Is There a Benefit of Antenatal Corticosteroid When Given < 48 Hours Before Delivery?

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Research Article

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Abstract

Objective

We assessed the association between a short Antenatal Corticosteroid Administration-to-Birth Interval and neonatal outcome.

Study design:

A retrospective study between 2010- 2020. Eligible cases were singleton preterm live-born neonates born between 24 0/7 and 33 6/7 weeks of gestation and were initiated an ACS course of Betamethasone. We divided the first 48 hours following 1st ACS administration to four-time intervals and compared each time interval to those born more than 48 hours following ACS administration. The primary outcome was a composite of adverse neonatal outcome, including neonatal mortality or any major neonatal morbidity.

Results

A total of 200 women gave birth less than 48 hours from receiving the first betamethasone injection, and 172 women gave birth within 2-7 days (48-168 hours) from ACS administration. Composite adverse neonatal outcome was higher for neonates born less than 12 hours from initial ACS administration compared to neonates born 2-7 days from first betamethasone injection (55.45% vs. 29.07%, OR 3.45 95% CI [2.02-5.89], p.value<0.0001). However, there was no difference in composite adverse neonatal outcomes between neonates born 12-48 hours following ACS administration and those born after 2-7 days. That was also true after adjusting for confounders.

Conclusions

12-24 hours following ACS Administration may be sufficient in reducing the same risk of neonatal morbidities as > 48 hours following ACS administration. It may raise the question regarding the utility of the second dose of ACS.

Introduction:

Preterm delivery, defined as a delivery occurring between 24-37 weeks` gestation is a leading cause for neonatal morbidity and mortality[1–3]. There have been several measures to try and reduce this morbidity. Administration of antenatal corticosteroids (ACS) to mothers with threatened preterm birth between 24 0/7 and 34 0/7 weeks of gestation, results in a significant decrease in the risk and severity of neonatal respiratory distress syndrome (RDS), intracranial hemorrhage (IVH), necrotizing enterocolitis (NEC) and death[4–13].

The recommended course of ACS consists of either two 12-mg doses of betamethasone given intramuscularly 24 hours apart or four 6-mg doses of dexamethasone every 12 hours administered intramuscularly[4,14,15]. The American College of Obstetricians and Gynecologists (ACOG) states that the benefit of corticosteroid administration is greatest at 2-7 days after the initial dose[15]. While there seems to be agreement that neonatal benefits are maximized when ACS are administered 48 hours to 7 days before delivery, less is known about shorter administration-to-birth intervals. Some studies, especially the EPICE trial from 2017,have challenged the ACOG recommendations and showed a reduction in neonatal adverse outcome even after 24 hours from initial dose[7,16–20]. However, they were not preliminary designed to assess adverse outcome in less than 48 hours but rather later than 7 days, or RDS, which is the most common adverse outcome, was not evaluated.

In this study we aimed to evaluate the effectiveness of ACS on neonatal adverse outcome in the first 48 hours after ACS administration.

Methods:

This was a retrospective cohort study including all singleton neonates born between 24 0/7 and 33 6/7 weeks of gestation at a university-affiliated medical center during January 2010 to July 2020. The study was approved by the local Research Ethics Board (RMB-0134-20), waiving informed consent for de-identified patient information acquisition. Information collected from the hospital's database.

We included only neonates, whom their mothers received an ACS course, partial or complete, and delivered at our center. Exclusion criteria included intra-uterine fetal death, unknown timing of administration of ACS, and administration of more than one course of ACS.

ACS course consisted of betamethasone (intramuscularly, two doses of 12 mg 24 hours apart). ACS Administration-to-Birth Interval was defined as the time between first betamethasone injection to delivery.

