Single Versus Weekly Courses of Antenatal Corticosteroids in Preterm Premature Rupture of Membranes

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OBJECTIVE: This study was performed to evaluate the efficacy of weekly courses of antenatal corticosteroids compared with a single course in women with preterm premature rupture of membranes (PROM).

METHODS: A planned secondary analysis of women with preterm PROM who participated in a multicenter, randomized trial of weekly courses of antenatal corticosteroids versus single-course therapy was performed. After their first course of standard antenatal steroid therapy, administered between 24 to 32–6/7 weeks of gestation, consenting women were randomly assigned to receive betamethasone versus placebo injections weekly until 34–0/7 weeks of gestation. Maternal and neonatal morbidities were compared between the 2 groups.

RESULTS: Of the 161 women with preterm PROM, 81 women were assigned to receive weekly courses of steroids and 80 to the single-course group. There were no significant differences in composite morbidity between the groups (27 [34.2%] of 81 patients versus 33 [41.8%] of 80 patients, $P = .41$). Chorioamnionitis was higher in patients who received weekly courses of antenatal steroids (39 [49.4%] of 81 patients versus 25 [31.7%] of 80 patients, $P = .04$).

CONCLUSION: Weekly courses of antenatal steroids in women with preterm PROM did not improve neonatal outcomes beyond that achieved with single-course therapy and was associated with an increased risk of chorioamnionitis. Antenatal steroid therapy should not be routinely repeated in patients with preterm PROM. (Obstet Gynecol 2004;103:274–81. © 2004 by The American College of Obstetricians and Gynecologists.)

LEVEL OF EVIDENCE: I

Preterm premature rupture of membranes (PROM) is responsible for more than 30% of all preterm births and has been a highly controversial management issue in the field of obstetrics.[1–3] In 1994, the National Institutes of Health (NIH) Consensus Development Conference strongly advocated antenatal corticosteroid administration to women at high risk for premature delivery to reduce neonatal complications of prematurity. After the release of the NIH consensus statement, most obstetricians adopted the NIH recommendations into their everyday practice, including the use of weekly steroid administration to women who remained at risk for preterm delivery (Planer BC, Ballard RA, Ballard PL, Cobum CE, Boardmann C, Cnaan A, et al. Antenatal corticosteroid [ANCS] use in preterm labor in the USA [abstract]. Pediatr Res 1996;39:110A).[4,5] Although obstetricians appear to be comfortable administering steroids to women with intact membranes, the policy of administering steroids to women with preterm PROM has not been received as enthusiastically because of concerns that steroid administration may increase infectious morbidities such as chorioamnionitis, postpartum endometritis, and neonatal sepsis.[6] In addition, obstetricians have long recognized that delivery after preterm PROM is unpredictable. Despite concerns about infection, many obstetricians have felt compelled to repeat antenatal steroids on a weekly basis in this setting.[7] To

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date, there is no definitive evidence that a policy of weekly steroids in the setting of preterm PROM is either efficacious or safe. The primary objective of this study was to evaluate the efficacy of single versus weekly courses of antenatal steroids in patients with preterm PROM. We also wished to identify any differences in infectious complications associated with steroid use in this setting.

