Association of Antenatal Corticosteroids with Mortality, Morbidity, and Neurodevelopmental Outcomes in Extremely Preterm Multiple Gestation Infants

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Abstract

Importance—Little is known about the benefits of antenatal corticosteroids on extremely preterm multiples.

Objective—To examine in extremely preterm multiples if use of antenatal corticosteroids is associated with improvement in major outcomes.

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Design, Setting, and Participants—Infants with gestational age 22–28 weeks born at an NICHD Neonatal Research Network center (1998–2013) were studied. Generalized estimating equation models were used to generate adjusted relative risks (aRR) controlling for important maternal and neonatal variables.

Main Outcome Measures—In-hospital mortality, the composite outcome of neurodevelopmental impairment at 18–22 months' corrected age or death before assessment.

Results—Of 6925 multiple-birth infants, 6094 (88%) were born to women who received antenatal corticosteroids. In-hospital mortality was lower among infants with exposure to antenatal corticosteroids vs no exposure (aRR=0.87, 95% CI 0.78–0.96). Neurodevelopmental impairment or death was not significantly lower among those exposed to antenatal corticosteroids vs no exposure (aRR=0.93, 95% CI 0.84–1.03). Other adverse outcomes that occurred less frequently among infants of women receiving antenatal corticosteroids included severe intraventricular hemorrhage (aRR=0.68, 95% CI 0.58–0.78) and the combined outcomes of necrotizing enterocolitis or death and severe intraventricular hemorrhage or death. Subgroup analyses indicated that exposure to antenatal corticosteroids was associated with a lower risk of mortality and the composite of neurodevelopmental impairment or mortality among non-small for gestational age multiples (aRR=0.82, 95% CI 0.74–0.92 and aRR=0.89, 95% CI 0.80–0.98, respectively) and a higher risk among small for gestational age multiples (aRR=1.40, 95% CI 1.02–1.93 and aRR=1.62, 95% CI 1.22–2.16, respectively). Antenatal corticosteroids were associated with higher neurodevelopmental impairment or mortality among multiple-birth infants of mothers with diabetes (aRR=1.55, 95% CI 1.00–2.38) but not among infants of mothers without diabetes (aRR=0.91, 95% CI 0.83–1.01).

Conclusion—In extremely preterm multiples, exposure to antenatal corticosteroids compared with no exposure was associated with a lower risk of mortality with no significant differences for the composite of neurodevelopmental impairment or death. Future research should investigate the increased risks of mortality and the composite of neurodevelopmental impairment or death associated with exposure to corticosteroids among small for gestational age multiples.

INTRODUCTION

Multiple gestation increases the risk of preterm delivery and the associated morbidities of prematurity.[1] Among singleton pregnancies, a single course of antenatal corticosteroids (ANS) administered 24 hours to 7 days before birth to women in labor before 34 weeks' gestation reduces early mortality, respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis.[2] Data on ANS effects on multiples, including extremely preterm multiples have been limited and conflicting. Such contradictory findings have been reflected in the 1995 National Institutes of Health Consensus Conference recommendations, which state that evidence is insufficient to assess the effectiveness of ANS use among women with multiple gestations.[3] The Cochrane review on ANS also called for further information to examine ANS effects in multiple pregnancies.[2]

We used data from the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) to examine whether ANS exposure in extremely preterm multiples at 22–28 weeks' gestation is associated with a lower incidence

of in-hospital mortality, the composite outcome of neurodevelopmental impairment or death, and other important morbidities.

METHODS

We analyzed data on multiples born at one of 28 NICHD NRN centers between January 1, 1998 and December 31, 2013 with gestational age (GA) 22–28 weeks included in a prospective registry. From 1998–2007, all inborn very low birth weight (VLBW, 401–1500 g) infants were included in the registry. In 2008, eligibility criteria changed to infants with GA 22–28 weeks or birth weight (BW) 401–1000 g or preterm infants enrolled in another NRN study. Trained research nurses prospectively entered maternal demographic, pregnancy and delivery information, and infant data collected from birth to discharge, transfer, death, or 120 days. The institutional review board at each center approved the registry.

Infants with a major congenital anomaly (n=211), infants with missing data on ANS administration (n=11), and twin infants where at least one of the set of twins died due to twin-to-twin-transfusion syndrome (n=26) were excluded from the analyses. Twin-to-twin-transfusion syndrome was only recorded if it was a cause of death. In our primary analyses, we also excluded 435 infants (251 at 22 weeks, 156 at 23 weeks, 21 at 24 weeks, and 7 at 25–28 weeks) who died within the first 12 hours after birth without receiving any intensive care (no ventilation, intubation, or medications) to ensure that postnatal care restriction did not affect our outcome estimates. In a sensitivity analysis, analyses were repeated with these infants included. Exposure to ANS was defined if the mother received 1 dose of betamethasone or dexamethasone. Data on whether the ANS course was full or partial were collected, but data on timing and dose were not available. Type of ANS was collected starting in 2002.