Neonatal outcomes were compared between two groups of neonates according to the ACS Administration-to-Birth Interval: 1) Partial course of ACS, defined as less than 48 hours interval between first injection of betamethasone to birth 2) Complete ACS course, defined as 2-7 days interval (48-168 hours) from first injection of betamethasone to birth. Additionally, we did a sub analysis of women who delivered less than 48 hours from the first ACS injection. We divided the first 48 hours into four groups of 12-hour interval comparing each group to the 2-7 days (48-168 hours) interval as the gold standard of optimal neonatal outcome.

The primary outcome was defined as a composite adverse neonatal outcome including one or more of the following: respiratory distress syndrome (RDS), Periventricular leukomalacia (PVL), Necrotizing enterocolitis (NEC), Bronchopulmonary Dysplasia (BPD), intraventricular hemorrhage (IVH) grade 3 or 4, or neonatal mortality. The individual components of the primary outcome were analyzed separately as secondary outcomes. Other variables collected included maternal age and parity, gestational week, mode

of delivery, birth weight, 5-minute Apgar score, overall neonatal hospitalization days and neonatal intensive care unit (NICU) hospitalization days.

Categorical variables were compared between the study groups using Chi-square test or Fisher's exact test. For continuous variables, the comparisons were made using Student t-test or Wilcoxon two-sample test. Univariate and multivariable logistic regression models were implemented for the probability of RDS and composite adverse neonatal outcome (separately), presenting the adjusted odds ratio (aOR) with their 95% confidence intervals (95%CI). Multivariable models were adjusted for gestational age, hypertension, severe preeclampsia and cesarean delivery.

P value was two-sided and was deemed significant if less than 0.05. All statistical analyses and data management were performed using the SAS 9.4 software (SAS Institute Inc., Cary, NC, USA).

Results:

The study population included a total of 372 neonates delivered between January 2010 to July 2020. Of these, 200 women delivered less than 48 hours from first injection of betamethasone, and 172 women delivered within 2-7 days (48-168 hours) from first injection of betamethasone (Figure 1).

Maternal characteristics of the study groups are presented in Table 1. Women who received a complete course of ACS were more likely to have hypertension and preeclampsia with severe features, compared to those who received partial course of ACS (14% vs. 4%, $p< 0.0006$; 24% vs. 7.5%, $p <0.0001$; respectively). There was no difference in gestational age at delivery, parity, or mode of delivery between the groups (Table 1).

Table 1
Maternal characteristics

	ACS Injection<2 days prior to delivery (N=200)	ACS Injection 2-7 days prior to delivery (N=172)	P-value
Maternal age, y	30.8±6.2	31.3±6.4	0.4268
Parity	2.3±1.8	2.1±1.6	0.6105
Primiparous	89 (44.5)	87 (50.58	0.2415
Gestational week at delivery	31.2±2.5	30.6±2.8	0.0777
Gestational/Pregestational Diabetes mellitus	20 (10)	12(7)	0.2998
Hypertension	8 (4)	24 (14)	**0.0006**
Preeclampsia without severe features	6 (3)	11 (6.4)	0.1179
Preeclampsia with severe features	15 (7.5)	42 (24.4)	**<0.0001**
Mode of delivery:			
Vaginal delivery	91 (45.5)	75 (54.6)	0.6705
Vacuum delivery	6 (3)	3 (1.7)	
Cesarean delivery	103 (51.5)	94 (54.6)	
Data are n (%) or mean standard deviation unless otherwise specified.			
Percentages calculated within each group.			
ACS= antenatal corticosteroids			

Neonatal outcomes are presented in Table 2. Women who received a complete ACS course were more likely to deliver after 28 weeks of gestation compared to those receiving a partial ACS treatment (19.7% vs. 11%, p<0.0001). Neonates within this group had significantly lower incidence of composite adverse outcome and RDS (45% vs. 29%, p=0.0016; 38% vs. 20%, p=0.0003; respectively). There was no difference in 5-min Apgar scores, NICU admissions, and hospitalization stay between the groups, or in any of the other neonatal adverse outcome.