MATERIALS AND METHODS

This was a planned secondary-group analysis of patients with preterm PROM enrolled in our multicenter Betamethasone Study Group trial of single versus weekly courses of steroids in women at high risk for preterm delivery.[8] To review, the parent trial was a randomized, double-blind, placebo-controlled, multicenter clinical trial in which women were recruited from 13 academic centers across the United States. All investigators followed a common protocol at the participating clinical centers. The investigational review board at each center approved the study protocol. Pregnant women between 24 and 32–6/7 weeks gestation, who had received a complete course of antenatal corticosteroids (2 doses of betamethasone [12 mg intramuscularly] or 4 injections of dexamethasone [6 mg intramuscularly] within a 48-hour period) because they had been judged by their managing obstetrician to be at high risk for preterm delivery, were evaluated for eligibility to participate in this trial. The focus of this particular analysis, preterm PROM, was one of the qualifying conditions for original study entry. Patients enrolled in the parent trial with indications other than preterm PROM, such as preterm labor, in whom preterm PROM subsequently developed were also included in this analysis. All women received a single initial course of antenatal steroids, and if she remained undelivered 1 week later, the patient was enrolled and randomized to receive either additional courses of betamethasone (12 mg intramuscularly) every 24 hours for 2 doses (weekly course group), or a similarly administered placebo (single-course group) in a double-blind fashion. Syringes of steroid or placebo were masked with opaque tape by each study site pharmacist before distribution to nursing staff for administration. One course of study drug was defined as 2 doses of betamethasone or placebo given 24 hours apart. Computer-generated randomization logs were prepared centrally and distributed to the research pharmacist at each clinical site. The randomization was simple and stratified by center. Consenting women were randomized on the day that the first course of study drug was due (ie, immediately before receiving their second course of corticosteroid or placebo injections). The injections were repeated weekly until either a preterm delivery occurred or the pregnancy reached 34 weeks of gestation. Figure 1 provides an overview of the framework for this secondary analysis. Exclusion criteria included the need for immediate delivery, known fetal anomalies incompatible with life, documented fetal lung maturity, or active tuberculosis or HIV-1 infection.

The primary neonatal outcome for the trial was termed composite morbidity.[9] Composite neonatal morbidity was defined as the presence of any of the following conditions: severe respiratory distress syndrome (RDS), bronchopulmonary dysplasia, severe intraventricular hemorrhage, periventricular leukomalacia, proven necrotizing enterocolitis, proven sepsis, and perinatal death at any time from randomization to discharge. Each morbidity was specifically defined before initiation of the trial. The definitions for each of the morbidities used in this analysis are identical to the parent trial (Appendix).[8] The latency interval was defined as the interval from the initial unblinded corticosteroid injection to delivery per the parent trial, rather than the time from PROM to delivery to permit comparisons between women with ruptured versus intact membranes. The analyses were stratified by both estimated gestational age at randomization and delivery to explore prognostic outcome data.

The infectious outcome variables that were evaluated included the administration of any antepartum antibiotic prophylaxis, clinical chorioamnionitis, endometritis, and culture-proven neonatal sepsis. Antepartum antibiotic prophylaxis was defined as the administration of antibiotics before the onset of labor associated with the delivery of the neonate. Clinical chorioamnionitis was defined as a patient having 2 or more of the following: maternal temperature of 38°C (100.4°F) or higher, uterine tenderness, foul smelling amniotic fluid, positive amniotic fluid studies, and maternal leukocytosis. The diagnosis of endometritis was made in women without prior intrapartum chorioamnionitis who developed 2 temperature elevations of greater than 38°C or a single temperature increase of more than 38°C accompanied by uterine tenderness or malodorous lochia without another obvious source of fever in the postpartum period. Proven neonatal sepsis was defined as the presence of a positive blood culture obtained in the first week of life in association with clinical findings suggestive of illness for which the neonate received antibiotics.

The statistical analysis included comparisons of demographic and pregnancy characteristics between women enrolled with the primary diagnosis of preterm PROM and women in whom preterm PROM subsequently developed by using χ^2 tests for discrete characteristics and 2 independent-samples t tests for continuous variables. Similar analyses were then conducted to compare characteristics between women assigned to the weekly

