

# Neurodevelopmental Outcomes of Triplets or Higher-Order Extremely Low Birth Weight Infants



**WHAT'S KNOWN ON THIS SUBJECT:** The incidence of cerebral palsy is higher in multiple births than in singleton infants. Twin extremely low birth weight (ELBW) infants have a higher incidence of death or neurodevelopmental impairment compared with ELBW singleton infants.



**WHAT THIS STUDY ADDS:** This study evaluates the risk of death or neurodevelopmental impairment in triplet or higher-order ELBW infants compared with twins and singleton infants. A similar study using such a large cohort of infants has not been previously performed.

## abstract

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**BACKGROUND:** Extremely low birth weight twins have a higher rate of death or neurodevelopmental impairment than singletons. Higher-order extremely low birth weight multiple births may have an even higher rate of death or neurodevelopmental impairment.

**METHODS:** Extremely low birth weight (birth weight 401–1000 g) multiple births born in participating centers of the Neonatal Research Network between 1996 and 2005 were assessed for death or neurodevelopmental impairment at 18 to 22 months' corrected age. Neurodevelopmental impairment was defined by the presence of 1 or more of the following: moderate to severe cerebral palsy; mental developmental index score or psychomotor developmental index score less than 70; severe bilateral deafness; or blindness. Infants who died within 12 hours of birth were excluded. Maternal and infant demographic and clinical variables were compared among singleton, twin, and triplet or higher-order infants. Logistic regression analysis was performed to establish the association between singletons, twins, and triplet or higher-order multiples and death or neurodevelopmental impairment, controlling for confounding variables that may affect death or neurodevelopmental impairment.

**RESULTS:** Our cohort consisted of 8296 singleton, 2164 twin, and 521 triplet or higher-order infants. The risk of death or neurodevelopmental impairment was increased in triplets or higher-order multiples when compared with singletons (adjusted odds ratio: 1.7 [95% confidence interval: 1.29–2.24]), and there was a trend toward an increased risk when compared with twins (adjusted odds ratio: 1.27 [95% confidence: 0.95–1.71]).

**CONCLUSIONS:** Triplet or higher-order births are associated with an increased risk of death or neurodevelopmental impairment at 18 to 22 months' corrected age when compared with extremely low birth weight singleton infants, and there was a trend toward an increased risk when compared with twins. *Pediatrics* 2011;127:e654–e660

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### KEY WORDS

extremely low birth weight, triplets, neurodevelopmental outcomes

### ABBREVIATIONS

ELBW—extremely low birth weight  
NDI—neurodevelopmental impairment

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There has been an exponential increase in the number of multiple births in United States over the past 2 decades.<sup>1</sup> This increase is attributed largely to artificial reproductive technology and fertility-inducing drugs.<sup>1</sup> The percentage increase in triplet and higher-order births (>400%) has been more dramatic compared with the increase in the percentage of twin deliveries.<sup>1</sup> Many of these multiple pregnancies result in premature births and a consequent increase in the number of infants born with very low birth weight<sup>2,3</sup> with triplets and higher-order multiples reported to be 30 times more likely to be born with very low birth weights compared with singletons.<sup>1</sup> Previous data regarding survival and morbidities in extremely low birth weight (ELBW) multiple births have been scarce and conflicting. Although some studies<sup>4</sup> have shown that higher-order multiples are associated with a higher mortality rate compared with twins, others<sup>5</sup> have shown that the survival rate is better. We have previously shown that ELBW twins have a higher risk of death or neurodevelopmental handicap compared with singletons in the same birth-weight category.<sup>6</sup> The objective of the current study was to evaluate the comparative risk of death or neurodevelopmental handicap in higher-order multiples (triplets or higher order) compared with twins and singletons. The primary outcome of interest was death or neurodevelopmental impairment (NDI) at 18 to 22 months of age. Death was included in the primary outcome because it is a competing variable for NDI.