Table 2
Neonatal Outcomes

	ACS Injection<2 days prior to delivery (N=200)	**ACS Injection 2-7 days prior to delivery (N=172)**	**P-value**
Gestational age at delivery	30.8 ± 6.2	30.6 ± 2.8	0.0777
Gestational age 28 weeks or less	22 (11)	34 (19.77)	**<.0001**
Birth weight (g)	1700 ± 500	1500 ± 500	**<.0001**
5-min Apgar score	9.2 ± 1	9.2 ± 1.1	0.8936
Hospitalization days	41.5 ± 35.2	42.9 ± 28.4	0.4161
NICU days	40.3 ± 35.4	41.8 ± 28.3	0.3541
In-hospital mortality	7 (3.5)	9 (5.23)	0.4115
RDS	76 (38)	36 (20.93)	**0.0003**
PVL	0 (0)	0 (0)	-
NEC	2 (1)	1 (0.58)	>0.99
Bronchopulmonary Dysplasia	1 (0.5)	1 (0.58)	>0.99
IVH Grade 3 or 4	4 (2)	7 (4.07)	0.2400
Composite adverse neonatal outcome	90 (45)	50 (29.07)	**0.0016**
Data are n (%) or mean standard deviation unless otherwise specified.			
Percentages calculated within each group.			
ACS = antenatal corticosteroids, NICU = neonatal intensive care unit, RDS = respiratory distress syndrome, PVL = periventricular leukomalacia, NEC = necrotizing enterocolitis, IVH = intraventricular hemorrhage.			
The composite adverse neonatal outcome included at least one of the following: RDS, PVL, NEC, Bronchopulmonary Dysplasia, intraventricular hemorrhage of newborn grade 3 or 4.			

When dividing the first 48 hours into 12-hour intervals, we found that composite adverse neonatal outcome was higher for neonates born less than 12 hours from initial ACS administration compared to neonates born 2-7 days from first betamethasone injection (55% vs. 29%, OR 3.45 95% CI [2.02-5.89]), p<0.0001). However, there was no difference in composite adverse neonatal outcomes between neonates born 12-48 hours following ACS administration and those born after 2-7 days (Table 3).

Table 3
Composite Adverse Neonatal Outcome by time interval

ACS Administration-to-Birth Interval, Hours	Composite outcome rate N (%)	Crude OR	Adjusted OR	P-value
0-12	56 (55.45%)	3.04 [1.82-5.07]	3.45 [2.02-5.89]	**<.0001**
12-24	18 (41.86%)	1.76 [0.88-3.5]	1.93 [0.95-3.94]	0.071
24–36	10 (32.26%)	1.16 [0.51-2.64]	1.26 [0.55-2.91]	0.5844
36–48	6 (24%)	0.77 [0.29-2.04]	0.73 [0.27-1.95]	0.5249
48-168 (2-7 days)*	50 (29.07%)			
Each time interval was compared to the 48-168-time interval (2-7 days)				
ACS=antenatal corticosteroids				
The composite adverse neonatal outcome included at least one of the following: RDS, PVL, NEC, Bronchopulmonary Dysplasia, intraventricular hemorrhage of newborn grade 3 or 4.				
Adjustment for gestational age, Hypertension, severe preeclampsia, and cesarean delivery				

The most common neonatal morbidity was RDS. RDS rate was significantly higher in the first two-time intervals (0-12 hours and 12-24 hours) when compared to RDS rate in neonates born 2-7 days from ACS course initiation (48.51% and 34.88% vs. 20.93%, OR 4.16 95% CI [2.36-7.33] and OR 2.33 95% CI [1.09-4.98]; respectively). There was no difference in RDS rate in neonates born between 24-48 and > 48 hours from ACS administration. That was also true when using a regression analysis model and adjusting for confounders (gestational age, hypertension, severe preeclampsia, and mode of delivery) (Table 4).

