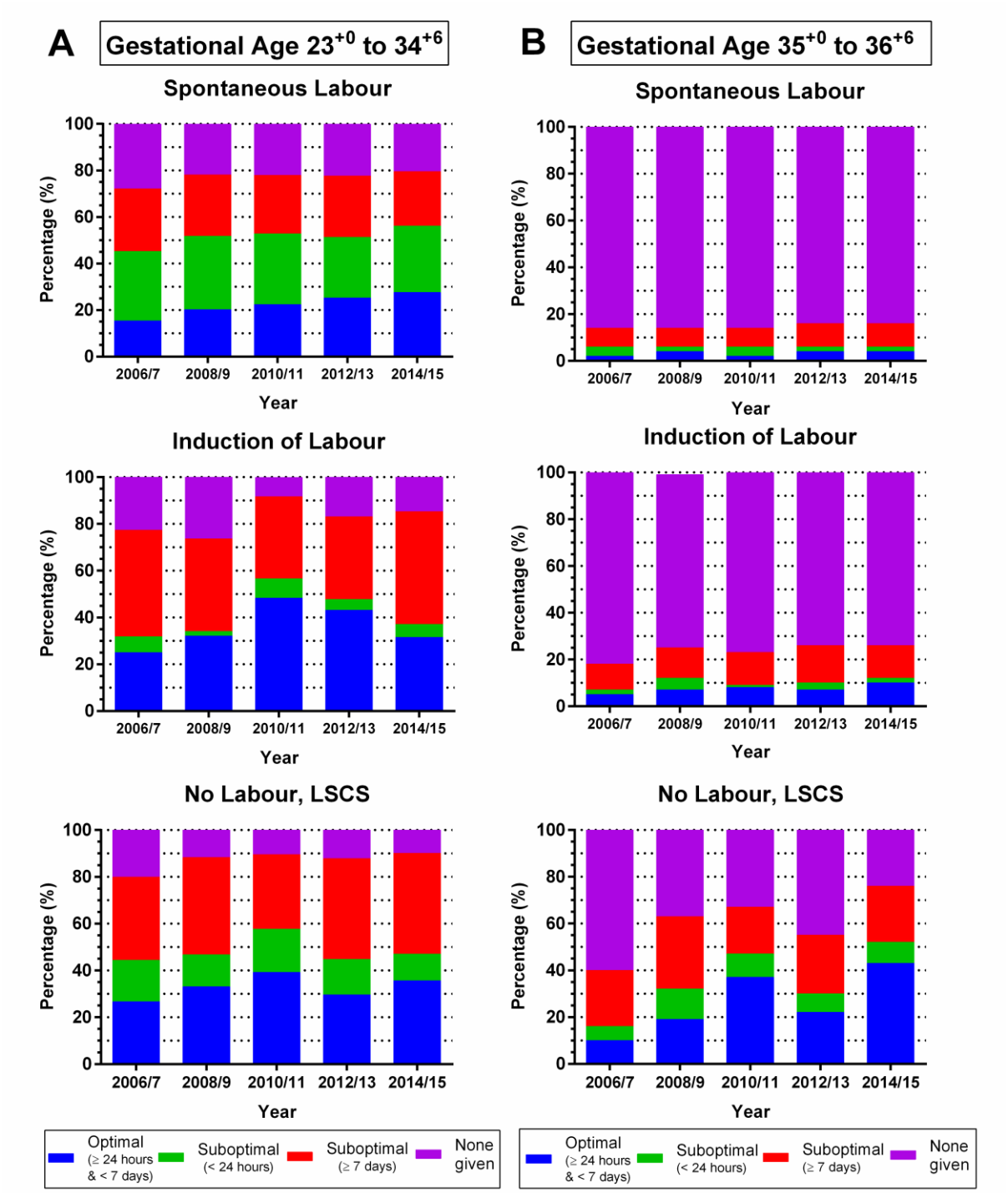

Figure 3. Temporal trends in the optimal and suboptimal timing of a single course of ACS according to labour onset among deliveries occurring between 23 and 34 weeks' gestation (A) and between 35 and 36 weeks' gestation (B), Adelaide, 2006-2015.