## METHODS

This is a retrospective cohort study of ELBW infants (birth weight between 401 g and 1000 g) admitted to 1 of 19 NICUs in the Eunice Kennedy Shriver National Institute of Child Health & Human Development Neonatal Research Network during calendar years 1996–

2005. Infants ( $n = 17\,429$ ) were categorized into 3 groups: singletons; twins; and triplets or higher-order multiple births. Infants who were outborn, those who died within 12 hours of birth, and those with missing or incomplete survival or follow-up information were excluded.

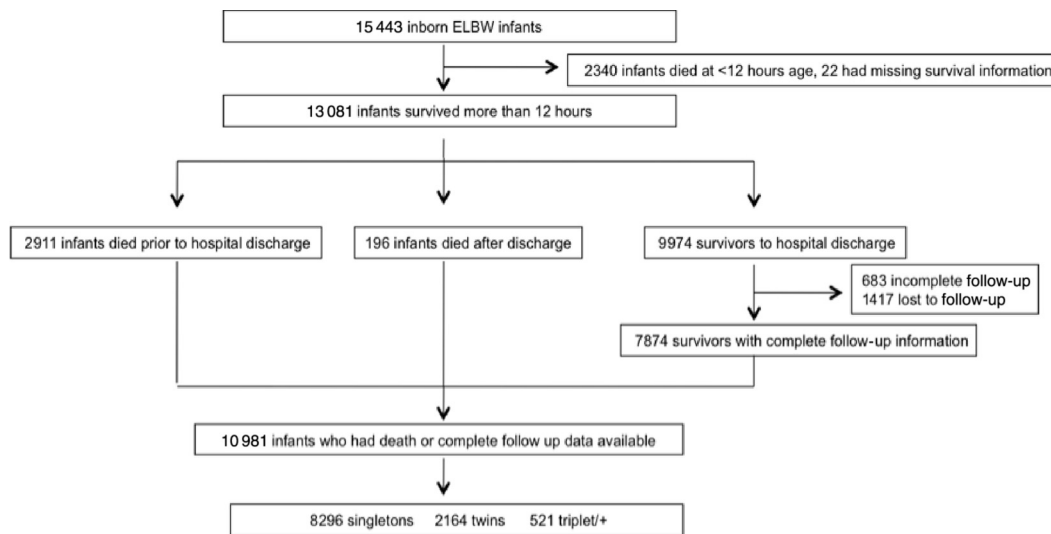
Prospectively collected data in the Neonatal Research Network Generic Database include maternal and neonatal information, treatment, and clinical outcomes. This study used retrospective analysis of this prospectively collected Generic Database data. All centers participating in the Neonatal Research Network received local institutional review board approval for data collection. Trained research coordinators obtained the data based on the specific definitions listed in the manual of operations.

At 18 to 22 months' corrected age, the study infants were seen in each center's follow-up clinic. Evaluation at the time of the follow-up visit consisted of the following evaluations: neurologic; hearing; vision; and development. The neurologic examination administered was based on the Amiel-Tison assessment.<sup>7</sup> The assessment was performed by certified examiners and included an evaluation of tone, strength, reflexes, angles, and posture. Cerebral palsy was defined as a nonprogressive central nervous system disorder characterized by abnormal muscle tone in at least 1 extremity and abnormal control of movement and posture. Hearing status was obtained by parental history, and deafness was confirmed by audiologic testing. Deafness was defined as the need for bilateral amplification. A history of eye examinations and procedures since initial discharge was obtained, and a standard eye examination was completed. Blindness was defined as bilateral corrected vision of less than 20/200. The Bayley Scales of Infant Development—II was adminis-

tered, and a mental developmental index and psychomotor developmental index were derived. Scores of  $100 \pm 15$  represent the means  $\pm 1$  SD, with a score less than 70 ( $\geq 2$  SDs below the mean) indicating significant delay. For statistical purposes, children who could not be assessed because of severe developmental delay were assigned mental developmental index and psychomotor developmental index scores of 49.