Table 4. RDS rate by time interval

ACS Administration-to-Birth Interval, Hours	Composite outcome rate N (%)	Crude OR	Adjusted OR	P-value
0-12	49 (48.51%)	3.56 [2.08-6.08]	4.16 [2.36-7.33]	**<0.0001**
12-24	15 (34.88%)	2.02 [0.98-4.19]	2.33 [1.09-4.98]	**0.0285**
24–36	7 (22.58%)	1.10 [0.44-2.76]	1.16 [0.45-2.95]	0.7631
36–48	5 (20%)	0.94 [0.33-2.69]	0.82 [0.28-2.39]	0.7159
48-168 (2-7 days)*	40 (20.93%)			

Each time interval was compared to the 48-168-time interval (2-7 days)

ACS=antenatal corticosteroids

The composite adverse neonatal outcome included at least one of the following: RDS, PVL, NEC, Bronchopulmonary Dysplasia, intraventricular hemorrhage of newborn grade 3 or 4.

Adjustment for gestational age, Hypertension, severe preeclampsia, and cesarean delivery

Discussion:

Main findings:

In this study we aimed to assess the effectiveness of ACS administration on adverse neonatal outcome when delivered within 48 hours from the first dose. We divided the first 48 hours to find out whether there was a shorter time frame sufficient to ensure similar neonatal outcome compared to 2-7 days from initial dose.

Our findings were as follows: 1) RDS rate was similar in neonate receiving ACS less than 24 hours prior to delivery to those born 2-7 days following ACS administration; 2) Neonates born only 12 hours from first ACS dose had similar composite adverse neonatal outcome as neonates born 2-7 days following ACS administration, even after adjusting for confounders.

Comparison with existing literature:

Our results match previous studies by showing a decrease in adverse neonatal outcome of ACS even 24 hours following the first dose[7,16,20] .

Crowley et al[7] showed, in their meta-analysis published in 1995, that the best benefit of ACS in neonatal outcome is when it is administered 1-7 days before delivery. In 2015, melamed et al[16] compared, in a

large retrospective cohort study, the effectiveness of ACS when administered less than 24 hours before birth, 1–7 days before birth, and more than 7 days before birth. They found that ACS had maximum benefit when given between 1 and 7 days before birth with lower neonatal mortality and composite adverse outcome.

The EPICE trial found that infant mortality rapidly and significantly reduced when ACS were administered only a few hours before delivery, with more than 50% risk reduction after an administration-to-birth interval of 18-36 hours[20]. The EPICE trial, to the best of our knowledge, was the first to break down the first 48 hours into a scale of hours rather than days. However, in these shorter time frames, they evaluated neonatal in-hospital mortality and IVH rates. They did not assess RDS rate or nay other adverse outcome.

Strengths and limitations

The main limitation of our study lies in its retrospective nature and small sample size. Nevertheless, it is one of the first studies to evaluate the effect of ACS Administration-to-Birth Interval on neonatal adverse outcome, specifically respiratory, in a scale of hours rather than days or weeks as previous studies.

Conclusions And Implications

Our findings suggest that there may be adequate benefit to ACS in reducing adverse neonatal outcome even when given only 12 hours prior to delivery. If that can be repeated in lager studies, it may raise a question regarding the need for the second ACS injection. Furthermore, it may make a difference in managing different and complicated cases when some opt to delay delivery to a full ACS effect.

Declarations

Author Contribution:

Y. Siegler: Protocol development, Data collection, Data analysis, Manuscript writing

N. Justman: Data collection, Data analysis, Manuscript editing

G. Bachar: Data collection, Manuscript editing

R. Lauterbach: Data collection, Manuscript editing

Y. Zipori: Protocol development, Data analysis, Manuscript editing

N. Khatib: Protocol development, Data analysis, Manuscript editing

Z. Weiner: Protocol development, Data analysis, Manuscript editing

D. Vitner: Protocol development, Data analysis, Manuscript writing

Conflict of Interest:

All authors declare no conflicts of interest or financial disclosures.

