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Rescue corticosteroids in twin pregnancies and short-term neonatal outcomes

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Objective To estimate the efficacy of a rescue course of antenatal corticosteroids in twin pregnancies.

Design Retrospective cohort study.

Setting Tertiary-care centre.

Population Twins born from 24 to <34 weeks of gestation in a single maternal and fetal medicine practice from 2006 to 2011.

Methods We compared neonatal outcomes in 88 twins exposed to a single course of corticosteroids with outcomes in 42 twins exposed to two courses of corticosteroids: the initial course and a single rescue course. Analyses were adjusted to control for correlation between twins born to the same mother.

Main outcome measure Short-term neonatal respiratory morbidity.

Results Rescue corticosteroids were associated with fewer days of mechanical ventilation (7.3 ± 3.3 versus 33.9 ± 25.3 days, $P = 0.003$), fewer days with a fraction of inspired oxygen of >21% (6.3 ± 4.3 versus 33.3 ± 25.8 days, $P = 0.003$), a lower incidence of mechanical ventilation >14 days or death while on mechanical ventilation (0 versus 12.5%, $P = 0.016$), and a lower incidence of retinopathy of prematurity (0 versus 12.5%, $P = 0.016$). The proportion of neonates with respiratory distress syndrome did not differ between the groups (adjusted odds ratio 1.28, 95% confidence interval 0.50–3.26). There were no differences found for birthweight, head circumference and length.

Conclusions In twins born before 34 weeks of gestation, exposure to rescue corticosteroids may be associated with improved neonatal outcomes. Further studies are warranted to assess the effect of rescue corticosteroids in twin pregnancies.

Keywords Corticosteroids, outcomes, preterm birth, rescue, twin.

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Introduction

The number and rate of twin births continues to rise, from 2.2% of all live births in the USA in 1990 to 3.2% of all live births in 2005.[1] Preterm birth is the most common morbidity associated with twin pregnancies. Based on randomised evidence, the National Institutes of Health,[2] the American College of Obstetricians and Gynecologists (ACOG),[3] and the Royal College of Medicine[4] all recommend antenatal corticosteroid administration to women at risk for preterm delivery before 34 weeks of gestation. It is unknown if the benefits of antenatal corticosteroids seen in singleton pregnancies are similar in twin pregnancies because of the small number of twin pregnancies included in the randomised trials. However, a number of observational studies suggest that antenatal corticosteroids are indeed beneficial in twin pregnancies[5–7] and current guidelines recommend administration of antenatal corticosteroids to women with multiple pregnancy and threatened premature delivery.[2]

Steroids appear to have maximum efficacy if administered 1–7 days before delivery, so a number of strategies aimed at optimising steroid timing have been studied. Multiple studies have compared weekly or biweekly corticosteroid therapy to standard single-course therapy.[8–11] Based on a risk–benefit analysis from these trials, the original recommendation against weekly antenatal corticosteroids has not been revised. However, a number of trials have studied the efficacy of a single rescue course of corticosteroids, which is defined as a second course of corticosteroids given to women who remain at increased risk for preterm birth.[12,13] These studies have shown certain benefits, such

as decreased rates of respiratory distress syndrome (RDS), surfactant use, and ventilator support, without evidence of harm. Based on these data, ACOG stated that a single course of rescue corticosteroids could be considered if the previous corticosteroid treatment was given more than 2 weeks previously, the gestational age is <33 weeks, and the woman is likely to delivery within the next 7 days.[3]

In relation to twin pregnancies and repeat corticosteroids, one study showed no benefit of routine corticosteroids administered once every 2 weeks in the third trimester when compared with standard indications for single-course corticosteroids.[14] However, rescue corticosteroid use, as defined in the singleton trials, has not been studied in twin pregnancies so it is not known if rescue corticosteroids are beneficial in twin pregnancies. In our practice, we administer rescue corticosteroids in both singleton and twin pregnancies who have received corticosteroids more than 2 weeks previously but that, in our best clinical judgement, remain at very high risk for delivery in the next week. The objective of this retrospective study was to estimate neonatal outcomes in twins based on exposure to single-course or rescue-course corticosteroid therapy.