The primary outcome was death or NDI at 18 to 22 months' corrected age. NDI was defined as the presence of any 1 of the following: cerebral palsy; bilateral blindness; bilateral hearing loss needing amplification; a Bayley Mental Developmental Index score less than 70; or a Bayley Psychomotor Developmental Index less than 70. Death occurring after 12 hours of age and before the follow-up assessment was included in our composite primary-outcome measure because it is a competing outcome for NDI in this high-risk ELBW population.

Unadjusted associations between the birth categories and maternal and neonatal characteristics, treatment, and clinical outcomes were assessed by contrasting pairs of birth categories (twins versus singletons, triplets or higher-order multiples versus singletons, and triplets or higher-order multiples versus twins) and testing for statistically significant differences using  $\chi^2$  tests for categorical variables and  $t$  statistics for continuous variables. The relationship between birth category and the primary outcome (NDI or death), adjusting for other variables, was explored in a logistic regression model, and the results were expressed as adjusted odds ratios and 95% confidence intervals. The relationship between birth category and NDI among survivors was similarly explored in an additional logistic regression model. Along with birth category,



**FIGURE 1**  
Study population.

the variables included in the models were those that had been shown to affect the outcome of NDI or death (excluding morbidities that lie in the causal pathway) or which were imbalanced across the birth categories. In addition, center also was included in the logistic regression model (results not shown). All analyses were done at the Neonatal Research Network's data center, Research Triangle Institute International, using SUDAAN software<sup>9</sup> and took into account the cluster-correlated nature of the data collected on infants from multiple births.

## RESULTS

The study population consisted of 10 981 infants (8296 singletons, 2164 twins, and 521 triplets or higher-order multiples) with complete survival and follow-up data (Fig 1). Of 9974 survivors available for follow-up, 7874 (79%) had complete follow-up data. Mothers of twins and triplets or higher-order multiples were more likely to be older, married, and of white race compared with mothers of singleton ELBW infants (Table 1). They were more likely to have a higher education (more than a high school diploma). They also were more likely to have re-

ceived prenatal care (defined as 1 or more antenatal visit) and prenatal steroids (defined as at least 1 dose). They were, however, less likely to have Medicaid insurance or to have preeclampsia or hypertension compared with mothers of singleton infants.

Infants in all birth categories were of similar birth weight and gestation (Table 2). There were no other consistently significant differences in infant characteristics among infants in the 3 groups, except that infants in the twin and triplet or higher-order multiple categories were more likely to have

1-minute and 5-minute Apgar scores of less than 3 and receive at least 1 dose of surfactant.

Twins had a higher rate of severe intraventricular hemorrhage and bronchopulmonary dysplasia compared with singleton and triplet or higher-order multiple-birth infants, whereas the rates of these morbidities between singleton and triplet or higher-order multiple-birth infants was similar. The incidence of necrotizing enterocolitis was higher in triplet or higher-order multiple-birth

**TABLE 1** Maternal Characteristics

Characteristics	Singletons, <i>n</i> = 8296	Twins, <i>n</i> = 2164	Triplets or Higher-Order Births, <i>n</i> = 521
Maternal age, means ± SD, y	26.7 ± 6.7	27.6 ± 6.6 <sup>a</sup>	30.3 ± 5.3 <sup>a</sup>
Maternal race, <i>n</i> (%)			
Black	3951 (47.7)	835 (38.6) <sup>a</sup>	74 (14.2) <sup>a</sup>
White	4043 (48.8)	1240 (57.4) <sup>a</sup>	435 (83.7) <sup>a</sup>
Other	298 (3.6)	87 (4.0) <sup>a</sup>	11 (2.1) <sup>a</sup>
Married, <i>n</i> (%)	3504 (42.5)	1152 (53.3) <sup>a</sup>	447 (85.8) <sup>a</sup>
Medicaid insurance, <i>n</i> (%) <sup>b</sup>	3612 (69)	731 (58.0) <sup>a</sup>	78 (25.0) <sup>a</sup>
Prenatal care, <i>n</i> (%)	7752 (93.5)	2077 (96.0) <sup>a</sup>	520 (99.8) <sup>a</sup>
Prenatal steroids, <i>n</i> (%)	6748 (81.4)	1819 (84.1) <sup>a</sup>	477 (91.6) <sup>a</sup>
Preeclampsia or hypertension, <i>n</i> (%)	2533 (30.6)	299 (13.8) <sup>a</sup>	77 (14.8) <sup>a</sup>
Maternal antibiotics, <i>n</i> (%)	5630 (68.0)	1562 (72.3) <sup>a</sup>	382 (73.3)
Maternal education less than high school, <i>n</i> (%)	1664 (27.5)	298 (20.9) <sup>a</sup>	38 (10.0)