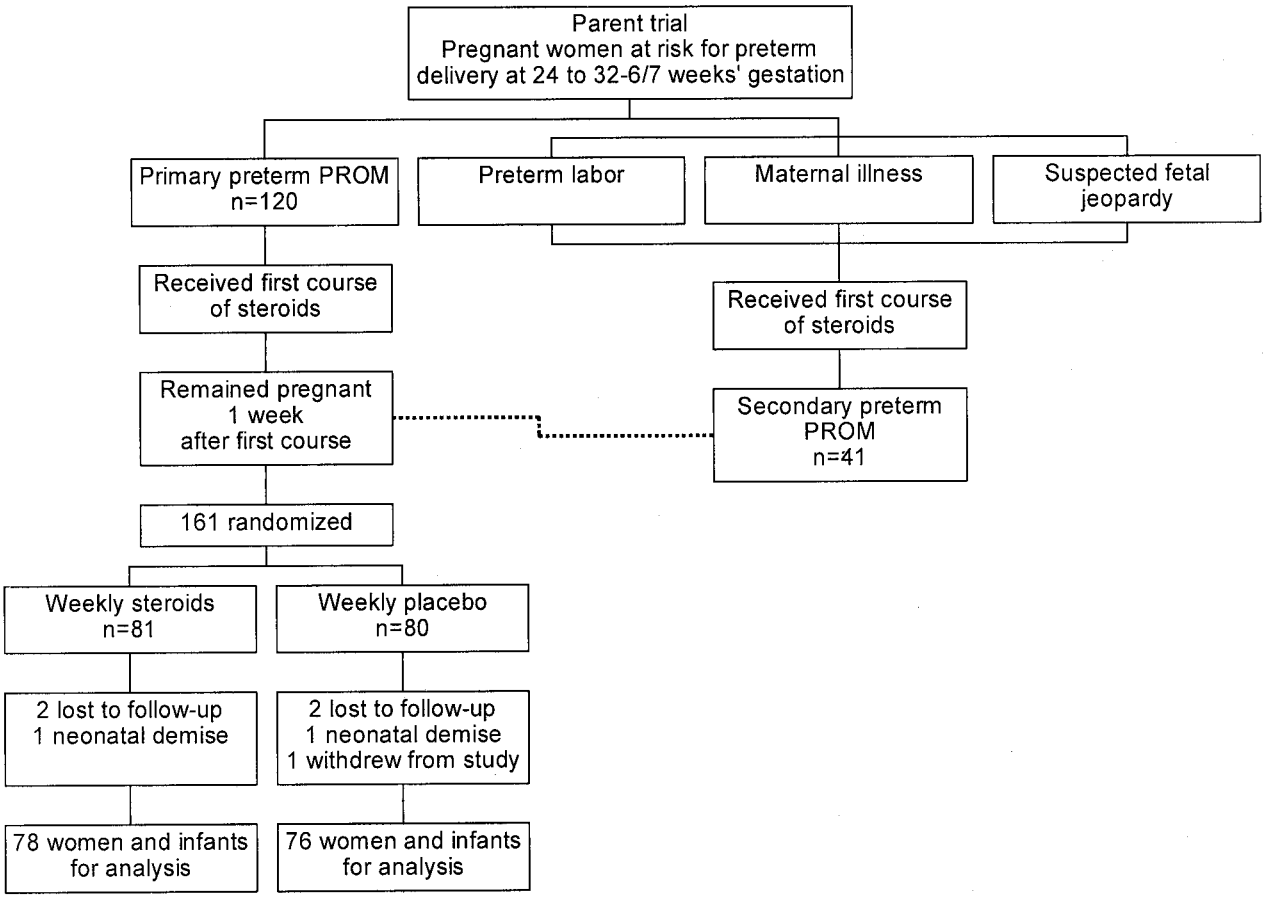

Figure 1. Overview of the clinical trial and secondary analysis. PROM = premature rupture of membranes.
Lee. Corticosteroids and Preterm PROM. Obstet Gynecol 2004.

course group and women assigned to the placebo group using the same tests applied to the combined sample of women with primary and secondary diagnosis of preterm PROM. We explored the number of courses of study drug for each group and present the medians and ranges. Pregnancy outcomes were compared between groups by using χ^2 tests for discrete outcomes and the 2 independent-samples t tests for continuous outcomes. The test of the primary outcome, composite morbidity, was performed using the Fisher exact test. The Fisher exact test was also used to compare individual neonatal outcomes, maternal outcomes, and infectious morbidities between groups because the numbers of events were generally small. The Wilcoxon test was used when comparing medians for nonnormally distributed data. Finally, analysis of variance was used to test for differences in gestational age, birthweight, and latency between women with intact membranes assigned to the weekly and single-course groups and women with preterm PROM assigned to the weekly and single-course groups. An overall test of the equality of means was performed followed by pairwise tests of means. Similar analyses were conducted to compare infectious morbidities among groups followed by pairwise comparisons between groups. To account for multiple testing, statistical significance was set to 0.0125 for pairwise tests based on the Bonferroni correction. The analysis was by intent to treat, and all tests were 2 sided. Analysis was performed using SAS 8.2 (SAS Institute, Cary, NC). We had a power of 80% to detect a reduction in composite morbidity from 42% down to 21%. The study was not powered for differences in infectious complications, but important clinical findings could still be described.

