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Long-term Outcomes of Single vs. Multiple Courses of Antenatal Corticosteroids in Mothers at Risk for Preterm Delivery

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INTRODUCTION

Although it is well-known that the administration of antenatal corticosteroids to mothers at risk of preterm birth improves outcomes in premature infants, premature births and associated morbidity and mortality are still prevalent. Typical mortality associated with premature births account for approximately one-third of all infant deaths in the United States. Infants born before 25 weeks gestation have the highest mortality rate, and if they survive, are at the greatest risk for severe morbidity, which translate into higher risk of hospital readmission and significant medical costs. Premature neonates are at a higher risk for acute complications, including necrotizing enterocolitis, growth difficulties, sepsis, intracranial bleeding, retinal detachment, bronchopulmonary dysplasia, chronic lung disease, and death. In early childhood, morbidities include motor delay, cerebral palsy, lower IQs, behavior problems, respiratory illness, difficulty with school work, and lower health-related quality of life.

For those reasons, corticosteroid administration prior to anticipated preterm birth is one of the most important and effective antenatal therapies available to improve newborn outcomes. The American College of Obstetricians and Gynecologists (ACOG) currently recommends the administration of a single course of antenatal corticosteroids for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation at risk of preterm delivery within 7 days[1]. A Cochrane meta-analysis concluded with a recommendation that a single course of antenatal corticosteroids should be given for all preterm deliveries[2]. However, one study showed multiple courses of antenatal corticosteroids were associated with a lower incidence of respiratory distress syndrome (P=.005; odds ratio, 0.44; 95% confidence interval, 0.25-0.79), patent ductus arteriosus

(20% vs 13%; P=.016), and mothers treated with multiple courses had a lower incidence of prolonged rupture of membranes (24% vs 33%; P=0.6)[3]. This paper reviews whether a single course of antenatal corticosteroid therapy compared to multiple courses of antenatal corticosteroid therapy in preterm infants is necessary to prevent mortality and disability within 10 years. Multiple versus single courses of betamethasone and dexamethasone will be examined as it is prudent to prevent premature births and assess the long-term risks and benefits of antenatal corticosteroids.

DISCUSSION

To answer this question, the current literature was searched using keywords and MeSH terms such as antenatal corticosteroids, single v. weekly course, long-term outcomes, and premature births. Online biomedical literature databases such as PubMed Central, Google Scholar, JSTOR, MEDLINE, and ACOG were searched. The relevant articles were filtered by limiting the selection to double-blinded, placebo-controlled, or randomized studies and then organized by publication date. In each trial, the long-term effects of a single dose or placebo of antenatal corticosteroids were compared with multiple doses.

In a meta-analysis of 11 full-text randomized controlled trials, benefits and risks of multiple courses of antenatal corticosteroids were investigated in 4,390 women and 5,227 neonates[4]. Groups given multi-courses of antenatal corticosteroids were associated with a significant decrease in respiratory distress syndrome, patent ductus arteriosus, ventilator support, surfactant use, and maternal side-effects compared to groups given a single-course of antenatal corticosteroids. This meta-analysis strengthened the association between multiple-courses of antenatal corticosteroids and reduced

complications in neonates. However, no details on the number of reviewers for the study selection process, data collection, or quality assessment were provided.

In a randomized, double-blind, placebo-controlled, intention-to-treat trial, effects of single vs. weekly courses of antenatal corticosteroids on neonatal morbidity and mortality were investigated in 502 pregnant women across 13 U.S. academic centers, but 32 women withdrew and 4 women were withdrawn by their Obstetrician[5]. No statistically significant reduction in neonatal morbidity and mortality (i.e., respiratory distress syndrome, bronchopulmonary dysplasia, severe IVH, sepsis, perinatal death, necrotizing enterocolitis) were noted between single vs. weekly courses of ACS. This trial was randomized, double-blind, and placebo-controlled, so the findings should not be preferentially biased. However, this investigation was limited by a lack of standardization of cranial ultrasonography and for neonatal biometry determinations. The table below summarizes Guinn et al.'s findings.