<sup>a</sup> *P* < .05 versus singletons.

<sup>b</sup> Denominator: 5271 singletons, 1252 twins, and 314 triplets or higher-order births, who were discharged alive, followed-up, and had insurance information available.

**TABLE 2** Infant Characteristics

Characteristics	Singletons, <i>n</i> = 8296	Twins, <i>n</i> = 2164	Triplets or Higher-Order Births, <i>n</i> = 521
Gestational age, means ± SD, wk	26.0 ± 2.1	25.8 ± 2.1	25.9 ± 2.0
Birth weight, means ± SD, g	757 ± 147	748 ± 151	759 ± 154
Male, <i>n</i> (%)	4045 (48.8)	1135 (52.5) <sup>a</sup>	254 (48.8)
1-minute Apgar score <3, <i>n</i> (%)	2368 (28.6)	550 (25.5) <sup>a</sup>	92 (17.7) <sup>a</sup>
5-minute Apgar score <3, <i>n</i> (%)	447 (5.4)	93 (4.3) <sup>a</sup>	15 (2.9%) <sup>a</sup>
Days on ventilator, means ± SD	24.4 ± 26.0	23.7 ± 25.2	21.5 ± 25.1 <sup>a</sup>
Surfactant, <i>n</i> (%)	6695 (80.9)	1861 (86.2) <sup>a</sup>	458 (88.3) <sup>a</sup>
Patent ductus arteriosus, <i>n</i> (%)	3678 (44.4)	1070 (49.5) <sup>a</sup>	259 (49.7)
Patent ductus arteriosus, surgery, <i>n</i> (%)	986 (26.8)	289 (27.0)	90 (34.8) <sup>a</sup>
Days on total parenteral nutrition, <i>n</i> (%)	30.1 ± 23.2	29.7 ± 23.9	29.1 ± 23.5
Postnatal steroids, <i>n</i> (%)	2255 (27.3)	548 (25.3)	150 (28.8)

<sup>a</sup> *P* < .05 vs. singletons.

infants when compared with singleton and twin infants (Table 3).

Twin ELBW infants had a higher rate of death or NDI compared with singleton ELBW infants. Triplet or higher infants, however, did not show a higher rate of death or NDI when compared with singleton infants on unadjusted analysis. NDI among survivors was similarly higher in twins but not triplets or higher-order multiple-birth infants compared with singleton ELBW infants (Table 3). When the individual compo-

nents of NDI were evaluated, twin ELBW infants had a higher incidence of having a mental developmental index of less than 70, a psychomotor developmental index of less than 70, and cerebral palsy compared with singletons (Table 4). Triplet or higher infants, however, did not show similar trends for these individual components of NDI.