In-Hospital Outcomes

Primary in-hospital outcome included in-hospital death, defined as death of an infant before discharge or by 120 days for infants still hospitalized at that age. In-hospital secondary outcomes were morbidities diagnosed during hospital stay and recorded for infants surviving >12 hours including: respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC) stage IIA,[4] severe intraventricular hemorrhage (IVH) (grade 3 or 4)[5] or periventricular leukomalacia (PVL), retinopathy of prematurity (ROP) defined for infants still hospitalized at 28 days with severe ROP defined as stage 3, bronchopulmonary dysplasia (BPD) defined as continuous use of supplemental oxygen at 36 weeks' postmenstrual age, and the composite outcome of each morbidity or death. The composite outcome of morbidity or death was defined as present if the infant had the morbidity or died before the outcome was evaluated (for NEC, BPD, and IVH or PVL, death before 36 weeks PMA; for ROP, death before discharge) and absent if the infant survived until evaluation and did not have the morbidity.

Follow-Up Outcomes

The primary follow-up outcome included the composite of severe neurodevelopmental impairment (NDI) or death before assessment at 18 to 22 months' corrected age (CA).

Secondary follow-up outcomes at 18 to 22 months' CA included death, NDI, and the individual components of NDI. Neurodevelopmental assessment was conducted by certified examiners for surviving infants if the infant weighed 401–1000 grams (those whose follow-up window opened before Jan. 1, 2008) at birth or was born at 26 weeks GA or was enrolled in an NRN study with follow-up (those whose follow-up window opened on or after Jan. 1, 2008). The definition of NDI at 18 to 22 months' CA changed during the study period. From 1994–2005, NDI was defined as 1 of: Bayley-II Mental Developmental Index score <70, Bayley-II Psychomotor Developmental Index score <70, moderate to severe cerebral palsy, bilateral blindness, hearing impairment requiring hearing aids in both ears. From 2006–2009, NDI was defined as 1 of: Bayley-III cognitive composite score <70, gross motor function level 2, blindness (little or no useful vision in either eye), deafness (functional hearing impairment in both ears). From 2010–2013, the Bayley-III motor score was collected and a motor composite score <70 was added to the 2006–2009 NDI definition.

Statistical Analysis

Maternal and infant characteristics were compared between infants of mothers exposed to any ANS and infants of mothers not exposed to ANS using standard descriptive statistics. Chi-square test or t-test determined statistical significance for unadjusted comparisons. Generalized estimation equation (GEE) models[6] were used to explore the association between exposure to ANS and outcomes, adjusting for maternal variables (age, marital status, race, diabetes, hypertension, rupture of membranes >24 hours), study center, and infant variables (sex, GA, small for gestational age (SGA)) while accounting for correlation due to clustering of multiple births within a mother. SGA was defined as <10th percentile using the Alexander et al. norms.[7] For models examining outcomes at 18–22 months' CA, we also adjusted for maternal education and study period to indicate Bayley-II vs Bayley-III assessments. In separate models, we examined potential effect modifiers of the primary outcomes by assessing the significance of the interaction term between ANS and each of: week of GA, diabetes vs no diabetes, hypertension vs no hypertension, chorioamnionitis vs no chorioamnionitis, vaginal vs cesarean delivery, SGA vs non-SGA, multiple vs singleton, twin vs higher-order multiple, and among twins, sex concordant vs sex discordant, and birth weight concordant vs birthweight discordant (where discordance was defined as a difference of >30% in BW between the twins, calculated by dividing the difference in BWs within a twin pair by the BW of the larger twin). Models with a significant interaction term were stratified by each subgroup accordingly. We also examined the associations between exposure to full or partial ANS and the primary outcomes. Adjusted relative risks (aRR) and 95% confidence intervals (CI) are reported based on robust GEE standard error estimates. A p-value <0.05 indicates statistical significance. P-values were not adjusted for multiple comparisons. Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

The study population for the primary analysis consisted of 6925 multiples (83.4% twins and 16.6% higher-order multiples) of whom 6094 (88%) were born to mothers who received ANS. Women who did not receive ANS were more likely to be black, unmarried, 19 years old or younger, and to have less than high school education (Table 1). Infants of mothers

who received ANS were more likely to be born by cesarean delivery and to have a higher BW and GA. The follow-up rate for NDI assessment was slightly higher for those exposed to ANS (85%) than for those not exposed (80%) (p=0.03) (Table 1). The percentage of multiples whose mothers received ANS across the years is shown in Figure 1. The usage of ANS did not differ significantly by birth year or GA.

