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Antenatal Corticosteroids for Preterm Premature Rupture of Membranes: Single or Repeat Course?

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Abstract

Objective—The aim of this article is to determine the risk of maternal chorioamnionitis and neonatal morbidity in women with preterm premature rupture of membranes (PPROM) exposed to one corticosteroid course versus a single repeat corticosteroid steroid course.

Study Design—Secondary analysis of a cohort of women with singleton pregnancies and PPRM. The primary outcome was a clinical diagnosis of maternal chorioamnionitis. Using multivariate logistic regression, we controlled for maternal age, race, body mass index, diabetes, gestational age at membrane rupture, preterm labor, and antibiotic administration. Neonatal morbidities were compared between groups controlling for gestational age at delivery.

Results—Of 1,652 women with PPRM, 1,507 women received one corticosteroid course and 145 women received a repeat corticosteroid course. The incidence of chorioamnionitis was similar between groups (single course = 12.3% vs. repeat course = 11.0%; $p = 0.8$). Women receiving a repeat corticosteroid course were not at increased risk of chorioamnionitis (adjusted odds ratio, 1.28; 95% confidence interval, 0.69–2.14). A repeat course of steroids was not associated with an increased risk of any neonatal morbidity.

Conclusion—Compared with a single steroid course, our findings suggest that the risk of maternal chorioamnionitis or neonatal morbidity may not be increased for women with PPRM receiving a repeat corticosteroid course.

Keywords

steroids; chorioamnionitis; fetal membranes; premature rupture

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Presentation

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Conflict of Interest

The authors report no conflict of interest.

Preterm premature rupture of membranes (PPROM) occurs in women with membrane rupture before labor and before 37 weeks of gestation. PPRM is the primary etiology for 25% of preterm births¹ which can result in major perinatal morbidity and mortality.^{1,2} In contemporary obstetric practice, antenatal corticosteroids have become integral to the clinical management of PPRM to reduce the risk of neonatal mortality and morbidity, including the following: respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC).^{3,4}

^{5,8,9} However, surveys from Australia and Canada indicate that, for women at risk of preterm labor and birth, steroid prescribing patterns of obstetricians vary markedly.^{10,11}

Although the opportunity to administer a second course of steroids is not an uncommon clinical scenario in the setting of PPRM, it remains uncertain whether rates of maternal chorioamnionitis and neonatal morbidity differ between those receiving a single repeat course of antenatal corticosteroids versus a single corticosteroid course. Therefore, analyzing perinatal outcomes of women with PPRM exposed to a single or a repeat course of corticosteroids has potentially important clinical relevance.

In this observational study, we sought to evaluate whether women with PPRM exposed to a single repeat course of antenatal corticosteroids were at increased risk of maternal chorioamnionitis compared with women with PPRM exposed to only one steroid course. For our secondary analysis, we compared outcomes of neonates born to women with PPRM who received one steroid course versus a single repeat steroid course.

Patients and Methods

This is a secondary analysis of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal–Fetal Medicine Units Network (MFMU) “Randomized Clinical Trial of the Beneficial Effects of Antenatal Magnesium Sulfate” (hereafter referred to as the BEAM study).¹² Details of the BEAM study will be summarized. Women with singleton or twin pregnancies between 24 and 31 weeks’ gestation who were determined to be at high risk for imminent preterm birth were randomized to receive either magnesium sulfate infusion for neuroprotection or placebo.¹² Women who met the inclusion criteria for this study were enrolled at 20 different US academic centers between December 1997 and May 2004. For our study, we abstracted data from the BEAM study database for women with singleton pregnancies with a diagnosis of PPRM who received one course or a single repeat course (two courses) of antenatal corticosteroids. The BEAM database did not contain data for the type of corticosteroid given or details of the corticosteroid dosing regimen. Although the data set did not specifically include dates of membrane rupture and onset of labor, the data set did contain data on the duration of membrane rupture and gestational age at time of membrane rupture. Because of unavailability of data, we were unable to determine whether labor preceded membrane rupture or the precise temporal association between steroid administration, labor, and membrane rupture. However, 86.7% of patients in the original BEAM study were diagnosed with PPRM at the time of enrollment. PPRM was diagnosed by the presence of at least

two of the following: pooling of amniotic fluid, positive nitrazine test, presence of ferning, indigo carmine pooling, or free flowing amniotic fluid.