RESULTS

A total of 502 women were enrolled in the parent trial from March of 1996 to March of 2000. One hundred twenty women were enrolled with the primary diagnosis of preterm PROM. An additional 41 women were iden-

Table 1. Subjects With Preterm PROM as a Primary Diagnosis Versus a Secondary Diagnosis Included in the Analyses

	Preterm PROM		
	Primary (n = 120)	Secondary (n = 41)	P
Mean (SD) maternal age (y)	27.7 (7.2)	26.5 (26.4)	.33
Race	.20		
White	36 (30.0)	14 (34.2)	
Hispanic	33 (27.5)	16 (39.0)	
Black	44 (36.7)	7 (17.1)	
Asian	3 (2.5)	2 (4.9)	
Other	4 (3.3)	2 (4.9)	
Nulliparity	40 (33.3)	17 (41.5)	.35
Mean (SD) estimated gestational age at randomization (wk)	28.6 (2.7)	29.0 (3.0)	.38
Randomization			.34
Weekly courses of steroids	63 (52.5)	18 (43.9)	
Single course	57 (47.5)	23 (56.1)	
Primary indication for enrollment			NA
Preterm labor	0 (0)	35 (85.4)	
Preterm PROM	120 (100)	0 (0)	
Maternal medical problem	0 (0)	5 (12.2)	
Suspected fetal jeopardy	0 (0)	1 (2.4)	

PROM = premature rupture of membranes; SD = standard deviation; NA = not applicable.
Data are presented as the number (percentage) of patients unless otherwise indicated.

tified who had been admitted either with preterm labor with intact membranes or with a medical complication of pregnancy and subsequently developed preterm PROM leading to delivery. These 41 women were also included in the analysis (Figure 1). The patient demographics and randomization assignments were similar between the 120 women with preterm PROM as a primary diagnosis and the 41 women in whom preterm PROM developed after entry into the trial for other reasons (Table 1). Of the 161 women with preterm PROM, 81 were randomized to the weekly course group and 80 were assigned to the single-course group. Seventy-eight women in the weekly course group and 76 women in the placebo (single-course) group had complete data for analysis. As a result, the denominators may vary slightly with different variables for analysis. Of the 3 patients with incomplete data who had been randomized to receive weekly courses, 2 women were lost to follow-up and 1 woman had a neonatal demise from necrotizing enterocolitis and sepsis. Of the 4 women assigned to receive placebo who had incomplete data for analysis, 1 neonate died from RDS, 1 woman had a presumed term delivery with neonate discharged to home, 1 patient withdrew from the study and subsequently had a preterm delivery of a neonate with RDS, and 1 patient was completely lost to follow-up.

At randomization the 2 groups (weekly versus single course) were well balanced for potential confounders (Table 2), including qualifying criteria (indication for receiving initial course of antenatal corticosteroids), payer status, and study site. The median number of injections received by all patients enrolled in this preterm PROM study was 3 (1 course of betamethasone plus 2 courses of study drug), with a range of 2 courses (1 course of betamethasone plus 1 course of study drug) to a maximum of 10 (1 course of betamethasone and 9 courses of study drug). Twenty-five women (16%) received more than 4 weeks of injections. Women randomized to a single course of steroids tended to receive more total injections (a median of 3 injections for placebo versus 2 for betamethasone, Wilcoxon P = .131), which reflects a trend toward a 1-week increase in latency period compared with women in the weekly course group (Table 3).