Overall, 5361 (77.6%) infants survived to discharge and 1,548 (22.4%) died. Among infants at 22–28 weeks' gestation, in-hospital mortality (20% with exposure vs 39% without exposure to ANS, aRR=0.87, 95% CI 0.78–0.96), IVH grade 3–4 and/or PVL (17% with exposure vs 29% without exposure to ANS, aRR=0.68, 95% CI 0.58–0.78), and the composite outcomes NEC and/or death and IVH grade 3–4 and/or PVL and/or death were significantly lower for multiples exposed to ANS compared to those without exposure (Table 2). There were no differences in the risks of RDS, BPD, NEC, and ROP between the two groups.

At the 18–22 month follow-up for eligible infants, mortality (30% vs 54%, aRR=0.71, 95% CI 0.60–0.84) was lower among those exposed to ANS compared to those not exposed to ANS. There were no differences in the risks of the composite outcome of NDI or death (54% vs 75%, aRR=0.93, 95% CI 0.84–1.03), NDI, or the individual components of NDI (Table 3).

Interaction analyses performed for the primary outcomes in-hospital mortality and NDI or death showed that the association of ANS with outcomes did not differ for maternal hypertension vs no hypertension, chorioamnionitis vs no chorioamnionitis, vaginal vs cesarean delivery, multiple vs singleton, and for twins, sex concordant vs sex discordant and BW concordant vs BW discordant. The association of ANS with both outcomes, mortality and NDI or death, differed across the GA groups and SGA vs non-SGA. Infants born at 24, and 25 weeks' gestation had a lower mortality with exposure to ANS compared to no exposure while there was no significant difference in mortality between the two groups for those born at 22, 23, 26, 27, and 28 weeks (Figure 2A). The composite outcome of NDI or death was only lower with exposure to ANS for those born at 24 and 27 weeks (Figure 2B). The relative risks of both in-hospital mortality and the composite outcome of NDI or death were lower by 18% and 11%, respectively, among non-SGA infants with exposure to ANS. Among SGA infants, however, the risks of mortality and the composite of NDI or death were significantly increased by 40% and 62%, respectively, among infants whose mothers were exposed to ANS compared to those not exposed (aRR=1.40, 95% CI 1.02–1.93; aRR=1.62, 95% CI 1.22–2.16) (eTable 1 in the Supplement). We explored further the risk for NDI or death and found that SGA multiples also had a higher NDI risk with exposure to ANS (aRR=2.40, 95% CI 1.24–4.65) (data not shown). ANS exposure was associated with increased NDI or death among multiple-birth infants of mothers with diabetes (aRR=1.55, 95% CI 1.00–2.38) but not among infants of mothers with diabetes (aRR=0.91, 95% CI 0.83–1.01) (eTable 1). For the in-hospital mortality outcome only, higher-order multiples had a higher reduction in mortality risk than twins with exposure to ANS (aRR= 0.66, 95% CI 0.53–0.82 vs aRR=0.90, 95% CI 0.81–1.01, respectively). Subgroup analysis showed that exposure to only full ANS treatment was associated with reduced risks of hospital mortality and NDI or death compared to no exposure, while exposure to partial ANS treatment was

not associated with either outcome (eTable 1). When data collected after 2002 were analyzed by type of ANS, estimates of the main outcomes for dexamethasone vs no ANS exposure did not change but in-hospital mortality for betamethasone vs no exposure lost statistical significance (eTable 1). When we added the 435 early deaths that occurred during the first 12 hours after birth without receiving delivery room resuscitation, we observed very similar relative risks for the association of ANS with in-hospital mortality (data not shown). However, the addition of these infants resulted in a significant association of ANS on NDI or death (aRR=0.90; 95% CI 0.83–0.98), whereas previously, this result had not reached statistical significance (aRR=0.93; 95% CI 0.84–1.03).

DISCUSSION

In this large cohort of extremely preterm multiples after adjustment for several potential confounders, exposure to ANS was associated with lower in-hospital mortality and reduced, albeit non-significantly, NDI or death risk. Subgroup analyses showed that exposure to ANS was associated with lower mortality at 24 and 25 weeks' gestation. For infants born at 22, 23, 27, and 28 weeks, while the aRRs were lower with exposure to ANS, the results were not statistically significant; however, the 95% confidence intervals were wide and the power was inadequate. Only infants born at 24 and 27 weeks had lower NDI or death risk. Among SGA infants, exposure to ANS was associated with a 40% higher in-hospital mortality risk and a 62% higher NDI or death risk. Only the secondary outcome of severe IVH and/or PVL was significantly reduced with exposure to ANS.