Our primary outcome was clinical chorioamnionitis. In the original BEAM study, the definition for chorioamnionitis was based on a clinical diagnosis of chorioamnionitis, a body temperature $\geq 37.8^{\circ}\text{C}$ and no other defined infection. Our secondary outcomes included a composite outcome for maternal infection (chorioamnionitis or postpartum endometritis), and the following neonatal outcomes: gestational age at delivery, culture-proven sepsis, intensive care unit (ICU) admission, small for gestational age, head circumference, birth weight, RDS, NEC, and IVH. We also compared rates of chorioamnionitis between steroid groups stratified by the gestational age at which membrane rupture occurred: <24 weeks, 24 to 27 weeks, 28 to 31 weeks, and 32 to 35 weeks. The use of the BEAM study data for secondary analysis was approved by the Stanford University Institutional Review Board.

Statistical Analysis

Categorical data were compared using the chi-square test or Fisher Exact test and the Student *t*-test or Mann–Whitney U test for continuous data. Univariate analysis was performed to investigate the association between the number of corticosteroid courses with maternal chorioamnionitis. Multiple logistic regression analysis was performed to account for maternal and obstetric confounders that may have influenced the association between the number of corticosteroid courses and chorioamnionitis (maternal age, body mass index, race, diabetes mellitus, duration of membrane rupture, receipt of antibiotics, gestational age at delivery, and delivery route). Collinearity was determined to be insignificant as variance inflation scores ranged from 1.02 to 1.52 with a mean inflation score of 1.15. We also performed logistic regression to account for gestational age at delivery that may have influenced the association between number of steroid courses and the following neonatal outcomes: culture-proven sepsis, ICU admission, small for gestational age, RDS, NEC, and IVH. For dichotomous outcomes, odds ratios (OR) and 95% confidence intervals (CI) were calculated. A general linear model was used to compare birth weight and head circumference between study groups, adjusting for gestational age at delivery. The results of these analyses are presented as adjusted least square means (standard error of the mean). Statistical analyses were performed using SPSS 20.0 (IBM Corp., Armonk, NY) and SAS 9.3 (SAS Institute Inc., Cary, NC), with $p < 0.05$ considered as statistically significant.

Results

Our cohort comprised 1,652 women with singleton pregnancies and PPRM who received one course or a single repeat course of antenatal corticosteroids. Within our cohort, 1,507 women received one course and 145 women received a single repeat course. A flow diagram of the study cohort is shown in Fig. 1. Baseline maternal characteristics for women receiving one course and a single repeat course are presented in Table 1. With the exception of the duration of membrane rupture and the gestational age at the time of membrane rupture, maternal and obstetric characteristics were similar in both the study groups.

The incidence of chorioamnionitis was similar in both the groups (one course = 12.3% vs. single repeat course = 11%, respectively; $p = 0.7$). The incidence of infectious maternal

morbidity (chorioamnionitis and postpartum endometritis) was also not significantly different between women receiving one steroid course versus a single repeat steroid course (16.7 vs. 17.2%, respectively; $p = 0.8$). For univariate and multivariate analyses, we combined Hispanics, Asians, and Others into one category for race because of small sample sizes for Asians ($n = 18$) and Others ($n = 19$). Data for the univariate and multivariate logistic regression analyses are presented in Table 2. On univariate analysis, women who received a single repeat course were not at increased risk of chorioamnionitis compared with women who received one steroid course (crude OR, 1.13; 95% CI, 0.66–1.94). On the basis of the multivariate analysis, the association between a repeat steroid course and chorioamnionitis was not significantly influenced by other patient and obstetric confounders (adjusted odds ratio [aOR], 1.21; 95% CI, 0.67–2.19). The risk of chorioamnionitis was associated with the gestational age at delivery (aOR, 1.16; 95% CI, 1.16–1.23).