Methods

We performed a retrospective cohort study of twins born between 24 and <34 weeks of gestation. After Mount Sinai School of Medicine Institutional Review Board approval was obtained, the charts of all women with twin pregnancies delivered by a single maternal and fetal medicine practice between January 2006 and January 2011 were reviewed. We ascertained whether the mothers received antenatal corticosteroids, at what gestational age and for what indication. We also recorded whether the mother received a course of rescue corticosteroids, and at what gestational age. In our institution, the antenatal corticosteroid used is betamethasone 12 mg, given intramuscularly as two doses 24 hours apart. For the purpose of this analysis, women who received a partial course of corticosteroids (i.e. only one dose) were not considered as having received that course of corticosteroids. Gestational age was determined by last menstrual period and confirmed by ultrasound scan in all women. The expected date of delivery was revised if the discrepancy was >5 days between the calculation from the last menstrual period and ultrasound scan up to 14 weeks gestation or >7 days if the dating ultrasound scan was performed after 14 weeks gestation (all women underwent first-trimester or second-trimester ultrasound scans). If the pregnancy was the result of *in vitro* fertilisation, gestational age was determined from the date of embryo transfer.

The charts of newborns were reviewed for outcome data. The investigators reviewing the newborn's charts for outcome data were blinded to whether the mother received any rescue course of corticosteroids. This was accomplished by having different reviewers for the newborn and maternal records. Paediatricians reviewed the newborn records to determine neonatal outcomes. The newborn records often indicate the presence of absence of antenatal corticosteroid exposure, but do not indicate the number of courses. For this reason, the paediatricians reviewing the neonatal outcomes were blinded to whether the newborn was exposed to a single course or any rescue course of antenatal corticosteroids. The obstetricians reviewing the mother's antenatal records to search for number of courses of corticosteroid did not review the newborn records at all.

We compared outcomes in twins exposed to one course of corticosteroids (Single-Course Corticosteroids Group) with outcomes in twins exposed to a rescue course of corticosteroids (Rescue Corticosteroids Group). Our primary outcome was the rate of RDS, which was diagnosed by an attending neonatologist caring for the infant neonatally using the criteria of radiographic findings consistent with RDS (ground glass appearance, bilateral haziness) and clinical presentation of severe respiratory distress (severe retractions, nasal flaring, grunting).

Other secondary respiratory outcomes studied were surfactant use, need for mechanical ventilation and prolonged ventilation >14 days, number of days requiring mechanical ventilation, peak fraction of inspired oxygen (Fio_2), and the number of days receiving $Fio_2 > 21\%$ (room air). In our institution, surfactant is given soon after admission to the neonatal intensive-care unit to a neonate who requires intubation for RDS or to a non-intubated neonate if the Fio_2 via noninvasive mechanical ventilation is ≥40%. Therefore, it is possible to have mild RDS without requiring surfactant. Also, typical practice for a non-intubated neonate who receives surfactant is intubation simply for surfactant administration with immediate extubation to noninvasive mechanical ventilation. This brief intubation alone was not considered as mechanical ventilation in our study. We also studied other neonatal outcomes including death before discharge, length of stay, necrotising enterocolitis (stage 2a or higher based on the Bell criteria[15]), intraventricular haemorrhage (of any degree, based on ultrasound diagnosis), patent ductus arteriosus, sepsis, retinopathy of prematurity (stage 1 or higher as defined by The International Classification of Retinopathy of Prematurity[16]), and chronic lung disease, defined as requiring oxygen therapy at a corrected age of 36 weeks. Finally, we studied a number of newborn growth parameters (birthweight, head circumference and body length using the Fenton tables[17]).

Assuming a baseline rate of RDS in neonates born <34 weeks of gestation of 62%,[12] 102 neonates (with a single corticosteroids to rescue corticosteroids ratio of 2:1) would be needed to have 80% power to detect a reduction in RDS from 62 to 31% with an α error of 5%. We

performed the power analysis per neonate and not per mother because the primary and secondary outcomes were all neonatal. Fisher's exact test, chi-square test and Student's *t* test were used when appropriate. Adjusted odds ratios were derived and compared using logistic regression or linear regression, as appropriate, for correlated outcomes employing generalised estimating equations to account for correlation between twins born to the same mother using SPSS FOR WINDOWS 19.0 (2007; SPSS Inc., Chicago, IL, USA). A P value ≤0.05 was considered significant. For outcomes in which odds ratios could not be calculated because there were zero events in one group (and so an odds ratio of infinity), a general linear model employing generalised estimating equations to account for twins was used to compare the two groups.