Supplemental Table 1. Number of Live Births and Rate of Any and Repeat Antenatal Corticosteroid Administration by Maternal Characteristics Among 47,105 Live Births Between 2006 and 2015

	All Live Births		Any Antenatal Corticosteroid Administration			Repeat Antenatal Corticosteroid Administration		
Maternal Characteristic	**n**	**%†**	**n**	**Rate/100**	**RR (95% CI)**	**n**	**Rate/100**	**RR (95% CI)**
Age								
<20	1719	3.7	204	11.9	1.41 (1.22,1.63)	41	2.4	1.26 (0.91,1.74)
20-24	7011	14.9	614	8.8	1.04 (0.95,1.14)	138	2.0	1.04 (0.85,1.27)
25-29	13715	29.1	1154	8.4	Ref	260	1.9	Ref
30-34	14792	31.4	1202	8.1	0.97 (0.89,1.04)	292	2.0	1.04 (0.88,1.23)
35	9868	21.0	1020	10.3	1.23 (1.13,1.33)	278	2.8	1.49 (1.26,1.76)
Missing	0	-	-	-	-	-	-	-
Parity								
0	21086	44.9	1723	8.2	1.01 (0.94,1.08)	379	1.8	0.88 (0.76,1.02)
1	15384	32.7	1244	8.1	Ref	313	2.0	Ref
2	6371	13.6	675	10.6	1.31 (1.20,1.43)	175	2.8	1.35 (1.12,1.62)
3 or more	4170	8.9	539	12.9	1.60 (1.45,1.76)	140	3.3	1.65 (1.35,2.01)
Missing	94	-	-	-	-	-	-	-
Ethnicity								
Caucasian	30460	64.7	3118	10.2	Ref	760	2.5	Ref
Aboriginal and/or TSI	1847	3.9	326	17.7	1.72 (1.55,1.92)	68	3.7	1.48 (1.16,1.88)
Asian	10436	22.2	530	5.1	0.50 (0.45,0.54)	116	1.1	0.45 (0.37,0.54)
Other	4361	9.3	219	5.0	0.49 (0.43,0.56)	65	1.5	0.60 (0.46,0.77)
Missing	1	-	-	-	-	-	-	-
Body Mass Index, kg/m^2								
<18.5	1360	3.5	100	7.4	1.29 (1.05,1.58)	21	1.5	1.13 (0.73,1.76)
18.5-24.9	19754	51.1	1128	5.7	Ref	269	1.4	Ref
25.0-29.9	9758	25.2	636	6.5	1.14 (1.04,1.26)	149	1.5	1.12 (0.92,1.37)

≥30	7782	20.1	750	9.6	1.69 (1.54,1.85)	177	2.3	1.67 (1.38,2.02)
Missing	8451	-	-	-	-	-	-	-
Socioeconomic Status								
5 (Highest)	8283	17.6	638	7.7	0.65 (0.59,0.72)	157	1.9	0.66 (0.55,0.81)
4	10858	23.1	920	8.5	0.72 (0.66,0.78)	216	2.0	0.70 (0.58,0.83)
3	9899	21.1	647	6.5	0.55 (0.50,0.61)	152	1.5	0.54 (0.44,0.65)
2	7670	16.3	758	9.9	0.84 (0.77,0.91)	186	2.4	0.85 (0.71,1.02)
1 (Lowest)	10316	21.9	1219	11.8	Ref	295	2.9	Ref
Missing	79	-	-	-	-	-	-	-
Smoking								
Non-Smoker	38640	83.8	2967	7.7	Ref	726	1.9	Ref
Quit Smoking	1705	3.7	154	9.0	1.18 (1.01,1.37)	30	1.8	0.94 (0.65,1.35)
Current Smoker	5767	12.5	776	13.5	1.75 (1.62,1.89)	175	3.0	1.62 (1.37,1.90)
Missing	4062	-	-	-	-	-	-	-
Pre-existing Diabetes								
No	46629	99.0	4079	8.8	Ref	986	2.1	Ref
Yes	476	1.0	115	24.2	2.76 (2.32,3.28)	23	4.8	2.29 (1.53,3.40)
Missing	0	-	-	-	-	-	-	-