The median duration of membrane rupture was significantly longer in women who received a single repeat course versus one steroid course (270 hours vs. 166 hours; $p < 0.001$). We observed no significant between group differences in rates of chorioamnionitis stratified by the gestational age at which membrane rupture occurred (<24 weeks [$p = 0.2$], 24–27 weeks [$p = 0.7$], and 28–31 weeks [$p = 0.7$]) (Fig. 2). Among the women who received a single repeat course of corticosteroids, we observed no significant difference in the time interval between the first and second dose of steroids for women diagnosed with versus without chorioamnionitis (median [interquartile range] number of days, 8 [7–16] vs. 11 [7–23] days, respectively; $p = 0.10$).

Neonatal outcomes are presented in Table 3. There were no significant differences between the two groups with respect to gestational age at the time of delivery or anthropometric characteristics. After adjustment, the risks of sepsis, RDS, NEC, IVH, and NICU admission were not increased for neonates in the repeat steroid group. Although the adjusted risk of SGA was lower in the repeat steroid group compared with the single steroid course group, the 95% CIs were wide and nearly intersected the null (aOR, 0.42; 95% CI, 0.18–0.98).

Comment

In this secondary analysis of BEAM study data, we observed that women with PPROM who received a single repeat course of antenatal corticosteroids were not at increased risk of chorioamnionitis compared with women who received one course of corticosteroids. In addition, we observed no differences in the rates of adverse neonatal morbidity (RDS, NEC, and IVH) between neonates whose mothers received one course versus a single repeat steroid course. As there is no consensus on the number of steroid courses to administer in the setting of PPROM,⁶ our findings suggest that a single repeat steroid course is associated with similar maternal and fetal outcomes as women exposed to one steroid course.

Data from a large number of clinical trials provide strong evidence that antenatal steroids reduce the risk of neonatal morbidity (RDS and IVH) and neonatal death compared with placebo or no treatment in women at risk of preterm birth.³ Interest in the use of a repeat steroid course is, in part, linked to data reported from animal and human studies. In these studies, fetal lung maturity was shown to accelerate in response to repeat antenatal steroid

courses before 34 weeks' gestation.^{13,14} On the basis of these data, current practice guidelines recommend that women with intact membranes less than 34 weeks' gestation who remain at risk of preterm delivery after completion of one course of steroids should receive a single repeat course.⁸ However, it has been uncertain whether the risk of maternal infectious morbidity among women with PPROM is significantly altered by exposure to a second course of steroids.

Our findings differ from those of a previous study that compared perinatal outcomes in women with PPROM who received one steroid course versus a weekly course of steroids.¹⁵ In this study, the incidence of chorioamnionitis was significantly higher in women who received a weekly steroid course versus one steroid course (49.4 vs. 31.7%, respectively; $p = 0.04$).¹⁵ In contrast, other studies did not report a significant difference in the incidence of maternal chorioamnionitis among women at risk of preterm delivery who received one steroid course versus weekly or biweekly steroid courses (range, 2.5–17.8 vs. 2–2.5%, respectively).^{16–18} However, these studies included women with intact membranes.^{16–18} Variation between studies in the rates of maternal chorioamnionitis may be because of inherent differences in the study populations, clinical characteristics of women with PPROM, and in the steroid dosing regimens (drug type, dose, and weekly or biweekly instead of a single repeat course).

Among women with PPROM who received a single repeat course of steroids, we observed no significant difference in the time interval between steroid courses for women diagnosed with versus without chorioamnionitis (8 vs. 11 days, respectively). These data suggest that the time interval between each course may not influence the risk of chorioamnionitis; however, the small number of women ($n = 16$) with chorioamnionitis who received a repeat steroid course limits more detailed interpretation. Although the rate of chorioamnionitis was highest for women who developed membrane rupture before 24 weeks' gestational age, the odds of chorioamnionitis increased 16% for every 1 week increase in gestational age at delivery. This association is opposite to that reported in the previous studies.^{15,19,20} Compared with our study, we note that these studies used different definitions for chorioamnionitis based on alternate clinical or histologic criteria.^{15,19,20} Despite these differences, because of the limited data availability in the BEAM data set, we could not account for other unmeasured variables in our logistic model which may have influenced the direction of the association between gestational age at delivery and chorioamnionitis.