References

1. Stoll BJ, Hansen NI, Bell EF et al (2010) Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics 126(3):443–456
2. Volpe JJ (1997) Overview: perinatal and neonatal brain injury. Mental Retardation Developmental Disabilities Research Reviews 3(1):1–2
3. Gynecologists ACoOa (2012) Prediction and prevention of preterm birth. ACOG Practice Bulletin No. 130. Obstet Gynecol 120:964–973
4. Gynecologists ACoOa (2016) Practice Bulletin No. 171: Management of Preterm Labor. Obstetrics gynecology 128(4):e155
5. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane database of systematic reviews*. 2017;(3)
6. CROWLEY P, CHALMERS I, KE1RSE MJ (1990) The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. BJOG: An International Journal of Obstetrics Gynaecology 97(1):11–25
7. Crowley PA (1995) Antenatal corticosteroid therapy: a meta-analysis of the randomized trials, 1972 to 1994. American journal of obstetrics gynecology 173(1):322–335
8. Liggins G. Premature delivery of foetal lambs infused with glucocorticoids. j. Endocrinol. 1969; 45: 515–23. 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
9. Briceño-Pérez C, Reyna-Villasmil E, Vigil-De-Gracia P (2019) Antenatal corticosteroid therapy: Historical and scientific basis to improve preterm birth management. European Journal of Obstetrics Gynecology Reproductive Biology 234:32–37
10. Braun T, Sloboda DM, Tutschek B et al (2015) Fetal and neonatal outcomes after term and preterm delivery following betamethasone administration. International Journal of Gynecology Obstetrics 130(1):64–69
11. Brownfoot FC, Gagliardi DI, Bain E, Middleton P, Crowther CA. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database of Systematic Reviews*. 2013;(8)
12. Gyamfi-Bannerman C, Thom EA, Blackwell SC et al (2016) Antenatal betamethasone for women at risk for late preterm delivery. N Engl J Med 374(14):1311–1320
13. Chawla S, Lua J, Natarajan G et al (2014) Postnatal respiratory compliance among premature ventilated neonates associated with variable timing and dosing of antenatal steroids. Am J Perinatol 31(12):1073–1078
14. Gilstrap LC, Christensen R, Clewell WH et al (1995) Effect of corticosteroids for fetal maturation on perinatal outcomes: NIH consensus development panel on the effect of corticosteroids for fetal

maturation on perinatal outcomes. Jama 273(5):413–418

15. Committee Opinion No (2017) 713: Antenatal Corticosteroid Therapy for Fetal Maturation: Correction. Obstetrics Gynecology 130(5):1159. doi:10.1097/aog.0000000000002356
16. Melamed N, Shah J, Soraisham A et al (2015) Association between antenatal corticosteroid administration-to-birth interval and outcomes of preterm neonates. Obstetrics Gynecology 125(6):1377–1384
17. Elimian A, Figueroa R, Spitzer AR, Ogburn PL, Wiencek V, Quirk JG (2003) Antenatal corticosteroids: are incomplete courses beneficial? Obstetrics Gynecology 102(2):352–355
18. Khandelwal M, Chang E, Hansen C, Hunter K, Milcarek B (2012) Betamethasone dosing interval: 12 or 24 hours apart? A randomized, noninferiority open trial. American journal of obstetrics gynecology 206(3):201. e1-201. e11
19. Ikegami M, Polk D, Jobe A (1996) Minimum interval from fetal betamethasone treatment to postnatal lung responses in preterm lambs. American journal of obstetrics gynecology 174(5):1408–1413
20. Norman M, Piedvache A, Børch K et al (2017) Association of short antenatal corticosteroid administration-to-birth intervals with survival and morbidity among very preterm infants: results from the EPICE cohort. JAMA pediatrics 171(7):678–686