Table 3. Composite Morbidity and Individual Neonatal Outcomes*

Variables	Antenatal Corticosteroid Therapy: Weekly Course (n = 256)	Antenatal Corticosteroid Therapy: Single Course (n = 246)	RR (95% CI)†	*P* Value
Composite Morbidity				
Composite morbidity	56 (22.5)	66 (28.0)	0.80 (0.59-1.10)	.16
Composite morbidity stratified by gestational age at delivery, wk				
24-27	24 (77.4)	27 (96.4)	0.80 (0.65-0.98)	.03
28-31	22 (35.5)	25 (49.0)	0.72 (0.47-1.12)	.15
32-34	9 (12.5)	11 (16.9)	0.74 (0.33-1.67)	.46
≥35	1 (1.2)	3 (3.3)	0.36 (0.04-3.44)	.36
Composite morbidity stratified by gestational age at randomization, wk				
24-27	37 (42.0)	39 (41.9)	1.00 (0.71-1.41)	.99
≥28	17 (10.8)	24 (17.4)	0.62 (0.35-1.10)	.10
Individual Neonatal Outcomes				
Perinatal death	5 (2.0)	9 (3.8)	0.53 (0.18-1.55)	.23
Respiratory distress syndrome	69 (27.8)	69 (29.4)	0.95 (0.71-1.25)	.70
Severe respiratory distress syndrome	38 (15.3)	57 (24.1)	0.63 (0.44-0.91)	.01
Bronchopulmonary dysplasia	28 (11.3)	26 (11.0)	1.00 (0.61-1.68)	.95
Total intraventricular hemorrhage‡	30 (25.2)	25 (24.5)	1.03 (0.65-1.63)	.90
Severe intraventricular hemorrhage‡	9 (7.6)	2 (2.0)	3.80 (0.85-17.45)	.06
Isolated periventricular leukomalacia‡	2 (2.0)	3 (3.0)	0.60 (0.09-3.40)	.44
Proven sepsis	13 (5.2)	10 (4.2)	1.20 (0.55-2.80)	.60
Proven necrotizing enterocolitis	10 (4.0)	9 (3.8)	1.06 (0.44-2.56)	.90

*Data are No. (%). Denominators may vary slightly because of 2 cases of intrauterine fetal demise and incomplete data on neonates who were lost to follow-up.
†There was no center effect on any of the outcomes presented. Therefore, unadjusted relative risks (RRs) and 95% confidence intervals (CIs) are presented.
‡A total of 221 neonates had 1 or more cranial ultrasonographic examinations. The most severe finding was recorded for analysis.

(Excerpted from: Guinn, D. A., Atkinson, M. W., Sullivan, L., Lee, M., Macgregor, S., Parilla, B. V., Muraskas, J. (2002). Single vs Weekly Courses of Antenatal Corticosteroids for Women at Risk of Preterm Delivery: A Randomized Controlled Trial. *Obstetrical & Gynecological Survey,* 57(3), 146-147. doi:10.1097/00006254-200203000-00008)

The Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study (MACS) investigated morbidity and mortality in infants exposed to placebo versus multiple antenatal corticosteroids at birth[6]. 1,858 women at 25-32 weeks gestation at high risk of preterm delivery were randomly assigned to multiple courses of antenatal corticosteroids

(n=937) or placebo (n=921), every 14 days until week 33 or delivery, whichever came first. Analysis of perinatal or neonatal mortality, severe respiratory distress syndrome, intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, and necrotizing enterocolitis was completed with intention to treat. No statistically significant reductions in neonatal morbidity and mortality were seen in infants exposed to multiple courses of antenatal corticosteroids versus placebo. However, infants who received multiple courses of antenatal corticosteroids were associated with a decreased weight (2216 g vs 2330 g, p=0.0026), decreased length (44.5 cm vs 45.5 cm, p<0.001), and smaller head circumference (31.1 cm vs 31.7 cm, p<0.001) at birth. This study has methodological strength as it is a randomized controlled study.