After controlling for gestational age at delivery, we found that a single repeat course of steroids was not associated with an increased risk for any neonatal morbidity compared with a single course. Although other studies have compared neonatal outcomes of mothers who received one steroid course versus a single repeat course of steroids, these studies only included mothers with intact membranes and accounted for different frequencies of repeat steroid dosing.^{5,21,22} Weekly steroid courses have been associated with an increased risk of low birth weight and reduced head circumference.^{18,23,24} In contrast, in a previous randomized controlled trial, neonatal anthropomorphic indices were similar among women with intact membranes before 33 weeks' gestation who received a repeat steroid course versus a single steroid course with placebo.²² In addition, the influence of a single versus repeat steroid course on RDS is also uncertain. Two studies reported that the incidence of

neonatal RDS was lower if a repeat steroid course was administered,^{21,22} whereas one study reported no difference in RDS incidence between groups.⁵ Because of the variation in the prescribed steroid dosing regimens in the previous studies, more research is needed to investigate the effects of differential steroid dosing regimens on neonatal outcomes.²⁵

The main strength of our study is the large cohort of women with PPROM with detailed clinical data derived from a large, multicenter clinical trial.¹² However, we acknowledge that our study has several limitations. In the original BEAM study, data on the type and dose of steroid were not collected and steroid regimens were not standardized; therefore, variation in prescribing patterns between treating physicians may have existed. Because of the unavailability of data, we were unable to determine whether labor preceded membrane rupture or the precise temporal association between steroid administration, labor, and membrane rupture. However, 86.7% of patients in the original BEAM study were diagnosed with PPROM at the time of enrollment. We were unable to assess the association between steroid courses and chorioamnionitis in all ethnic and racial groups which limits the generalizability of our findings. The BEAM data set did not contain detailed steroid prescribing information, including the following: the number of doses given per steroid course, clinical indicators for prescribing a second steroid course, and the timing of the second steroid course relative to the time of delivery. Therefore, we could not account for variation in steroid prescribing practices in our analysis. Although these factors may be important in influencing maternal and neonatal outcomes in response to antenatal steroids, to the best of our knowledge, there is a lack of pharmacokinetic and pharmacodynamic studies investigating commonly used antenatal steroid regimens for pregnant women with PPROM. Finally, in our analyses of neonatal morbidities, we could not account for other confounders, except gestational age at delivery, in our logistic models because of the low number of neonates with morbidities (such as sepsis, SGA, NEC, and IVH) in the repeat steroid course group.

Using data sourced from the BEAM study, we observed that the risks of maternal chorioamnionitis and adverse neonatal outcomes are not increased in women with PPROM who received a single repeat steroid course compared with those who received one steroid course. Among women with PPROM, future studies are needed to assess corticosteroid pharmacokinetics pharmacodynamics and to compare maternal and neonatal outcomes between those receiving a single steroid course versus a repeat steroid course.

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Clinical Perspective

It is currently unknown whether one repeat course of steroids in the setting of PPROM increases the risk of maternal chorioamnionitis. We found the rates of chorioamnionitis are similar among women with preterm premature rupture of membranes who receive one corticosteroid course versus a repeat corticosteroid course.

Fig. 1.

Flow diagram of study cohort. PPROM, preterm premature rupture of membranes.

Fig. 2.
Rate of chorioamnionitis stratified by gestational age at time of membrane rupture.

Table 1

Maternal and obstetric characteristics for women receiving single or repeat corticosteroid courses

	Single course, (N = 1,507)	Repeat course, (N = 145)	<i>p</i>
Maternal age, y			
<20	218 (14.4)	21 (14.5)	0.9
20–33	1068 (70.9)	104 (71.7)	
34	221 (14.7)	20 (13.8)	
Maternal BMI, kg/m ²	24.8 [21.3, 30.0] ^a	23.9 [20.6, 28.4] ^b	0.08
Race			
African American	663 (44.0)	71 (49.0)	0.3
Caucasian	578 (38.4)	56 (38.6)	
Hispanic/Asian/Other	266 (17.7)	18 (12.4)	
Gestational age at ROM, wk	28.2 [25.7, 30.1] ^c	26.9 [24.7, 29.1] ^d	<0.001
Diabetes	72 (4.8)	5 (3.4)	0.7
Chorioamnionitis	185 (12.3)	16 (11.0)	0.8
Endometritis	90 (6.0)	13 (9.0)	0.2
Duration of ROM, h	166 [79, 372] ^e	270 [168, 532] ^f	<0.001
Antibiotics administered	1,451 (96.3)	144 (99.3)	0.06
Delivery route			
Vaginal	943 (62.6)	92 (63.4)	0.8
Cesarean	564 (37.4)	53 (36.6)	

Abbreviations: BMI, body mass index; ROM, rupture of membranes.