Previous studies examining exposure to ANS and morbidities in multiples are limited. While there are no stand-alone clinical trials examining the impact of ANS in multiples, a recent meta-analysis of clinical trials with subgroup analysis in multiples reported no significant differences between multiples treated with ANS and controls for neonatal death (RR=0.79, 95% CI 0.39–1.61, two studies, 236 infants), RDS (RR=0.85, 95% CI 0.60–1.20, four studies, 320 infants), and cerebroventricular hemorrhage (RR=0.39, 95% CI 0.07–2.06, one study, 137 infants).[2] Data from observational studies in multiples have been conflicting. Three studies, with sample sizes ranging between 168 and 1038 twin infants, showed that ANS had no association with the odds of RDS.[8–10] However, in another report (n=416), premature twins treated with ANS compared to those without treatment had significantly lower odds of RDS (OR=0.49, 95% CI 0.27–0.91) and surfactant use (OR=0.58, 95% CI 0.34–0.99), while no significant differences were reported for mortality (OR=0.53, 95% CI 0.26–1.08) and severe IVH.[11] A study of 259 twin infants showed a lower incidence of RDS only among those born at 28–32 weeks' gestation.[12] Similarly, in another study with a subgroup analysis of 88 twin infants, RDS was significantly reduced among those exposed to ANS.[13]

The efficacy of ANS therapy in multiples is a controversial topic. A study comparing the pharmacokinetics of betamethasone in singleton and twin pregnancies showed a shorter half-life and a greater clearance of the drug in twin pregnancies, suggesting that the dosage used in singleton pregnancies might be inadequate to yield a therapeutic level in multiple pregnancies.[14] Another small twin study (n=18) suggested that the current regimen of ANS used in singleton pregnancies is adequate in preterm twin pregnancies as it results in similar

fetal physiologic and behavioral changes.[15] We did not find any evidence that the association between ANS and the main outcomes differed between singletons and multiples.

The higher mortality and NDI risk among SGA multiples exposed to ANS in our cohort is difficult to explain. Few studies limited to singletons have examined the association between ANS and SGA, and their results have been conflicting.[16] In one study of 1931 SGA VLBW infants born between 22 and 33 weeks in Japan, there were no significant differences in hospital morbidities and neurodevelopmental outcomes assessed at 3 years between the ANS group and the non-ANS group.[17] Similar results were found in another study of 220 SGA infants weighing 1750 g that examined only in-hospital morbidities without examining whether baseline differences in GA existed between the two groups.[18] The same study, however, found improved in-hospital outcomes among appropriate for gestational age infants exposed to ANS compared to those not exposed.[18] In a recent study of singletons and multiples born at 22 to 25 weeks using data from the NICHD NRN, Carlo et al. showed that exposure to ANS compared with no exposure was associated with a lower rate of NDI or death among non-SGA infants only; no significant results were seen among SGA infants.[19] A review of cohort studies with 1067 SGA preterm infants found no evidence that ANS affected RDS, IVH, NEC, or death.[20] However, data from a large cohort of 19,759 VLBW infants from the Vermont Oxford Network showed that ANS reduced RDS, IVH, and death in SGA infants born between 25 and 30 weeks.[21] A matched case-control study of 62 growth restricted pairs due to placental insufficiency reported higher survival without disability at 2 years' CA in the ANS group but a negative effect on physical growth at school age.[22] Growth restricted infants are known to be stressed and have high levels of endogenous steroids, which might alter their response to ANS.[23] The etiology of growth restriction in multiples is different from that in singletons, and the response to ANS might vary based on the cause of growth restriction. We did not have data on the etiology of SGA, a proxy for growth restriction, to explore this further, but future studies should reassess the benefits of ANS among SGA multiples.

Aside from SGA, higher-order multiples had a lower in-hospital mortality risk than twins only but no difference in NDI or death. Infants of mothers with diabetes had a higher NDI or death risk (aRR=1.55, 95% CI 1.00–2.38) while there was no difference for infants of mothers without diabetes. It is difficult to speculate on the reasons for this finding; maternal diabetes might impact how newborns respond to ANS. Data on the benefits of ANS among mothers with diabetes are limited as randomized controlled trials have usually excluded women with insulin-dependent or gestational diabetes.[2]

Strengths of this study are the large number of infants and the rigorous prospective data collection. Other strengths include the high follow-up rate for the assessment of neurodevelopmental outcomes (85%) and the adjustment for several maternal and neonatal variables. The inherent weaknesses of a cohort study design, however, must be acknowledged. While we adjusted for several factors, the baseline differences between the groups might indicate a number of co-interventions during and after delivery that could have resulted in better neonatal outcomes in the ANS group. We attempted to address this by doing a sensitivity analysis excluding infants who died during the first 12 hours without receiving delivery room resuscitation and showed similar outcome estimates. And while

hospitals differ in providing active treatment for infants born at 22, 23, and 24 weeks' gestation, this is less likely to impact infants born at 25 weeks' gestation,[24] a group for which we still showed lower mortality with ANS exposure. We did not have data on the timing and number of ANS doses; it is not known if and how these factors impact the ANS treatment effect.