Abbreviations: RR, relative risk; CI, confidence interval

† Percentages are calculated from non-missing values

Supplemental Table 2. Rate of Any and Repeat Antenatal Corticosteroid Administration by Obstetric Characteristics Among 47,105 Live Births Between 2006 and 2015

	All Live Births		Any Antenatal Corticosteroid Administration			Repeat Antenatal Corticosteroid Administration		
Obstetric Characteristic	**n**	**%†**	**n**	**Rate/100**	**RR (95% CI)**	**n**	**Rate/100**	**RR (95% CI)**
Plurality								
Singleton	45864	97.4	3526	7.7	Ref	828	1.8	Ref
Twins	1199	2.6	631	52.6	6.85 (6.42, 7.29)	165	13.8	7.62 (6.51, 8.92)
Triplets or more	42	0.1	37	88.1	11.46 (10.20, 12.87)	16	38.1	21.10 (14.06, 31.68)
Missing	0	-	-	-	-	-	-	-
Previous Obstetric History of Preterm Birth								
No	23736	50.4	1867	7.9	Ref	461	1.9	Ref
Yes	2283	4.9	604	26.5	3.36 (3.09, 3.66)	169	7.4	3.81 (3.21, 4.52)
Not Applicable	21086	44.8	-	-	-	-	-	-
Missing	0	-	-	-	-	-	-	-
Gestational Diabetes								
No	42855	91.0	3754	8.8	Ref	887	2.1	Ref
Yes	4250	9.0	440	10.4	1.18 (1.07, 1.30)	122	2.9	1.39 (1.15, 1.68)
Missing	0	-	-	-	-	-	-	-
Cervical Suture								
No	46866	99.5	4060	8.7	Ref	962	2.1	Ref
Yes	239	0.5	134	56.1	6.47 (5.74, 7.30)	47	19.7	9.58 (7.44, 12.34)
Missing	0	-	-	-	-	-	-	-
Threatened Miscarriage								
No	46423	98.6	4077	8.8	Ref	974	2.1	Ref
Yes	682	1.4	117	17.2	1.95 (1.65, 2.31)	35	5.1	2.45 (1.76, 3.40)
Missing	0	-	-	-	-	-	-	-

Threatened Preterm Labour								
No	43779	92.9	2569	5.9	Ref	637	1.5	Ref
Yes	3326	7.1	1625	48.9	8.33 (7.90, 8.77)	372	11.2	7.69 (6.80, 8.69)
Missing	0	-	-	-	-	-	-	-
Antepartum Haemorrhage								
No	45530	96.7	3551	7.8	Ref	815	1.8	Ref
Yes	1575	3.3	643	40.8	5.23 (4.89, 5.60)	194	12.3	6.88 (5.93, 7.98)
Missing	0	-	-	-	-	-	-	-
Preterm Pre-labour Rupture of Membranes								
No	44646	94.8	2994	6.7	Ref	711	1.6	Ref
Yes	2459	5.2	1200	48.8	7.28 (6.89, 7.68)	298	12.1	7.61 (6.68, 8.67)
Missing	0	-	-	-	-	-	-	-
Delivery								
Vaginal	33125	70.3	1593	4.8	Ref	319	1.0	Re
LSCS, in labour	6765	14.4	740	10.9	2.27 (2.09, 2.47)	190	2.8	2.92 (2.44, 3.49)
LSCS, no labour	7215	15.3	1861	25.8	5.36 (5.03, 5.72)	500	6.9	7.20 (6.26, 8.28)
Missing	0	-	-	-	-	-	-	-
Labour Onset								
Spontaneous	24960	53.0	1660	6.7	Ref	353	1.4	Ref
No Labour (Elective LSCS)	7215	15.3	1861	25.8	3.88 (3.64, 4.13)	500	6.9	4.90 (4.28, 5.61)
Induction	14930	31.7	673	4.5	0.68 (0.62, 0.74)	156	1.0	0.74 (0.61, 0.89)
Missing	0	-	-	-	-	-	-	-
Type of preterm birth								
Spontaneous	3001	52.4	1449	48.3	Ref	307	10.2	Ref
Medically Indicated	2725	47.6	1691	62.1	1.29 (1.23, 1.35)	468	17.2	1.68 (1.47, 1.92)
Not Applicable	41379	-	-	-	-	-	-	-
Missing	0	-	-	-	-	-	-	-
Year of Delivery								

