HHS Public Access

Author manuscript

Am J Perinatol. Author manuscript; available in PMC 2023 September 08.

Published in final edited form as:

Am J Perinatol. 2008 August ; 25(7): 449–453. doi:10.1055/s-0028-1085070.

A Case-Control Comparison of the Effectiveness of Betamethasone to Prevent Neonatal Morbidity and Mortality in Preterm Twin and Singleton Pregnancies

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Abstract

We compared the effectiveness of antenatal betamethasone for the prevention of neonatal morbidity and mortality in preterm twin and singleton gestations. We conducted a case-control study of women with twin versus singleton gestations who received betamethasone for risk of prematurity in a university-affiliated, community-based, tertiary care center between 1997 and 2005. Cases were identified from clinical care and pharmacy databases, then matched for neonatal gender and gestational age (GA) at delivery. Sixty cases and 60 controls of deliveries occurring between 24 and 34 weeks' gestation were identified. The mean GA was 30.4 ± 2.7 weeks. There were no differences between the groups in maternal demographics (with the exception of maternal age), birth weight, head circumference, Apgar scores, need for mechanical ventilation, days on ventilator, intraventricular hemorrhage grade 3 or 4, necrotizing enterocolitis suspected sepsis, total days in neonatal intensive care unit, or neonatal deaths. No differences in major morbidities or mortality were found in singletons versus twins. Concerns that the added maternal plasma volume in multiple gestations could lessen the neonatal benefits of antenatal betamethasone were not substantiated. This study may be affected by β-error due to small sample size and sampling bias as a result of a retrospective study.

Keywords

Betamethasone; twin gestation; prematurity

Since the NIH Consensus Statement in 1994 regarding the effects of antenatal corticosteroids to improve perinatal outcomes in preterm birth,[1] this therapeutic approach has been used routinely in pregnancies less than 34 weeks at high risk for preterm delivery.[2] The benefits of corticosteroids include prevention of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and mortality in singleton preterm neonates.[3] Over the past three decades, the number of live-born twin pregnancies has increased significantly from 1.85% of live births in 1971 to 3.2% in 2004.[4,5] Multiple gestation is recognized as a risk factor for preterm delivery, with one report noting 40% of twins delivering

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before 37 weeks' gestation[6] and another report noting 58.2% of twins delivering prior to 37 weeks' gestation and 11.9% prior to 32 weeks' gestation.[7] Based on the benefits of antenatal corticosteroids in singleton preterm births, betamethasone is commonly given to twin pregnancies at risk at the same dose. However, there is controversy regarding the appropriate dosing of antenatal corticosteroid use in this circumstance.[8,9] In fact, there is no consensus about the effectiveness of antenatal steroid use in multiple gestations.[10]

This investigation was undertaken to compare the effectiveness of the recommended betamethasone regimen for the prevention of RDS, IVH, necrotizing enterocolitis, and overall mortality in twin neonates compared with singletons and delivered before 34 weeks' gestation.

METHODS

Subjects with twin pregnancies who were administered betamethasone at Women's Pavilion at Long Beach Memorial Medical Center from January 1995 to December 2005 were identified through the pharmacy database. During this time, we identified 92 cases of twin gestations that met inclusion criteria. Maternal medical records were reviewed for the following data: age, parity, ethnicity, smoking, illicit drug use, birth number and order, gestational age and dating criteria, diabetes mellitus, presence of infection, preeclampsia, premature rupture of membranes, preterm labor, presentation, and neonatal medical record number. The neonatal medical records were reviewed for gestational age at delivery, birth weight, birth length, head circumference, Apgar scores, gender, admission to neonatal intensive care unit (NICU), meconium passage, perinatal death, number of days from birth to discharge, discharge weight, length, head circumference, need for and duration of mechanical ventilation as a proxy for RDS, severe intraventricular hemorrhage, sepsis, necrotizing enterocolitis, surfactant use, postnatal corticosteroid exposure, and perinatal death. These outcome measures for the first-born twin were compared with singletons born to women at risk for preterm delivery between 24 and 34 weeks' gestation who received betamethasone.

Cases were excluded for the following criteria: delivery occurred at another facility, known fetal anomalies, twin–twin transfusion syndrome, deliveries at less than 24 weeks' gestation or greater than 34 weeks' gestation, in utero demise of one or both twins, and unknown antenatal steroid therapy status. Twin–twin transfusion syndrome was defined as presentation in the midtrimester with the oligopolyhydramnios sequence (deepest vertical pocket of amniotic fluid in the donor being less than or equal to 2 cm and in the recipient greater than 8 cm) associated with weight discordance among the fetus greater than 20%.