Logistic regression analysis performed for the primary outcome of death or NDI (Fig 2) showed a higher risk of death or NDI in triplet or higher-

order multiple-birth infants compared with singleton-gestation infants (adjusted odds ratio: 1.70 [95% confidence interval: 1.29–2.24]). When compared with twins, a similar trend of higher death or NDI was observed for triplets or higher-order multiple births (adjusted odds ratio: 1.27 [95% confidence interval: 0.95–1.71]). Other factors associated with increased risk of death or NDI were male gender, Apgar scores less than 3 at 1 and 5 minutes, postnatal steroids, diagnosis of patent ductus arteriosus, and bronchopulmonary dysplasia. Higher birth weight, maternal married status, white race, maternal preeclampsia, prenatal care, and prenatal steroids were, however, associated with a lower risk of death or NDI on logistic regression analysis.

Logistic regression analysis performed for NDI among survivors (Fig 3) showed an increased risk in triplets or higher-order multiple-birth infants compared with singleton-gestation infants (adjusted odds ratio: 1.86 [95% confidence interval: 1.40–2.47]) and

**TABLE 3** Short-Term and 18- to 22-Months Outcomes by Univariate Analysis

Outcome	Singletons, <i>n</i> = 8296	Twins, <i>n</i> = 2164	Triplets or Higher-Order Births, <i>n</i> = 521	<i>P</i> , Twins vs Singletons	<i>P</i> , Triplets or Higher-Order Births vs Singletons	<i>P</i> , Triplets or Higher-Order Births vs Twins
Severe intraventricular hemorrhage, <i>n</i> (%)	1361 (17.0)	415 (20.4)	79 (16.0)	.0016	.61	.048
Bronchopulmonary dysplasia, <i>n</i> (%) <sup>a</sup>	3002 (47.9)	756 (50.9)	165 (44.0)	.05	.21	.038
Late-onset sepsis, <i>n</i> (%)	3042 (38.8)	782 (40.2)	183 (39.5)	.27	.77	.80
Necrotizing enterocolitis, <i>n</i> (%)	933 (11.3)	252 (11.7)	35 (6.7)	.61	.0002	.0003
Death before discharge, <i>n</i> (%)	2080 (25.1)	694 (32.1)	137 (26.3)	<.0001	.64	.043
Death or NDI, <i>n</i> (%)	4418 (53.3)	1324 (61.2)	289 (55.5)	<.0001	.44	.064
NDI, <i>n</i> (%) <sup>b</sup>	2190 (36.1)	585 (41.1)	149 (39.1)	.0018	.3341	.57

<sup>a</sup> Defined as supplementary oxygen at 36 weeks (yes or no) for survivors to 36 weeks.

<sup>b</sup> Denominator: surviving infants with complete follow-up data (singletons, *n* = 6068; twins, *n* = 1425; triplets or higher order, *n* = 381).