In a cohort follow-up study of these MACS participants, the effects of single vs. multiple courses of antenatal corticosteroids on morbidity and mortality were investigated at 2 years and 5 years of age in children whose mothers participated in MACS between 25 and 32 weeks gestation and remained pregnant 14 to 21 days following an initial course of antenatal corticosteroids[7]. Of 2,305 infants eligible for follow-up evaluation, 2,104 infants were evaluated at 18 to 24 months of age. Although more than 90% of the cohort successfully followed up after 2 years, no statistically significant differences were found for the risk of death, neurologic impairment, height, weight, and head circumference between infants in the multiple antenatal corticosteroid group (n=1,069) and the placebo group (n=1,035).

To investigate 5-year outcomes of these MACS participants, 1,728 children were selected by central randomization with stratification according to center and gestational age at enrollment[8]. Although more than 80% of the cohort successfully followed up after

5 years, no statistically significant differences were found for the risk of death, neurodevelopmental disability, weight, head circumference, and visual-motor abilities and integration. Due to the lack of evidence supporting short-term and long-term benefits, multiple courses of antenatal corticosteroids were not recommended in women at risk for preterm delivery.

In a retrospective review, medical records of 256 preterm newborns with and without maternal use of antenatal corticosteroids were evaluated[9]. Of the 256 total infants, 174 neonates went without maternal use of antenatal corticosteroids, 37 infants received a single dose and 45 infants received multi-courses of antenatal corticosteroids. Over the 10 years examined, the incidence of intubation and surfactant use were significantly less in single and multi-dose corticosteroid groups compared to groups without maternal use of antenatal corticosteroids. No statistical significance in the rate of survival, IVH, NEC, retinopathy of prematurity, long-term neurologic outcomes, or neonatal sepsis were found among the 3 groups. The findings in this 10-year retrospective review revealed that infants of mothers who received both single and multiple doses of antenatal corticosteroids had fewer respiratory interventions than infants without maternal use of antenatal corticosteroids.

In a randomized, controlled trial the neurodevelopment and health outcomes of 2-mL Celestone Chronodose versus placebo were investigated in 1,146 infants[10]. At ages 6-8 years, children were evaluated by a pediatrician. Of the infants who were given a single dose of antenatal corticosteroids, 41% developed respiratory distress syndrome and 20% developed severe lung disease. Treatment with repeated doses of antenatal

corticosteroids, however, significantly decreased these adverse respiratory outcomes. Of note is that lung function of most children was not reported in this study.

In an observational study, the 3-year outcomes of repeated antenatal corticosteroids on birth size, growth, and development were followed in 477 singleton infants enrolled in a regional cohort study[11]. Of the infants who were given single versus multiple doses of antenatal corticosteroids, birth weight ratio and head circumference significantly decreased with increasing number of corticosteroids courses. Reduction of head circumference by 4% represents approximately 11% reduction in cranial volume. This is a critical finding as poor developmental, intellectual, and behavioral outcomes are associated with small head circumference in preterm infants. This significant decrease in birth weight ratio with multiple courses of antenatal corticosteroids was seen regardless of pregnancy complications (i.e., preeclampsia, preterm labor rupture of membranes, antepartum hemorrhage, idiopathic preterm labor). Notably, the group that had received 3 or more courses of corticosteroids showed a higher frequency of severe chronic lung disease. Of the 477 infants, 385 survived to 3 years. Univariate and multivariate analyses of weight, height, and head circumference at age 3 did not show any differences between antenatal corticosteroids groups. However, the relationship between antenatal corticosteroid use and behavioral outcomes was not analyzed.

CONCLUSION

The evidence in the available literature does not answer whether single or multiple ACS is preferable. These conflicting statistically significant results call for further research on the efficacy of single versus multiple courses of antenatal corticosteroids. Based on these findings, further research on any associations between antenatal corticosteroid

therapy and the development of chronic illnesses is warranted. The results of future research may have a great impact on clinical practice as it is prudent to prevent premature births and reduce the long-term risks and benefits of antenatal corticosteroids. One limitation noted across several studies was the small sample size of women at risk for preterm delivery. Prospective randomized controlled trials with larger sample sizes are recommended to circumvent limitations of future studies. Another limitation is that most studies were either retrospective or observational and may have relied heavily on associations; therefore, caution should be used when generalizing and applying the results in these studies.

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