CONCLUSIONS

Exposure to ANS among multiples was associated with lower overall mortality and lower NDI or death risk in some but not all GA groups. SGA multiples who survived had a higher mortality and NDI risk with exposure to ANS, calling for future studies to reassess the benefits of ANS in this subgroup of infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Appendix

Group Information: We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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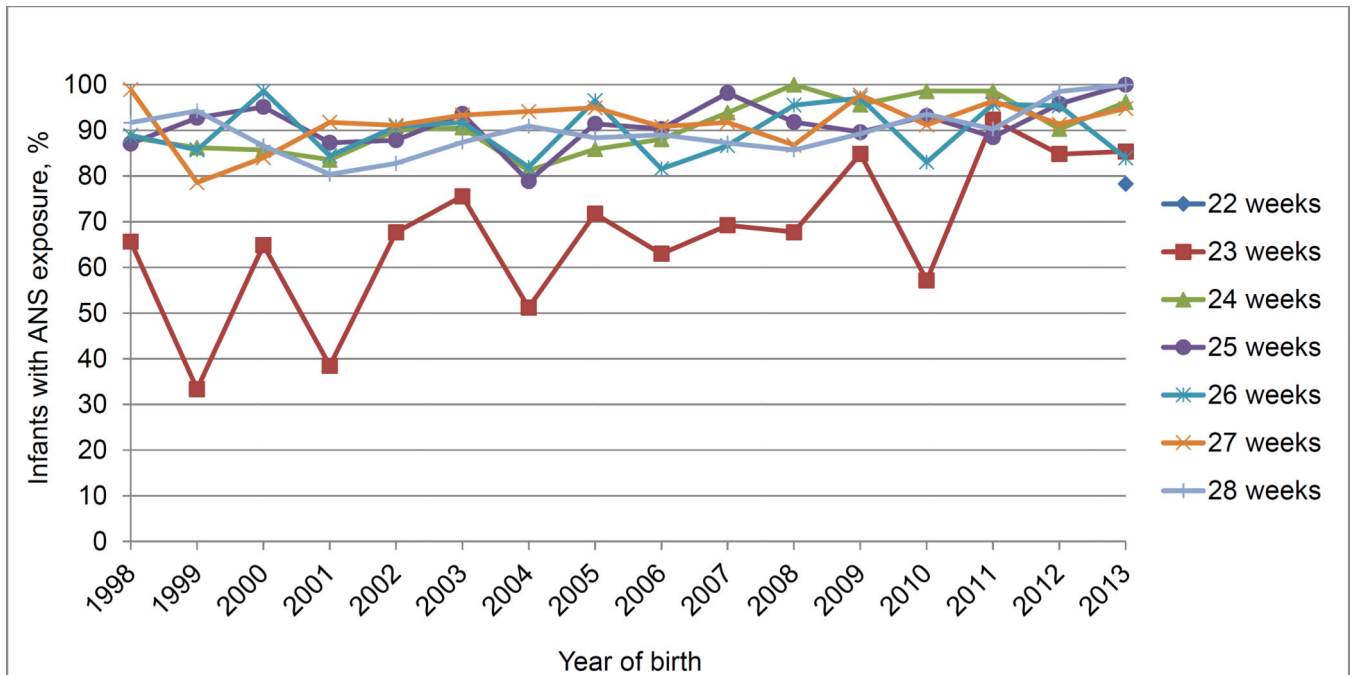
Figure 1.
Frequency of Exposure to Antenatal Corticosteroids by Gestational Age and Year of Birth Among Multiples.
Cells with fewer than 20 infants per gestational age per year of birth are not reported.
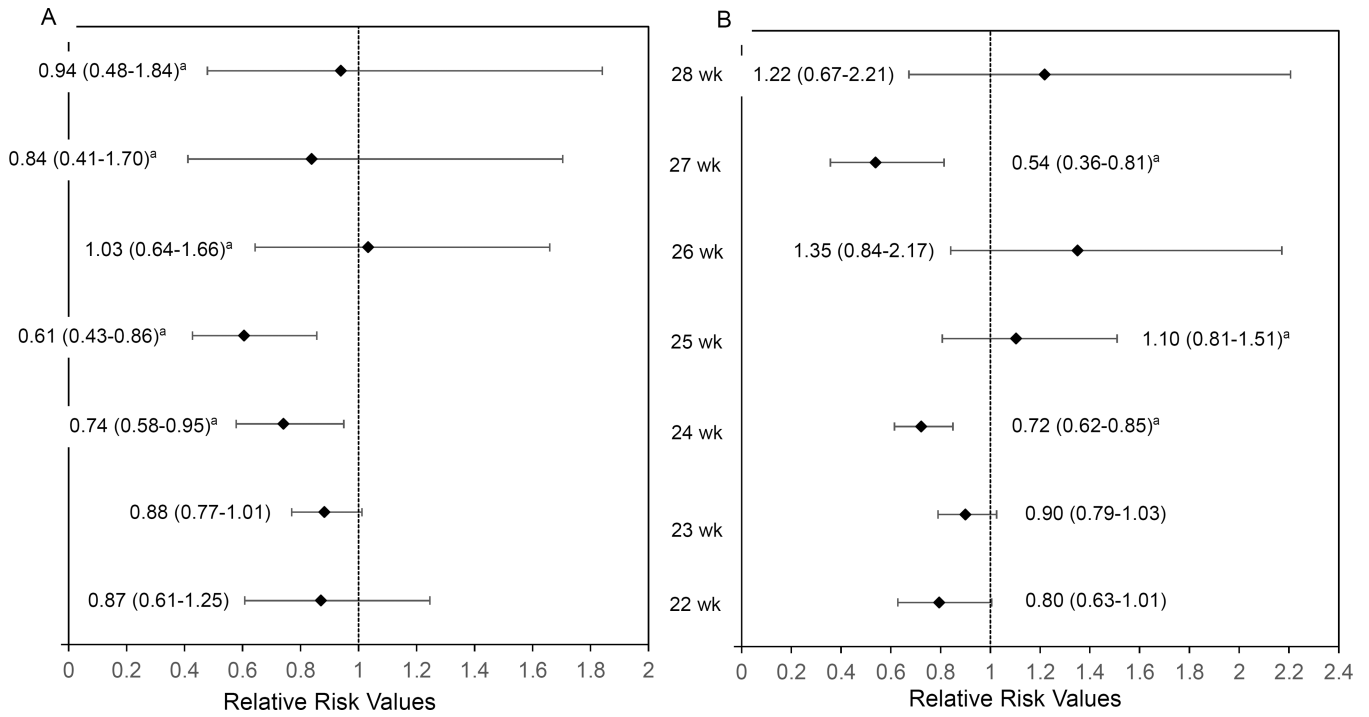
Figure 2.
A. Adjusted relative risks by gestational age at 22–28 weeks for in-hospital mortality; B. Adjusted relative risks by gestational age at 22–28 weeks for neurodevelopmental impairment (NDI) or death at 18–22 months' corrected age.