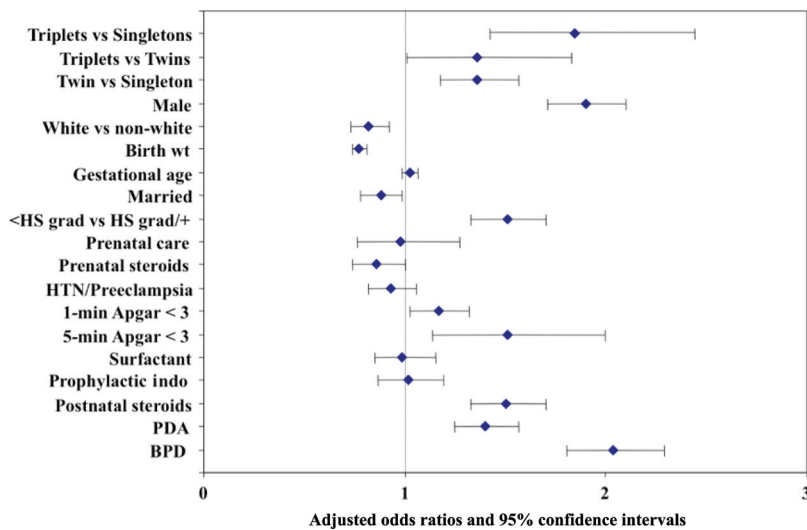
**TABLE 4** NDI Components

Outcome	Singletons, <i>n</i> = 6068	Twins, <i>n</i> = 1425	Triplets or Higher-Order Births, <i>n</i> = 381	<i>P</i> , Twins vs Singletons	<i>P</i> , Triplets or Higher-Order Births vs Singletons	<i>P</i> , Triplets or Higher-Order Births vs Twins
Mental developmental index <70, <i>n</i> (%)	1816 (30.3)	496 (35.2)	118 (31.6)	.0015 <sup>a</sup>	.64	.28
Psychomotor developmental index <70, <i>n</i> (%)	1226 (20.5)	336 (24.0)	83 (22.6)	.0090 <sup>a</sup>	.38	.61
Cerebral palsy, <i>n</i> (%)	298 (5.0)	97 (6.9)	21 (5.6)	.0143 <sup>a</sup>	.61	.34
Blindness, <i>n</i> (%)	100 (1.7)	31 (2.2)	10 (2.6)	.25	.29	.65
Deafness, <i>n</i> (%)	106 (1.8)	31 (2.2)	9 (2.4)	.34	.44	.83

The total *n* for the NDI components is 7874. It includes all those who had a complete follow-up examination and who had either a yes or no response to the assignment of NDI.

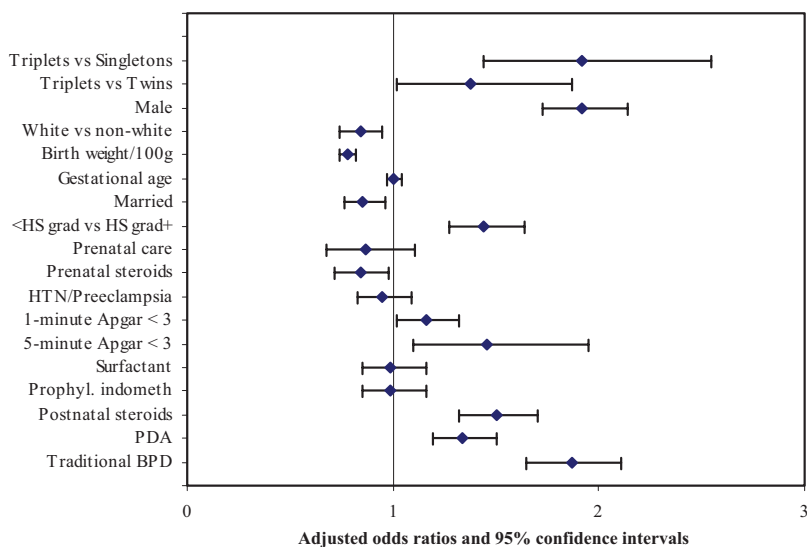
<sup>a</sup> *P* < .05.





**FIGURE 2**

Results of logistic regression: death or NDI. Factors in the regression analysis included the ones known to be associated with death or NDI and the ones that were significantly different on univariate analysis. Birth weight represents each 100-g increase in birth weight. PDA indicates patent ductus arteriosus.



**FIGURE 3**

Results of logistic regression: NDI among survivors with follow-up. Factors in the regression analysis included the ones known to be associated with death or NDI and the ones that were significantly different on univariate analysis. Birth weight represents each 100-g increase in birth weight. PDA indicates patent ductus arteriosus.

twins (adjusted odds ratio: 1.36 [95% confidence interval: 1.00–1.85]). Risk of death or NDI and NDI among survivors was increased in twins compared with singleton-gestation infants (data not shown).

## DISCUSSION

In this retrospective cohort analysis of ELBW infants, we showed that the risk of

death or NDI in triplet or higher-order multiples is higher compared with both twins and singletons. We also showed that the risk of neurodevelopmental handicap among survivors was similarly higher. To our knowledge, this is the first report of a large cohort of ELBW multiples evaluating their outcomes at 18 to 22 months' corrected age.