Overall, there was no difference in composite neonatal morbidity between the 2 groups (Table 4). Next we sought to explore whether any subgroup of patients was particularly affected by weekly courses of antenatal corticosteroids. Regardless of gestational age of randomization (a surrogate for gestational age of preterm PROM), there were no differences in composite morbidity in women treated with single versus weekly courses of steroids. However, neonates born between 24 and 27 weeks of gestation who had been exposed to weekly steroids tended to have lower composite morbidity than neonates treated with only a single course. After closer examination, most of the decrease in composite morbidity was attributed to severe RDS in the lowest-age-group category (9 patients [26.5%] in the weekly course group versus 16 patients [100%] in the single-course group, P = .001), but this was not associated with lower rates of

Table 2. Demographic Data of Study Patients

	Weekly courses (n = 81)	Single course (n = 80)	P
Mean (SD) maternal age (y)	27.3 (7.2)	27.5 (6.9)	.80
Race			.94
White	24 (29.6)	26 (32.5)	
Hispanic	27 (33.3)	22 (27.5)	
Black	25 (30.9)	26 (32.5)	
Asian	2 (2.5)	3 (3.8)	
Other	3 (3.7)	3 (3.7)	
Nulliparity	34 (42.0)	23 (28.8)	.08
Mean (SD) estimated gestational age at randomization (wk)	29.0 (2.8)	28.4 (2.6)	.12
Distribution of estimated gestational age at randomization (wk)			.51
24–27	33 (40.7)	34 (43.0)	
28–31	30 (37.0)	33 (41.8)	
32–24	18 (22.2)	12 (15.2)	
Mean (SD) estimated gestational age at delivery (wk)	31.0 (3.4)	31.3 (3.6)	.59
Distribution of estimated gestational age at delivery (wk)			.90
24–27	18 (22.5)	16 (20.3)	
28–31	29 (36.3)	26 (32.9)	
32–34	25 (31.3)	27 (34.2)	
> 34	8 (10.0)	10 (12.7)	

SD = standard deviation.

Data are presented as number (percentage) of patients unless otherwise indicated. Column percentages do not equal 100 because of missing data.

bronchopulmonary dysplasia or decreased length of neonatal hospital stay.

All patients in the 2 groups received antepartum prophylactic antibiotics (n = 135). Fifty-two (38.5%) of all the patients received a combination of a penicillin (most commonly ampicillin) and a macrolide (most commonly erythromycin). Forty-four women (32.6%) were given ampicillin or penicillin alone, and 18 women (13.3%) received penicillin plus some other nonmacrolide antibiotic. The antibiotic regimens were not significantly different in women assigned to weekly courses versus a single course (data not presented, P = .79, χ^2 test). Despite these antibiotics, clinical chorioamnionitis developed more frequently in the weekly course group (Table 3), although the differences were not statistically significant. There were no differences in rates of chorioamnionitis when the data were stratified by gestational age at randomization. The higher rates of intrauterine infection were not associated with increased rates of neonatal sepsis. Finally, rates of both composite morbidity and chorioamnionitis declined as gestational age increased in both groups of patients (Figure 2). However, after 32 weeks of gestation, the rates of chorioamnionitis surpassed the rates of composite neonatal morbidities in both groups.

The results of this preterm PROM secondary analysis were also compared with outcomes of patients with intact membranes from the parent trial to examine the effects of preterm PROM and antenatal corticosteroids on pregnancy outcomes (Table 5).[8] In pairwise tests of estimated gestational age at delivery, birthweight, and latency, women and neonates with preterm PROM

Table 3. General Maternal and Neonatal Outcomes

	Weekly courses (n = 81)	Single course (n = 80)	P
Mean (SD) latency interval (wk)	2.9 (2.4)	3.9 (3.0)	.02
Mean (SD) birthweight (g)	1641 (680)	1704 (704)	.57
Mean (SD) neonatal hospital days	31.7 (31.3)	32.6 (35.3)	.87
Chorioamnionitis	39 (49.4)	25 (31.7)	.04
Neonatal sepsis	9 (11.4)	6 (7.6)	.59
Endometritis	4 (5.1)	7 (8.9)	.53

SD = standard deviation.