Models adjusted for center, year of birth, maternal age (19 vs. 20 years), sex, race/ethnicity (black, white, or other), marital status, diabetes, hypertension, small for gestational age, and rupture of membrane more than 24 hours. Regression for NDI or death also adjusts for epoch and maternal education.

[a]Not adjusted for center; model did not converge with center included.

The error bars indicate 95% CIs.

Table 1

Infant and maternal characteristics among multiples by exposure to ANS (N=6925)

Characteristic	No. (%)											p-value[a]
	22 wk		23 wk		24 wk		25 wk		Total 22–28 wk			
	ANS (n=68)	No ANS (n=68)	ANS (n=394)	No ANS (n=181)	ANS (n=893)	No ANS (n=93)	ANS (n=885)	No ANS (n=89)	ANS (n=6094)	No ANS (n=831)		
Infant												
BW, mean (SD), g	511 (75)	502 (60)	567 (81)	574 (87)	635 (100)	656 (113)	746 (118)	749 (145)	866 (235)	794 (251)		<0.001
SGA	2 (3%)	1 (1%)	20 (5%)	8 (4%)	67 (8%)	7 (8%)	45/883 (5%)	6 (7%)	390/6091 (6%)	50 (6%)		0.71
Male sex	33(49%)	35 (51%)	213 (54%)	94 (52%)	469 (53%)	53 (57%)	508/884 (57%)	45 (51%)	3238/6092 (53%)	420 (51%)		0.16
Twins	57 (84%)	61 (90%)	346 (88%)	144 (80%)	751 (84%)	83 (89%)	734 (83%)	82 (92%)	5034 (83%)	741 (89%)		<0.001
Higher order[b]	11 (16%)	7 (10%)	48 (12%)	37 (20%)	142 (16%)	10 (11%)	151 (17%)	7 (8%)	1060 (17%)	90 (11%)		
Apgar score 3 at 5 min	21 (31%)	30/66 (45%)	104/390 (27%)	65/175 (37%)	140 (16%)	23 (25%)	81/882 (9%)	17/88 (19%)	566 (9%)	165/820 (20%)		<0.001
Intubation	63 (93%)	45/67 (67%)	365/393 (93%)	166/180 (92%)	816/891 (92%)	90 (97%)	719 (81%)	84 (94%)	4228/6089 (69%)	665/829 (80%)		<0.001
Delivery room resuscitation	68 (100%)	67/67 (100%)	388/393 (99%)	180/180 (100%)	892/892 100%	93 (100%)	884 (100%)	89 (100%)	6045/6090 (99%)	828/829 (100%)		0.04
Surfactant use	61 (90%)	41 (60%)	360 (91%)	159 (88%)	843 (94%)	87 (94%)	811/884 (92%)	85 (96%)	5105/6081 (84%)	722 (87%)		0.03
Maternal												
Age 19 y	4 (6%)	14 (21%)	40 (10%)	12 (7%)	70 (8%)	16 (17%)	51 (6%)	16 (18%)	447 (7%)	98 (12%)		<0.001
Unmarried	27/66 (41%)	39/67 (58%)	159/393 (40%)	80/180 (44%)	347/889 (39%)	55 (59%)	316/882 (36%)	62/87 (71%)	2232/6052 (37%)	442/820 (54%)		<0.001
Race/ethnicity												<0.001
Black	23 (34%)	41 (60%)	142/392 (36%)	73/177 (41%)	284/877 (32%)	38 (41%)	281/880 (32%)	56 (63%)	1835/6039 (30%)	384/825 (47%)		
White	45 (66%)	27 (40%)	231/392 (59%)	91/177 (51%)	539/877 (61%)	55 (59%)	563/880 (64%)	32 (36%)	3868 (64%)	408 (49%)		