Results

In the study period there were 144 twin neonates born from 24 to <34 weeks of gestation. Of those, 12 (8.3%) from six pregnancies were exposed to no antenatal corticosteroids, 90 (62.5%) from 46 pregnancies (two pregnancies experienced a fetal demise of one twin) were exposed to a single course of antenatal corticosteroids, and 42 (29.2%) from 21 pregnancies were exposed to a rescue course of antenatal corticosteroids. No neonates were exposed to more than two courses of antenatal corticosteroids. Among neonates exposed to antenatal rescue corticosteroids, 42 (100%) of the rescue courses complied with the ACOG recommendations of being 14 or more days from the initial course and at a gestational age of <33 weeks. Neonatal outcome data were unavailable for one set of twins in the Single-Course Corticosteroids Group. A search of medical records and attempts to reach the mother of these twins were unsuccessful and these two infants were excluded from analysis. Therefore, the final cohort includes 42 neonates in the Rescue Corticosteroids Group and 88 neonates in the Single-Course Corticosteroids Group (total of 130 neonates).

Baseline characteristics of the Single-Course and Rescue Corticosteroid Groups are shown in Table 1. The two groups were similar with regard to gestational age at delivery, reason for preterm delivery (spontaneous or iatrogenic), birthweight, time interval from completion of corticosteroid treatment to delivery, ethnicity and mode of delivery. There was a significantly higher proportion of males in the Rescue Corticosteroids Group. All of the women had private health insurance. The prevalence of the use of rescue corticosteroid treatment was similar throughout the study period.

Neonatal outcomes are shown in Table 2. The proportion of neonates with RDS did not differ between the groups. However, a number of other adverse respiratory outcomes were less frequent in the Rescue Corticosteroids Group, including the number of days on mechanical ventilation overall (0.7 ± 2.3 versus 5.0 ± 15.3, $P = 0.011$), the number of days on mechanical ventilation for neonates who required mechanical ventilation (7.3 ± 3.3 versus 33.9 ± 25.3, $P = 0.003$) and the number of days requiring an Fio_2 of >21% (6.3 ± 4.3 versus 33.3 ± 25.8, $P = 0.003$). Additionally, in the Rescue Corticosteroids Group there was a very low rate of severe RDS requiring prolonged ventilation. There were no neonates in the Rescue Corticosteroids Group with mechanical ventilation >14 days or death on the ventilator, compared with 11 (12.5%) neonates in the Single-Course Corticosteroids Group ($P = 0.016$). The likelihood of retinopathy of prematurity was also significantly decreased in the Rescue Corticosteroids Group (0 vesrus 12.5%, $P = 0.016$). Our results were not different when we controlled for gender. On adjusted analysis

Table 1. Baseline characteristics of twins born from 24 to <34 weeks of gestation, based on exposure to a single course or a rescue course of antenatal corticosteroids

	Single course (n = 88)	Rescue course (n = 42)	P
Gestational age at delivery (mean ± SD)	31.3 ± 2.6	31.5 ± 2.0	0.603
Date of delivery			
Before 1 July 2008*	32 (36.4%)	20 (47.6%)	0.301
After 1 July 2008*	56 (63.6%)	22 (52.4%)	
Birthweight (grams) (mean ± SD)	1549 ± 465	1576 ± 359	0.718
Preterm delivery			
Spontaneous	65 (73.9%)	30 (72.4%)	0.935
Iatrogenic	23 (26.1%)	12 (28.6%)	
Gestational age at first corticosteroid course (mean ± SD)	29.3 ± 2.8	25.7 ± 1.9	<0.001
Gestational age at rescue corticosteroid course (mean ± SD)		29.6 ± 1.7	
Interval (days) from steroid completion to delivery (mean ± SD)	14.0 ± 13.8	13.4 ± 11.7	0.774
Delivery within 7 days from steroid completion	41 (46.6%)	20 (47.6%)	0.913
Gender			
Female	44 (50%)	13 (31%)	0.041
Male	44 (50%)	29 (69%)	
Ethnicity			
White	68 (77.3%)	30 (72.4%)	0.613
Non-white	20 (22.7%)	12 (28.6%)	
Private health insurance	88 (100%)	42 (100%)	>0.999
Mode of delivery			
Vaginal	15 (17%)	6 (14.3%)	0.689
Caesarean	73 (83%)	36 (85.7%)	

*1 July 2008 is the mid-point of the study period.