Data are presented as the number (percentage) of patients unless otherwise indicated. Column percentages do not equal 100 because of missing data.

Table 4. Composite and Individual Neonatal Morbidities

	Weekly courses (n = 81)	Single course (n = 80)	P
Composite morbidity	27 (34.2)	33 (41.8)	.41
Composite morbidity by estimated gestational age at randomization (wk)			
24–27	17 (53.13)	21 (61.76)	.61
28–31	5 (17.24)	11 (34.38)	.15
32–34	5 (27.78)	0 (0)	.07
Composite morbidity by estimated gestational age at delivery (wk)			
24–27	12 (70.6)	16 (100)	.04
28–31	10 (34.5)	14 (53.9)	.18
32–34	5 (20.0)	3 (11.1)	.46
> 34	0 (0)	0 (0)	NA
Composite neonatal morbidity*			
RDS	30 (38.0)	36 (45.6)	.42
Severe RDS	15 (19.0)	31 (39.2)	.01
Bronchopulmonary dysplasia	15 (19.0)	18 (22.8)	.70
Intraventricular hemorrhage	15 (19.0)	15 (19.0)	1.00
Severe intraventricular hemorrhage	5 (6.3)	2 (2.5)	.44
Periventricular leukomalacia	1 (1.3)	2 (2.5)	1.00
Necrotizing enterocolitis	5 (6.3)	5 (6.3)	1.00
Perinatal death	3 (3.8)	6 (7.6)	.49

NA = not applicable; RDS = respiratory distress syndrome.
Data are presented as the number (percentage) of patients. Column percentages do not equal 100 because of missing data.
* See the Appendix for definitions of terms.

faired worse than those with intact membranes, regardless of whether they received weekly courses or a single course of steroids. In pairwise tests of infectious outcomes, there were significant differences in chorioamnionitis between women with preterm PROM and those with intact membranes, and between preterm PROM patients who received weekly courses of therapy and those who received a single course of therapy. Neonates born to women with preterm PROM who had received weekly courses of steroids had significantly higher rates of proven sepsis when compared with women with intact membranes or women with ruptured membranes who had received only a single course of steroids.

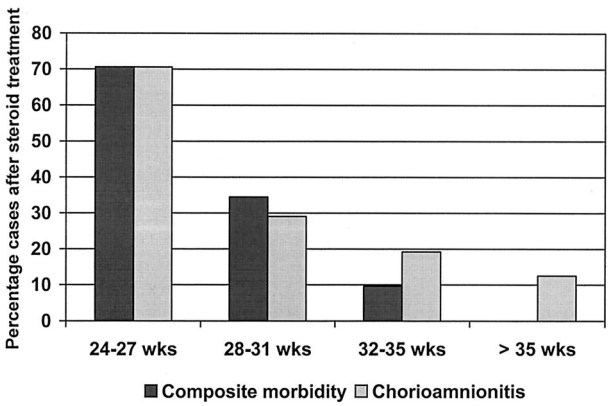

Figure 2. Risk versus benefits of weekly and single-course antenatal corticosteroids after preterm premature rupture of membranes by estimated gestational age at delivery.
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Regardless of treatment assignment, pregnancies complicated by preterm PROM delivered earlier with accordingly lower birth weights, had shorter latency intervals, and were more likely to have chorioamnionitis and higher rates of neonatal complications. Exposure to weekly courses of antenatal steroids did not significantly reduce composite neonatal morbidity in either group (preterm PROM or intact membranes). However, in the setting of preterm PROM, weekly courses trended toward higher rates of chorioamnionitis and neonatal sepsis, despite widespread use of antibiotic prophylaxis.