Figures

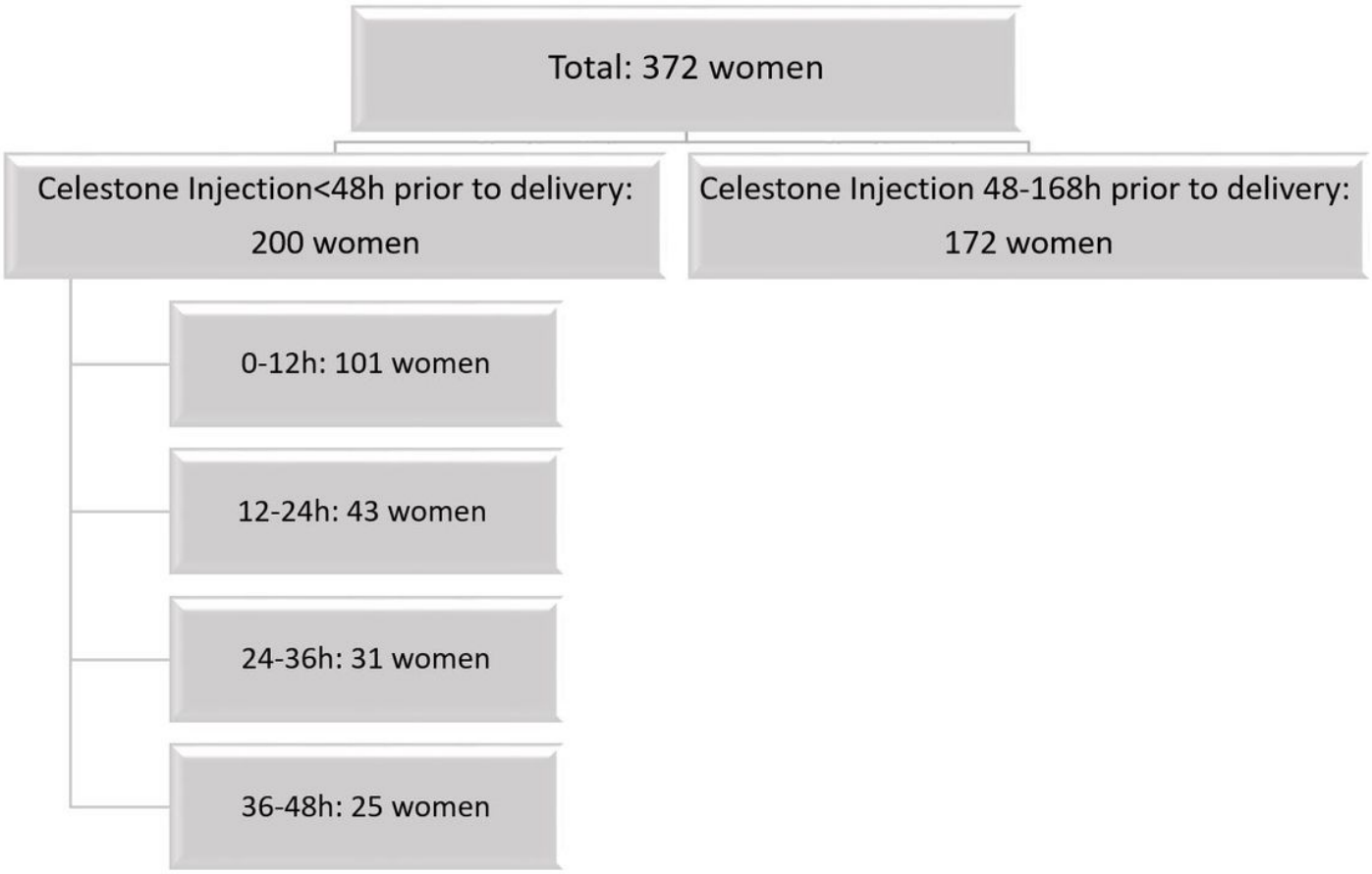

Figure 1

study population by ACS administration-to-birth intervals in hours.