Characteristic	No. (%)										p-value[a]
	22 wk		23 wk		24 wk		25 wk		Total 22–28 wk		
	ANS (n=68)	No ANS (n=68)	ANS (n=394)	No ANS (n=181)	ANS (n=893)	No ANS (n=93)	ANS (n=885)	No ANS (n=89)	ANS (n=6094)	No ANS (n=831)	
Other	0 (0%)	0 (0%)	19/392 (5%)	13/177 (7%)	54/877 (6%)	0 (0%)	36/880 (4%)	1 (1%)	336 (6%)	33 (4%)	
Cesarean delivery	11 (16%)	12 (18%)	150 (38%)	63/180 (35%)	611/892 (69%)	60 (65%)	707/884 (80%)	61 (69%)	4661/6092 (77%)	492/830 (59%)	<0.001
Diabetes	0 (0%)	0/67 (0%)	7 (2%)	7 (4%)	30 (3%)	3 (3%)	26/884 (3%)	3 (3%)	246/6093 (4%)	37/830 (4%)	0.57
Hypertension	3 (4%)	4/67 (6%)	34 (9%)	21 (12%)	88 (10%)	3 (3%)	116/884 (13%)	10 (11%)	870/6091 (14%)	99/830 (12%)	0.07
Less than high school degree[c]	9/45 (20%)	3/31 (10%)	50/273 (18%)	31/105 (30%)	104/690 (15%)	26/70 (37%)	119/757 (16%)	27/65 (42%)	729/4578 (16%)	164/545 (30%)	<0.001
Income <$20,000[d]	4/7 (57%)	0/1 (0%)	13/75 (17%)	13/28 (46%)	80/345 (23%)	16/32 (50%)	129/473 (27%)	26/39 (67%)	576/2021 (29%)	109/221 (49%)	<0.001
Medicaid[c]	30/52 (58%)	35/53 (66%)	148/345 (43%)	70/129 (54%)	320/784 (41%)	50/75 (67%)	317/825 (38%)	45/77 (58%)	2169/5333 (41%)	369/664 (56%)	<0.001
Non-speaking English[e]	0/9 (0%)	0/6 (0%)	11/103 (11%)	3/27 (11%)	80/426 (19%)	2/27 (7%)	65/535 (12%)	8/46 (17%)	287/2265 (13%)	33/230 (14%)	0.47
Follow-up rate (NDI)[f]	9/9 (100%)	6/7 (86%)	102/113 (90%)	23/32 (72%)	400/464 (86%)	24/37 (65%)	508/596 (85%)	45/48 (94%)	2134/2509 (85%)	210/263 (80%)	0.03

Abbreviations: ANS, antenatal corticosteroids; BW, birth weight; GA, gestational age; NDI, neurodevelopmental impairment; SGA, small for gestational age.

[a] P-value comparing total 22–28 wk ANS vs no ANS obtained from Fisher's exact test for categorical variables and from non-parametric Wilcoxon 2-sample tests for BW and GA

[b] Higher order multiples include: 937 triplets (92% with ANS), 162 quadruplets (96% with ANS), 34 quintuplets (85% with ANS), and 17 sextuplets (100% with ANS).

[c] For infants born from 1998 to 2001, maternal education and Medicaid are only available if provided during follow-up. In 2002, both variables were collected for all infants irrespective of follow-up.

[d] For infants born from 1998 to 2011, income is only available if provided during follow-up. Income was removed entirely in 2012.

[e] Primary language of mother is only available if provided during follow-up.

[f] Follow-up rate based on non missing NDI for 2772 infants, with an overall follow-up rate of 85%. Follow-up is only given for infants born between 1998 and June 2012.