DISCUSSION

This study was a part of the first randomized, double-blind, placebo-controlled trial to evaluate single versus weekly courses of antenatal corticosteroids in women at high risk for preterm delivery. Women with preterm PROM are at the highest risk for preterm delivery and infectious complications, which makes the post hoc analysis of women in this particular subgroup especially important. Although we acknowledge that our current sample size limits our ability to explore all of the complications of therapy, the study design is robust enough to allow us to examine the relationship between weekly steroid exposure and general perinatal outcomes in women with preterm PROM. The design also allowed

Table 5. Effects of Preterm PROM and Antenatal Corticosteroids on Outcomes

	Intact membranes* (n = 327)		Preterm PROM (n = 161)		
	Weekly courses	Single course	Weekly courses	Single course	P
Estimated gestational age at delivery (wk)	34.1 (0.3)	34.6 (0.3)	31.0 (0.4)†	31.3 (0.4)†	< .001†
Birth weight (g)	2,181 (63)	2,356 (65)	1,641 (92)†	1,704 (92)†	< .001†
Latency (wk)	6.0 (0.3)	6.7 (0.3)	2.9 (0.4)†	3.9 (0.4)†	< .001†
Chorioamnionitis	21 (12.4)	17 (10.8)	39 (49.4)†	25 (31.7)†	.001†
Proven neonatal sepsis	4 (2.4)	4 (2.6)	9 (11.4)†	6 (7.6)	.005†
Endometritis	9 (5.3)	7 (4.5)	4 (5.1)	7 (8.9)	.56

PROM = premature rupture of membranes.

Data are presented as mean (standard error of the mean) values.

* Data were derived from the parent trial.[8]

† Significant difference among 4 group means. Because there was no difference in proportions of endometritis in the global test, pairwise tests were not conducted.

us to make comparisons between the efficacy and safety of weekly courses in women with preterm PROM and women with intact membranes.

Despite significantly higher risk of both maternal and neonatal complications in patients with preterm PROM, treatment with weekly courses of antenatal steroids were not associated with lower rates of composite morbidity compared with a single course of therapy. In addition, weekly courses of steroids led to a slightly shorter latency period and higher rates of chorioamnionitis, despite widespread use of antibiotic prophylaxis. However, weekly courses of antenatal steroids were significantly associated with decreased rates of severe RDS, especially among the lowest-birthweight neonates. The decrease in severe RDS resulted in less composite neonatal morbidity in the neonates delivered between 24 and 27 weeks of gestation, although the reduction in composite morbidity was not statistically significant when using the P value of .013 following Bonferroni correction for multiple comparisons. These findings were similar to those in the parent trial that included the entire study population. One could argue that the treatments that prevent severe RDS can ultimately reduce neonatal death, prevent chronic lung disease, and minimize the risk of severe intraventricular hemorrhage. Unfortunately, our sample size is too small to fully address this important question. Our findings suggest that the reduction in severe RDS with weekly courses did not translate to decreased mortality, development of chronic lung disease, severe intraventricular hemorrhage, or shorten the mean neonatal lengths of stay even in this very premature subgroup of neonates. More sensitive measures of the effect of severe RDS on other measures of long-term neonatal outcome are required to determine if weekly antenatal steroids in the very premature 24–27-week preterm PROM subgroups are worth the increased infectious risks. Given the paucity of clinical studies in such an important gestational age group that is at high risk for neonatal morbidity, our initial description of improved outcome in this subgroup suggests that a one-time "rescue" course of steroids before 28 weeks of gestation could be considered in the setting of preterm PROM if more than 10 days have lapsed after the first course and delivery is more imminent. However, we defer to the NIH Consensus Panel's recommendation to avoid treating patients with multiple courses of steroids.

After evaluating the effect of preterm PROM on infectious morbidity, weekly steroid use in the setting of PROM was associated with some clinically relevant findings. As expected, to chorioamnionitis developed more frequently in patients with preterm PROM than in women with intact membranes, and patients with preterm PROM were at further risk when treated with weekly antenatal steroids. The significantly higher rate of culture-proven sepsis in offspring of women with preterm PROM who had received weekly antenatal steroids when compared to all other patients is particularly worrisome. Given recent concerns over the association of intrauterine infection and subsequent development of cerebral palsy, long-term follow-up of these neonates is warranted.[9–11]

Interestingly, our data strengthen the original recommendation of the 1994 NIH Consensus Panel that antenatal corticosteroids not be routinely used after 30–32 weeks of gestation in women with preterm PROM. Using women with prematurely ruptured membranes treated with either steroid regimen in our protocol as a surrogate for women with preterm PROM, we have demonstrated that the risk of developing chorioamnionitis after 32 weeks of gestation is indeed greater than the risk of major adverse neonatal outcome after this gestational age (Figure 2).