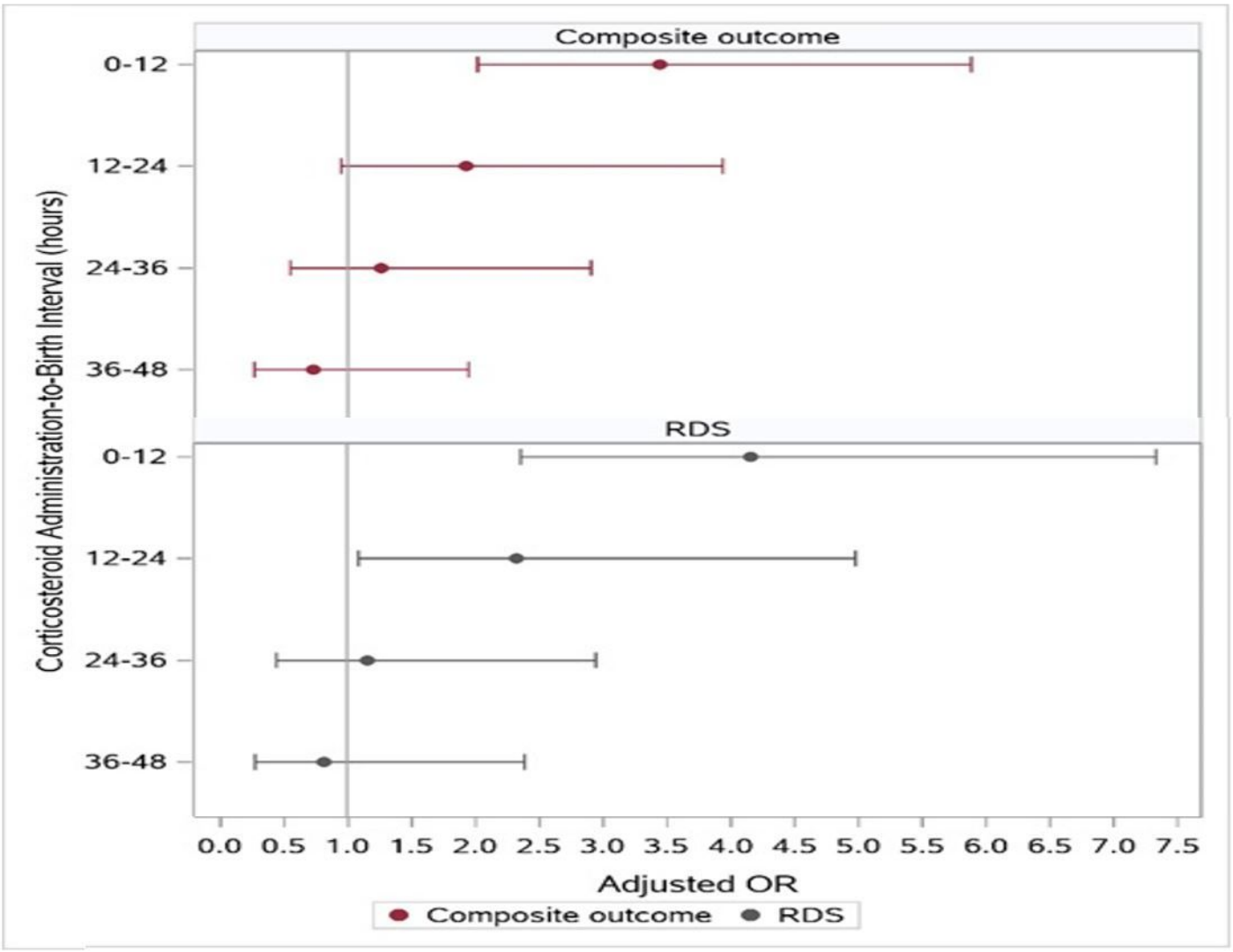

Figure 2

Adjusted odds ratio of composite neonatal outcome and RDS by time interval as compared to the 48-168-time interval