Previous population-based studies of very low birth weight infants have shown varying results. Shinwell et al<sup>4</sup> analyzed a large Israeli very low birth weight registry and showed that triplets have a higher death rate compared with twins and singleton-gestation infants, after controlling for several confounding variables. They also showed a higher risk of respiratory distress syndrome in both twins and triplets compared with singletons. However, they did not show any difference in chronic lung disease or adverse neurologic findings. Adverse neurologic findings were defined as short-term outcomes of intracranial hemorrhage, periventricular leukomalacia, and posthemorrhagic hydrocephalus instead of the longer-term outcomes that we analyzed in our study. Ziadeh et al<sup>9</sup> compared short-term outcomes of triplet pregnancies with twin pregnancies and showed a higher mortality rate in triplets. They did not show any difference in any other short-term outcomes evaluated. This study included more mature infants, however, with a mean birth weight of 1600 g in triplets and 2320 g in twins. Other studies<sup>10–15</sup> have evaluated outcomes of triplet or higher-gestation infants in comparison to twins, but they had small sample sizes and none of them had evaluated ELBW infants exclusively. Russell et al,<sup>5</sup> using National Center for Health Statistics data, showed that the mortality rate for very low birth weight and moderately low birth weight multiple-gestation infants was lower than for singletons in similar birth-weight categories. However, they did not evaluate ELBW infants separately. Kaufman et al<sup>16</sup> reported experience with outcomes of multiple births from a single center. They did not show any differences in outcomes of triplets compared with twins and singletons, except for a higher incidence of retinopathy of prematurity in triplets.

Their study cohort, however, was smaller than the current study, and the infants were more mature and of a higher birth weight. Sutcliffe et al<sup>17</sup> found a higher risk of cerebral palsy and speech and language delays in multiple-birth infants compared with singletons, but their study was not restricted to ELBW infants. Similarly, Petterson et al<sup>18</sup> showed a 47-fold-higher risk of cerebral palsy after triplet births compared with singleton infants, when using a population-based sample from western Australia that included infants of all birth-weight categories. They proposed that most of this increased risk of cerebral palsy was attributed to the tendency of multiple pregnancies to result in very low birth weight. Unlike our study, this study did not evaluate ELBW infants exclusively and did not control for factors other than multiple gestation that may impact neurodevelopmental outcomes in these infants.

In our study, we found that higher-order ELBW multiple births were more likely to be born to women who were older, of white race, and had private insurance. Mothers of these infants also were more likely to have received prenatal care and prenatal steroids. Others also have shown similar trends of higher maternal age and greater use of prenatal care and prenatal steroids in mothers with multiple pregnancies compared with singleton pregnancies.<sup>5</sup> The reasons for these differences are not clear and may be related to multiple factors, including a

higher use of artificial reproductive technologies in the triplet or higher-order multiple-birth population.

Mothers of multiples were less likely to have preeclampsia or hypertension. This may be related to hypertension or preeclampsia being the reason for an indicated extreme preterm delivery in singleton infants. Both twins and triplets or higher were more likely to receive surfactant compared with singleton ELBW infants. This finding is in agreement with the findings of Shinwell et al,<sup>4</sup> who showed a higher incidence of respiratory distress syndrome in multiple-gestation infants despite a higher exposure to prenatal steroids in that group.

The follow-up rate of infants who were eligible for follow-up was 79% (Fig 1). The percentage of infants lost to follow-up or with incomplete follow-up was similar in the 3 categories (data not shown). We also contrasted the short-term in-hospital outcomes of infants with follow-up with those with missing or incomplete follow-up. Infants with follow-up had a higher rate of severe intraventricular hemorrhage, late-onset sepsis, and necrotizing enterocolitis compared with infants who were either lost to follow-up or had incomplete follow-up. The bronchopulmonary dysplasia rates in the 2 groups were similar (data not shown).