The original NIH Consensus Panel reconvened in August of 2000 to discuss the role of repeated courses of

antenatal steroids, after enrollment into this trial ended. Based on the review of all of relevant data, the experts agreed that repeated courses of antenatal corticosteroids should be restricted to women participating in clinical trials until additional data are available to determine the efficacy and safety of repeated courses of antenatal steroids in a variety of clinical settings, including preterm PROM. The demonstration in this study of no overall improvement in neonatal status and the tendency toward a higher rate of chorioamnionitis after weekly courses of antenatal steroids, despite widespread use of antibiotics, supports this restrictive approach to steroid prophylaxis in the setting of preterm PROM.

REFERENCES

1. Kaltreider DF, Kohl S. Epidemiology of preterm delivery. Clin Obstet Gynecol 1980;23:17–31.
2. Leitich H, Egarter C, Reisenberger K, Kaider A, Berghammer P. Concomitant use of glucocorticoids: a comparison of two metaanalyses on antibiotic treatment in preterm premature rupture of membranes. Am J Obstet Gynecol 1998;178:899–908.
3. Khong TY, Vigneswaran P, Crowther CA. Repeat doses of prenatal corticosteroids do not increase the risk of acute chorioamnionitis. Aust N Z J Obstet Gynaecol 2001;4: 214–5.
4. Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes [see comments]. JAMA 1995;273:413–8.
5. Mercer BM, Goldenberg RL, Meis PJ, Moawad AH, Shellhaas C, Das A, et al. The Preterm Prediction Study: prediction of preterm premature rupture of membranes through clinical findings and ancillary testing. The National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol 2000;183:738–45.
6. Quinlivan JA, Evans SF, Dunlop SA, Beazley LD, Newnham JP. Use of corticosteroids by Australian obstetricians–a survey of clinical practice. Aust N Z J Obstet Gynaecol 1998;38:1–7.
7. Brocklehurst P, Gates S, McKenzie-McHarg K, Alfirevic Z, Chamberlain G. Are we prescribing multiple courses of antenatal corticosteroids? A survey of practice in the UK. Br J Obstet Gynaecol 1999;106:977–9.
8. Guinn DA, Atkinson MW, Sullivan L, Lee M, MacGregor S, Parilla BV, et al. Single vs weekly courses of antenatal corticosteroids for women at risk of preterm delivery: a randomized controlled trial. JAMA 2001;286:1581–7.
9. Yoon BH, Jun JK, Romero R, Park KH, Gomez R, Choi JH, et al. Amniotic fluid inflammatory cytokines (interleukin-6, interleukin-1beta, and tumor necrosis factor-alpha), neonatal brain white matter lesions, and cerebral palsy. Am J Obstet Gynecol 1997;177:19–26.
10. Gilstrap LC III, Ramin SM. Infection and cerebral palsy. Semin Perinatol 2000;24:200–3.
11. Grether JK, Nelson KB. Maternal infection and cerebral palsy in infants of normal birth weight [see comments] [published erratum appears in JAMA 1998;279:118]. JAMA 1997;278:207–11.

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APPENDIX

Definitions of Specific Neonatal Morbidities

Severe respiratory distress syndrome: Respiratory distress syndrome and mechanical ventilation greater than 24 hours and surfactant therapy.

Bronchopulmonary dysplasia: Oxygen requirement and chest X-ray abnormalities at 28 days of life.

Severe intraventricular hemorrhage: Grades III and intravenously intraventricular hemorrhages.

Periventricular leukomalacia: Echolucency of brain parenchyma proximal to ventricles.

Necrotizing enterocolitis: 1) unequivocal presence of intramural air or perforation on X-ray; 2) clinical evidence of perforation; or 3) characteristic findings at surgery or autopsy.

Proven neonatal sepsis: Positive blood culture.

Death: Perinatal death from randomization to discharge.