Table 2

Hospital outcomes at 22 to 28 weeks' gestation for multiples by exposure to ANS

Outcome	ANS (n=6094)	No ANS (n=831)	No. missing
Death			
No. (%)	1220/6078 (20%)	328 (39%)	16
RR (95% CI)			
Unadjusted	0.52 (0.46–0.59)		16
Adjusted[a]	0.87 (0.78–0.96)		256
RDS			
No. (%)	5767/5892 (98%)	708/722 (98%)	311
aRR (95% CI)[a]	1.00 (0.99–1.02)		523
BPD[b]			
No. (%)	2206/4947 (45%)	222/514 (43%)	1464
aRR (95% CI)[a]	1.08 (0.97–1.21)		1618
NEC			
No. (%)	549/5895 (9%)	62/723 (9%)	307
aRR (95% CI)[a]	1.30 (0.98–1.72)[c]		519
ROP			
No. (%)	2840/4875 (58%)	307/517 (59%)	1533
aRR (95% CI)[a]	1.05 (0.97–1.14)		1683
Severe ROP			
No. (%)	814/4865 (17%)	115/516 (22%)	1544
aRR (95% CI)[a]	0.96 (0.80–1.15)		1693
IVH grade 3–4 and/or PVL			
No. (%)	948/5725 (17%)	192/672 (29%)	528
aRR (95% CI)[a]	0.68 (0.58–0.78)		727
BPD[b] or death			
No. (%)	3322/6063 (55%)	536/828 (65%)	34
aRR (95% CI)[a]	1.07 (1.01–1.14)		272
NEC and/or death			
No. (%)	1512/6090 (25%)	362 (44%)	4
aRR (95% CI)[a]	0.91 (0.83–0.996)		244
ROP and/or death			
No. (%)	1992/5934 (34%)	432/824 (52%)	167
aRR (95% CI)[a]	1.04 (0.96–1.13)		398
IVH grade 3–4 and/or PVL and/or death			
No. (%)	1739/6061 (29%)	416/828 (50%)	36

Outcome	ANS (n=6094)	No ANS (n=831)	No. missing
aRR (95% CI)[a]	0.83 (0.76–0.90)		273

Abbreviations: ANS, antenatal corticosteroids; aRR, adjusted relative risk; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; RR, relative risk.

[a]Generalized estimation equation models adjusted for center, year of birth, maternal age (19 vs. 20 years), sex, race/ethnicity (black, white, or other), marital status, diabetes, hypertension, rupture of membrane more than 24 hours, gestational age, and small for gestational age. Composite outcomes include death by the age of diagnosis of morbidity (36 weeks for BPD, NEC, and IVH/PVL; discharge for severe ROP).

[b]BPD defined as supplemental oxygen at 36 weeks, or discharged/transferred on oxygen prior to 36 weeks' postmenstrual age and after 28 days of life.

[c]Not adjusted for center; model did not converge with center included.

Table 3

Outcomes by 18 to 22 months' corrected age for eligible multiples by exposure to ANS

Outcome	ANS (n=3588)	No ANS (n=575)	No. missing
Death by follow-up			
No. (%)	1076/3586 (30%)	312 (54%)	2
RR (95% CI)			
Unadjusted	0.57 (0.51–0.63)		2
Adjusted[a]	0.71 (0.60–0.84)[c]		870
NDI or death			
No. (%)	1723/3210 (54%)	392/522 (75%)	431
aRR (95% CI)[a]	0.93 (0.84–1.03)		1209
Among survivors	N=2510	N=263	
NDI			
No. (%)	647/2134 (30%)	80/210 (38%)	429
aRR (95% CI)[a]	0.97 (0.79–1.19)[c]		521
MDI <70			
No. (%)	419/1202 (35%)	56/128 (44%)	1443
aRR (95% CI)[a]	0.95 (0.76–1.20)		1481
PDI <70			
No. (%)	277/1180 (23%)	40/127 (32%)	1466
aRR (95% CI)[a]	0.76 (0.57–1.02)		1505
Bayley III cognitive score <70			
No. (%)	79/953 (8%)	9/83 (11%)	1737
aRR (95% CI)[a]	1.14 (0.52–2.51)[c]		1789
Moderate to severe cerebral palsy			
No. (%)	155/2241 (7%)	21/231 (9%)	301
aRR (95% CI)[a]	0.98 (0.59–1.64)[c]		400
Blindness[b]			
No. (%)	29/2248 (1%)	2/230 (1%)	295
aRR (95% CI)[a]	Model did not converge		
Deafness[b]			
No. (%)	59/2245 (3%)	7/229 (3%)	299
aRR (95% CI)[a]	0.69 (0.31–1.53)[c]		398

Abbreviations: ANS, antenatal corticosteroids; aRR, adjusted relative risk; MDI, mental development index; NDI, neurodevelopmental impairment; PDI, psychomotor development index; RR, relative risk.

[a]Generalized estimation equation models adjusted for center, year of birth, maternal age (19 vs. 20 years), sex, race/ethnicity (black, white, or other), marital status, diabetes, hypertension, rupture of membrane more than 24 hours, gestational age, small for gestational age, and maternal education. Model for NDI or death and model for NDI also adjust for epoch.

[b]From 1998 to 2005, blindness was defined as no functional vision (both eyes); deafness was defined as hearing impairment with aids in both ears. From 2006 to 2013, blindness was defined as no/some functional vision (both eyes); deafness was defined as hearing impairment (regardless of amplification).

[c]Not adjusted for center; model did not converge with center included.