Subject information for twin gestations was then cross-referenced against the labor and delivery database known as ObStat. A control group of singleton pregnancies who received betamethasone and delivered between 24 and 34 weeks' gestation was identified using the following individual matching criteria: estimated gestation age at delivery (24 weeks to 27 weeks and 6 days, 28 weeks to 31 weeks and 6 days, and 32 weeks to 33 weeks and 6 days) and neonatal gender. If multiple controls were identified during the same time period, that

subject who delivered in closest temporal proximity to the case was used for our analysis. Sixty cases and 60 matching controls were identified.

Statistical Analysis

Continuous variables such as birth weight, head circumference, and days of mechanical ventilation were compared using Student *t* tests. Categorical variables such as IVH, RDS, or composite neonatal morbidity (defined as IVH, need for mechanical ventilation [representing RDS], necrotizing enterocolitis, patent ductus arteriosus, suspected sepsis, and neonatal death) were compared using chi-square, Mann-Whitney *U*, and Fisher exact tests where appropriate. Multivariable regression analyses were performed to evaluate the influence of time of betamethasone administration to delivery on the occurrence of neonatal complications. For this analysis, the time interval from betamethasone dosing was the independent variable, and each of the neonatal morbidities were both independently and then in a composite were the dependent variables. Statistical significance was set at a level of $p < 0.05$.

RESULTS

There were no differences in the twin group compared with the singleton group in most maternal demographics (height, weight, body mass index, or ethnicity), except for maternal age (Table 1). This is a reflection of a higher need for infertility treatment in older women resulting in twin gestations. There were no differences between the groups in birth weights (1434.5 ± 466.5 versus 1481.3 ± 573.6 g), head circumference at delivery (28.3 ± 2.7 versus 27.4 ± 3.4 cm), Apgar scores at 1 and 5 minutes (Table 2), need for mechanical ventilation (48.3% versus 56.7%), number of days on ventilator (16.9 ± 17.7 versus 21.6 ± 18.3), or total NICU days. IVH grade 3 or 4 (13.3% versus 20.0%) and necrotizing enterocolitis (11.7% versus 16.7%) occurred with similar frequencies among the groups. Although there were more singleton neonates treated for suspected sepsis, the number of culture-proven sepsis cases was not different between the groups (nine versus three for twins and singletons, respectively, $p = 0.08$). Neonatal deaths (1.7% versus 6.7%) occurred more frequently in the control group, but this difference was not statistically different. We also evaluated composite neonatal morbidity and found that it was not different between groups (Table 3).

To evaluate the effect of the interval from betamethasone dosing on the presence of the major neonatal morbidities, we performed a multivariable regression analysis model and found no significant differences between groups for any of the major neonatal morbidities (data not presented). The interval between dosing and delivery was 12.7 ± 15.3 days for the twins and 9.1 ± 10.1 days for the singleton controls ($p = 0.14$). The frequency of the major neonatal morbidities also did not vary in the twins group when comparing mono-chorionic versus dichorionic gestations (data not presented).

DISCUSSION

No differences in neonatal morbidities such as RDS, IVH, suspected sepsis, patent ductus arteriosis, or neonatal death occurred more frequently in twins than in singletons in this case-control investigation evaluating the effectiveness of antenatal betamethasone. In

addition, there were no differences found in neonatal biometric measures between groups. Concerns that the added maternal plasma volume in multiple gestations could lessen the neonatal benefits of antenatal betamethasone were not substantiated. A small sample size confers the possibility of β-error, and the retrospective nature of this investigation invites the possibility of sampling bias leading to the differences in major adverse outcome measures. It is possible that with a different study methodology such as group matching, significant differences between the major morbidities could have been identified.

The recommended dose of betamethasone is two 12-mg doses intramuscularly 24 hours apart. In animal studies, dose occupies 75% of the singleton fetal corticosteroid receptors, invoking a near maximal induction of receptor-mediated response in fetal target tissues.[11–13] By inference, because similar transient reductions in fetal heart rate caused by antenatal corticosteroid administration have been described in both singleton and twin pregnancies, a portion of each betamethasone dose enters the fetal compartments.[14–17]

In clinical practice, the same dose of betamethasone is given irrespective of the pregnancy plurality. Pharmacokinetic data indicate that higher doses of betamethasone are needed in twin gestations to reduce neonatal morbidity and mortality.[13] A study measuring serial betamethasone levels in twin and singleton pregnancies indicates that betamethasone clearance is more rapid and the half-life shorter in patients with twin pregnancies, supporting the theory that subtherapeutic blood levels of betamethasone are achieved in twin pregnancies.[13,18] Because of this, Ballabh et al recommend a possible schedule of three doses of betamethasone, 12 mg given every 18 hours.[13]