2006-2007	9222	19.6	664	7.2	Ref	142	1.5	Ref
2008-2009	9582	20.3	811	8.5	1.18 (1.07, 1.30)	244	2.6	1.65 (1.35, 2.03)
2010-2011	9516	20.2	875	9.2	1.28 (1.16, 1.41)	171	1.8	1.17 (0.94, 1.45)
2012-2013	9585	20.4	962	10.0	1.39 (1.27, 1.53)	276	2.9	1.87 (1.53, 2.29)
2014-2015	9200	19.5	882	9.6	1.33 (1.21, 1.47)	176	1.9	1.24 (1.01, 1.55)
Missing	0	-	-	-	-	-	-	-

Abbreviations: RR, relative risk; CI, confidence interval; LSCS, lower segment caesarean section

† Percentages are calculated from non-missing data

Supplemental Table 3. Receipt of a single course of optimally timed antenatal corticosteroids according to maternal characteristics among 2,926 live births occurring between 23 and 34 weeks' gestation, 2006-2015

	All Live Births		Optimal Timing[‡] of ACS Administration		
Maternal Characteristic	**n**	**%[†]**	**n**	**Rate/100**	**RR (95% CI)**
Age					
<20	162	5.5	52	32.1	1.15 (0.89, 1.47)
20-24	421	14.4	115	27.3	0.97 (0.81, 1.18)
25-29	835	28.5	234	28.0	Reference
30-34	839	28.7	216	25.7	0.92 (0.78, 1.08)
35	669	22.9	178	26.6	0.95 (0.80, 1.12)
Missing	0	-	-	-	-
Parity					
0	1365	46.8	381	27.9	1.04 (0.90, 1.20)
1	796	27.3	214	26.9	Reference
2	409	14.0	110	26.9	1.00 (0.82, 1.22)
3 or more	344	11.8	85	24.7	0.92 (0.74, 1.14)
Missing	12	-	-	-	-
Ethnicity					
Caucasian	2219	75.9	583	26.3	Reference
Aboriginal and/or TSI	231	7.9	84	36.4	1.38 (1.15, 1.67)
Asian	329	11.3	87	26.4	1.01 (0.83, 1.23)
Other	146	5.0	41	28.1	1.07 (0.82, 1.40)
Missing	1	-	-	-	-
Body Mass Index, kg/m^2					
<18.5	60	3.7	14	23.3	0.83 (0.52, 1.33)
18.5-24.9	715	44.1	201	28.1	Reference
25.0-29.9	415	25.6	127	30.6	1.09 (0.90, 1.31)
≥30	433	26.7	135	31.2	1.11 (0.92, 1.33)
Missing	1303	-	-	-	-
Socioeconomic Status					
5 (Highest)	455	15.6	102	22.4	0.78 (0.64, 0.95)
4	611	21.0	164	26.8	0.93 (0.79, 1.11)

3	467	16.0	129	27.6	0.96 (0.80, 1.15)
2	485	16.7	140	28.9	1.01 (0.84, 1.20)
1 (Lowest)	895	30.7	257	28.7	Reference
Missing	13	-	-	-	-
Smoking					
Non-Smoker	1974	74.6	531	26.9	Reference
Quit Smoking	100	3.8	38	38.0	1.41 (1.09, 1.83)
Current Smoker	572	21.6	170	29.7	1.10 (0.96, 1.28)
Missing	280	-	-	-	-
Pre-existing Diabetes					
No	2837	97.0	770	27.1	Reference
Yes	89	3.0	25	28.1	1.03 (0.75, 1.43)
Missing	0	-	-	-	-

Abbreviations: ACS, antenatal corticosteroid; RR, relative risk; CI, confidence interval

‡ Optimal ACS administration defined as administration of the first single course of ACS >24 hours but <7 days prior to delivery

† Percentages are calculated from non-missing data