Table 2. Neonatal outcomes of twins from 24 to <34 weeks of gestation, based on exposure to a single course or a rescue course of antenatal corticosteroids

	Single course (*n* = 88)	Rescue course (*n* = 42)	*P*	Adjusted OR (95% CI) or linear coefficient ± SEM	Adjusted *P**
Respiratory distress syndrome	40 (45.5%)	22 (52.4%)	0.23	1.28 (0.50–3.26)	0.60
Surfactant use	38 (43.2%)	17 (40.5%)	0.85	0.87 (0.33–2.26)	0.77
Mechanical ventilation	13 (14.8%)	4 (9.5%)	0.41	0.54 (0.11–2.78)	0.46
Days on mechanical ventilation, all infants	5.0 ± 15.3	0.7 ± 2.3	0.01	– 4.6 ± 2.2	0.32
Days on mechanical ventilation, among those with mechanical ventilation (mean ± SD)	33.9 ± 25.3	7.3 ± 3.3	0.003	–26.3 ± 7.8	0.001
Mechanical ventilation >14 days or death while on mechanical ventilation	11 (12.5%)	0 (0%)	0.02	– 0.136 ± 0.046	0.003
Peak Fio_2 (mean ± SD)	68.1 ± 25.9	48.8 ± 34.2	0.36	– 19.4 ± 12.7	0.13
Days on Fio_2 >21%, among those with mechanical ventilation (mean ± SD)	33.3 ± 25.8	6.3 ± 4.3	0.003	– 26.3 ± 7.8	0.001
Fio_2 > 21% for >14 days or death while on Fio_2 > 21%	10 (11.4%)	0 (0%)	0.03	– 0.126 ± 0.046	0.006
NICU admission	86 (97.7%)	42 (100%)	0.82	0.034 ± 0.019	0.07
Days in hospital (mean ± SD)	40.6 ± 30.6	43.1 ± 30.9	0.67	1.8 ± 7.9	0.82
Death before discharge	4 (4.5%)	1 (2.4%)	>0.99	0.48 (0.05–4.74)	0.53
Intraventricular haemorrhage	8 (9.1%)	3(7.5%)	0.77	0.74 (0.14–4.05)	0.73
Necrotising enterocolitis	5 (5.7%)	3 (7.1%)	0.71	1.23 (0.22–7.07)	0.82
Patent ductus arteriosus	17 (19.3%)	5 (11.9%)	0.33	0.55 (0.16–1.94)	0.35
Sepsis	13 (14.8%)	6 (14.3%)	0.94	0.96 (0.31–2.95)	0.94
Retinopathy of prematurity	11 (12.5%)	0 (0%)	0.02	– 0.137 ± 0.049	0.006
Chronic lung disease	9 (10.2%)	4 (9.5%)	0.90	0.86 (0.16–4.69)	0.86

NICU, neonatal intensive care unit.
*Adjusted for twin–twin interactions.

controlling for correlation between twins born to the same mother, our significant findings remained: rescue corticosteroids were independently associated with improved short-term outcomes (Table 2).

We compared newborn growth parameters between the two groups and the results are shown in Table 3. There were no differences in the growth parameters measured immediately after birth such as birthweight, head circumference and length.

Table 3. Measures of growth parameters at birth of twins born from 24 to 34 weeks of gestation, based on exposure to a single course or a rescue course of antenatal corticosteroids

Growth parameter at birth	Single-course (*n* = 88)	Rescue course (*n* = 42)	*P*
Weight percentile	41.0 ± 20.1%	41.6 ± 22.7%	0.894
Weight Z score	–0.28 ± 0.6	–0.28 ± 0.7	0.974
Head circumference percentile	48.3 ± 22.7%	45.7 ± 29.2%	0.582
Head circumference Z score	–0.07 ± 0.7	–0.47 ± 2.2	0.125
Length percentile	41.5 ± 28.7%	41.7 ± 30.0%	0.978
Length Z score	–0.31 ± 1.1	–0.80 ± 3.0	0.184

Data expressed as mean ± SD

Discussion

In this study, we compared neonatal outcomes in twins born before 34 weeks of gestation based on exposure to a single course or a rescue course of antenatal corticosteroids. We did not find a difference in the primary outcome, RDS; however, we found that a number of secondary outcomes were improved in the twins exposed to a rescue course of corticosteroids. These included the number of days on mechanical ventilation, and the number of days requiring an Fio_2 > 21% (room air). Additionally, we found that the likelihood of requiring mechanical ventilation >14 days or an Fio_2 > 21% for >14 days was significantly lower in the

Rescue Corticosteroids Group; in fact, there were no neonates in the Rescue Corticosteroids Group who required mechanical ventilation >14 days. The definition of RDS we employed for this study was the presence of radiographic findings consistent with RDS (ground glass appearance, bilateral haziness) and clinical presentation with severe respiratory distress (severe retractions, nasal flaring, grunting), which do not indicate severe disease. In fact, although 48% of neonates (62/130) in our cohort had the diagnosis of RDS, only 15% (19/130) required any mechanical ventilation. Our data suggest that rescue corticosteroids do not eliminate the overall possibility of RDS, especially in very premature twin neonates at <34 weeks of gestation, but they do decrease the likelihood of severe disease. Therefore, although rescue corticosteroids were not associated with a lower incidence of RDS, it may still improve respiratory function in twins born <34 weeks gestation because they were associated with a significantly lower incidence of mechanical ventilation >14 days.