Although some researchers report a similar incidence of RDS in twins and singletons antenatally exposed to betamethasone,[19,20] others failed to reproduce these results.[21–23] Turrentine et al found no decrease in the incidence of RDS between 21 twins who received ante-natal corticosteroids compared with 63 who did not receive β-methasone.[21] Similarly, Quist-Therson et al, with a larger sample size (232 twin and 708 singleton pregnancies), also showed no significant reduction in RDS among twins with birth weights between 500 and 1500 g.[22] Marttila et al found that twins born before 28 weeks had a higher incidence of RDS compared with singletons. In contrast, the same study found that this risk was lower in twins born between 32 and 36 weeks.[23] Unfortunately, in this investigation, treatment with betamethasone was not well described. Finally, a recent study in Israel demonstrated that although a complete course of antenatal corticosteroids significantly reduced the incidence of respiratory distress syndrome irrespective of plurality, steroid effectiveness appeared to decrease with increasing plurality.[24] Each of these studies is limited by their retrospective natures.

We acknowledge the weaknesses of our investigation, which include its retrospective nature and a small sample size. A post hoc power analysis indicates that this investigation had a 28% power to detect a difference in the most common outcome of suspected sepsis; for other outcomes, the power was less. Strengths of this investigation include the homogeneity of clinical care given that the data were collected from a single institution in which the perinatal medical care has been overseen largely by a single group of perinatal practitioners

and neonatologists, and its case-control design with attention to matching for potential confounders.

Our findings, along with these published clinical and pharmacokinetic reports, suggest that a prospective evaluation of the effectiveness of the recommended dose of betamethasone for the reduction of neonatal morbidity and mortality in twin compared with singleton gestations is needed.

ACKNOWLEDGMENTS

Financial support was received from the Memorial Healthcare Systems Foundation for this report. These data were presented at the 54th Annual Meeting of the Society for Gynecologic Investigation, Reno, NV, March 2007.

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Table 1

Maternal Demographic Characteristics

	Twin (*n* = 60)	Singleton (*n* = 60)	*p*
Age (y)	31.8 ± 5.6	27.4 ± 6.4	< .001
Gravidity	3.32 ± 2.23	3.26 ± 2.4	0.86
Parity	1.20 ± 1.59	1.18 ± 1.26	0.95
Ethnicity *			0.59
Caucasian	22 (37.3%)	15 (30.6%)	
African-American	15 (25.4%)	14 (28.6%)	
Hispanic	16 (27.1%)	16 (32.6%)	
Asian	5 (8.5%)	1 (2.0%)	
Other	1 (1.7%)	3 (6.1%)	
Missing	1	11	
Body mass index	31.8 ± 7.2	31.0 ± 2.9	0.54
Gestational age at betamethasone dosing (wk)	29.0 ± 2.9	29.0 ± 2.9	0.16
Interval from betamethasone to delivery (d)	12.1 ± 15.0	9.0 ± 10.0	0.16

* Missing values.

Data presented as mean ± standard deviation, or *n* (%).

Table 2

Birth Characteristics

	Twin (*n* = 60)	**Singleton (*n* = 60)**	***p***
Birth weight (g)	1434±468	1481±573	0.63
Apgar score < 7 at 1 min	17 (28.3%)	23/60 (38.3%)	0.25
Apgar score < 7 at 5 min	1 (1.7%)	5 (8.3%)	0.09 *
Birth length (cm)	39.3 ± 3.9	39.8 ± 4.9	0.58
Birth head circumference (cm)	28.3 ± 2.7	27.6 ± 3.4	0.21
Birth chest circumference (cm)	24.2 ± 3.8	24.7 ± 3.3	0.60

* Fisher exact test.

Data presented as mean ± standard deviation or *n* (%).

Table 3

Neonatal Outcomes

	Twin	Singleton	*p*
Mechanical ventilation	29/60 (48.3%)	34/60 (56.7%)	0.36
Number of days of mechanical ventilation if needed	16.9 ± 17.7	18.3 ± 21.6	0.78
Intraventricular hemorrhage *	8/60 (13.3%)	12/60 (20.0%)	0.33
Grade III or IV	2	1	
Patent ductus arteriosus	23/60 (38.3%)	16/60 (26.7%)	0.17
Suspected sepsis *	45/60 (75.0%)	51/60 (85.0%)	0.17
Necrotizing enterocolitis	7/60 (11.7%)	10/60 (16.7%)	0.36
Neonatal death	1/60 (1.7%)	4/60 (6.7%)	0.36 *
Total NICU days	46.8 ± 31.6	42.0 ± 32.8	0.43
Median	30 (1–138)	40.5 (4–164)	

* Fisher exact test.

Data presented as mean ± standard deviation, median (range), or *n* (%). NICU, neonatal intensive care unit.