Note: Data presented as number (percentage); median [interquartile range].

^aMissing data for 147 patients.^bMissing data for 11 patients.^cMissing data for 6 patients.^dMissing data for 2 patients.^eMissing data for 68 patients.^fMissing data for 11 patients.

Table 2

Univariate and multivariate analyses for maternal chorioamnionitis

	Univariate Analyses		Multivariate Analyses	
	OR (95% CI)	<i>p</i> Value	aOR (95% CI)	<i>p</i> Value
Number of steroid courses				
One	Reference		Reference	
Two	1.13 (0.66–1.94)	0.7	1.21 (0.67–2.19)	0.5
Prepregnancy BMI ^a	0.98 (0.96–1.0)	0.1	0.99 (0.97–1.02)	0.8
Maternal age, y				
<20	Reference		Reference	
20–33	0.87 (0.55–1.36)	0.5	0.79 (0.46–1.34)	0.4
34	0.64 (0.37–1.11)	0.1	0.63 (0.34–1.17)	0.1
Race				
Caucasian	Reference		Reference	
African American	0.84 (0.60–1.16)	0.3	0.91 (0.64–1.30)	0.6
Hispanic/Asian/Other	0.86 (0.56–1.31)	0.5	0.82 (0.52–1.32)	0.4
Duration of ROM (h) ^a	1.00 (0.99–1.00)	0.1	1.00 (0.99–1.00)	0.3
Gestational age at delivery (wk) ^b	1.13 (1.07–1.19)	<0.001	1.16 (1.09–1.23)	<0.001
Diabetes	0.66 (0.36–1.23)	0.2	0.60 (0.31–1.19)	0.2
Antibiotics administered	0.39 (0.12–1.27)	0.12	0.34 (0.1–1.12)	0.08

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence intervals; OR, crude odds ratio; ROM, rupture of membranes.

^aPer 1 unit increase.^bPer 1 week increase.

Table 3

Neonatal characteristics for women receiving a single or repeat corticosteroid course

	Single course, <i>N</i> = 1,507	Repeat course, <i>N</i> = 145	<i>p</i> Value	aOR (95% CI) ^a	Data missing
Gestational age at delivery, wk	29.8 (3.1)	29.7 (2.6)	0.6	NA	0
Culture proven sepsis in neonate	243 (16.2)	25 (17.2)	0.7	0.84 (0.52–1.37)	11
Neonate admitted to ICU	1402 (93.7)	139 (95.9)	0.3	0.93 (0.34–2.58)	11
Neonate SGA	33 (2.2)	7 (4.8)	0.08	0.42 (0.18–0.98)	0
Respiratory distress syndrome	732 (48.9)	79 (54.5)	0.2	0.81 (0.56–1.19)	11
Necrotizing enterocolitis	121 (8.1)	17 (11.7)	0.1	0.63 (0.37–1.10)	11
Intraventricular hemorrhage	291 (20.6)	31 (22)	0.7	0.93 (0.61–1.43)	96
Head circumference at birth, cm ^b	27.1 (0.04)	27.0 (0.2)	0.5	NA	33
Birth weight, g ^b	1,441 (6)	1401 (18)	0.04	NA	0

Abbreviations: aOR, adjusted odds ratio; ICU, intensive care unit; NA, not applicable; SGA, small for gestational age.

Note: Data presented as *n* (%), least-square mean (standard error of the mean).

^a Odds ratios were adjusted for gestational age at delivery. Reference group is the women receiving a single course of steroids.

^b Head circumference and birth weight values were adjusted for gestational age at delivery.