We were originally powered to demonstrate a 50% reduction in RDS from 62 to 31%. Based on our actual sample size and rate of RDS in the Single-Course Corticosteroid Group, post-hoc power analysis reveals that we had enough women to demonstrate with 80% power and an α error of 5% a reduction in RDS from 45.5 to 20%. Therefore, there does remain the possibility that a smaller significant difference in RDS could be seen with a larger sample size.

We also found a significantly decreased likelihood of retinopathy of prematurity in neonates exposed to rescue corticosteroids, which is a common cause of blindness in premature neonates. This finding is plausible considering that prolonged mechanical ventilation is often associated with the need for supplemental oxygen and with neonates at the extremes of prematurity. Excessive oxygen use was identified as a risk factor for retinopathy of prematurity more than 50 years ago[18] and neonates at the extremes of prematurity are known to have higher rates of retinopathy of prematurity.[19,20] In this study, the two groups were similar with regards to birthweight and gestational age, but neonates in the rescue group had significantly fewer days of an Fio_2 > 21%. Therefore rescue steroids appear to have resulted in fewer days exposed to supplemental oxygen, and could explain the lower rates of retinopathy of prematurity in this group. Studies of singleton pregnancies have also showed decreased respiratory morbidity in newborns exposed to rescue corticosteroids.[12,13] However, our finding of decreased retinopathy of prematurity in newborns exposed to rescue corticosteroids was not seen in the study of rescue steroids in singleton pregnancies that assessed this outcome,[12] nor was it seen in the studies of multiple courses of repeat steroids[8,10,11] and further studies are warranted to address this potentially important clinical benefit of rescue corticosteroids.

In relation to the potential risks of rescue corticosteroids, we did not find any significant differences in newborn growth parameters, which have been found in the setting of repeated corticosteroid courses in singleton pregnancies.[8–10] Therefore, a single course of rescue corticosteroids in twin pregnancies appears to be a reasonable strategy, as rescue corticosteroids are associated with certain improved outcomes and no apparent negative effects.

Our study is limited by its retrospective design and sample size. As this was a retrospective study and the study period began before the publication of specific criteria for the administration of rescue corticosteroids, the decision to administer rescue corticosteroids or not was based on our clinical judgment, and not on predefined clinical criteria. Ideally, this study would be conducted prospectively with predefined criteria for the administration of rescue corticosteroids. A prospective study could also reduce the bias in establishing a treatment and control group in a retrospective study. In our current design, the two groups were inherently unequal as one group was deemed by us to be at higher risk for imminent preterm birth. It is possible that the clinical situation that led to the decision to administer a rescue course of corticosteroids is associated with neonatal outcomes as well and is a confounding factor. However, we found no difference in the time from completion of corticosteroid treatment to delivery between the two groups, nor did we find any difference in the indications for delivery <34 weeks of gestation (spontaneous labour versus iatrogenic preterm birth). Another potential limitation is the fact that our study population was mostly white women and all of them had private health insurance, which may limit the degree to which our findings can be generalised to other populations.

A large, randomised, prospective trial would be an ideal way to study the efficacy of rescue corticosteroids in twin pregnancies. However, given that the recommendation to administer even a single course of corticosteroids to women with twin pregnancies is based on observational data, and that there has never been a large, randomised study designed to study the efficacy of corticosteroids in twin pregnancies, it is unlikely that a randomised trial evaluating the use of rescue corticosteroids in twin pregnancies will be undertaken soon. Further observational studies in larger cohorts of twins are warranted to increase the power to find differences in other neonatal outcomes, as well as increase our confidence in the safety of a rescue course of corticosteroids in twin pregnancies.

Conclusion

In twins born before 34 weeks of gestation, exposure to rescue corticosteroids may be associated with improved neonatal outcomes, including decreased severe respiratory

morbidity and decreased retinopathy of prematurity. Rescue corticosteroids do not appear cause growth abnormalities. Further studies are warranted to assess the effect of rescue corticosteroids in twin pregnancies.

Disclosure of interests
None.

Contribution to authorship
All the authors contributed to the research idea, the interpretation of the data, and the writing and editing of the manuscript. CB, LD and NF performed the the record review and collected the data. NF and RG performed the statistical analyses.

Details of ethics approval
This study was approved by the Program for the Protection of Human Subjects of the Mount Sinai School of Medicine, #GCO-10-1651 on 19 January 2011.

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