Our study had several limitations. We did not have data on the use of artificial reproductive technology. It is likely that the rate of use of artificial

reproductive technology was significantly different in the groups. Some studies<sup>19,20</sup> have shown outcomes to be worse in infants conceived with artificial reproductive technology compared with spontaneously conceived multiple births, whereas others<sup>21,22</sup> have shown the opposite to be true. This may have had an influence on outcomes of these infants. We similarly did not have the data on the birth order of these infants, which has been proposed by some to have an influence on outcomes in multiple births.<sup>23</sup> We also did not have data on zygosity of the multiple birth infants, which has been proposed to have an effect on outcomes.<sup>10,20,24</sup>

The strengths of the study are the large cohort of ELBW patients and the availability of follow-up data at 18 to 22 months of age. Although ~21% of the eligible infants had either missing or incomplete follow-up data, the percentage of infants with missing or incomplete data were similar in the 3 categories.

## CONCLUSIONS

This retrospective cohort study shows that triplet or higher-order births are associated with an increased risk of death or NDI at 18 to 22 months' corrected age when compared with ELBW singleton infants. Although statistically not significant, ELBW triplets or higher-order multiples showed a trend toward increased risk of death or NDI when compared with twins.

## REFERENCES

- Martin JA, Park MM. Trends in twin and triplet births: 1980–97. *Natl Vital Stat Rep*. 1999;47(24):1–16
- Warner BB, Kiely JL, Donovan EF. Multiple births and outcome. *Clin Perinatol*. 2000; 27(2):347–361, ix
- Alexander GR, Kogan M, Martin J, Papiernik E. What are the fetal growth patterns of singletons, twins, and triplets in the United States? *Clin Obstet Gynecol*. 1998;41(1): 114–125
- Shinwell ES, Blickstein I, Luskay A, Reichman B. Excess risk of mortality in very low birth-weight triplets: a national, population based study. *Arch Dis Child Fetal Neonatal Ed*. 2003;88(1):F36–F40
- Russell RB, Petrini JR, Damus K, Mattison DR, Schwarz RH. The changing epidemiology of multiple births in the United States. *Obstet Gynecol*. 2003;101(1):129–135
- Wadhawan R, Oh W, Perritt RL, et al. Twin gestation and neurodevelopmental outcome in extremely low birth weight infants. *Pediatrics*. 2009;123(2). Available at: [www.pediatrics.org/cgi/content/full/123/2/e220](http://www.pediatrics.org/cgi/content/full/123/2/e220)
- Amiel-Tison C. A method for neurologic eval-

- uation within the first year of life. *Curr Probl Pediatr*. 1976;7(1):1–50
8. SUDAAN Software [computer program]. Release 10.0. Research Triangle Park, NC: Research Triangle Institute International; 2008
  9. Ziadeh SM. The outcome of triplet versus twin pregnancies. *Gynecol Obstet Invest*. 2000;50(2):96–99
  10. Fitzsimmons BP, Bebbington MW, Fluker MR. Perinatal and neonatal outcomes in multiple gestations: assisted reproduction versus spontaneous conception. *Am J Obstet Gynecol*. 1998;179(5):1162–1167
  11. Gonen R, Heyman E, Asztalos EV, et al. The outcome of triplet, quadruplet, and quintuplet pregnancies managed in a perinatal unit: obstetric, neonatal, and follow-up data. *Am J Obstet Gynecol*. 1990;162(2):454–459
  12. Seoud MA, Toner JP, Kruithoff C, Muasher SJ. Outcome of twin, triplet, and quadruplet in vitro fertilization pregnancies: the Norfolk experience. *Fertil Steril*. 1992;57(4):825–834
  13. Sassoon DA, Castro LC, Davis JL, Hobel CJ. Perinatal outcome in triplet versus twin gestations. *Obstet Gynecol*. 1990;75(5):817–820
  14. Albrecht JL, Tomich PG. The maternal and neonatal outcome of triplet gestations. *Am J Obstet Gynecol*. 1996;174(5):1551–1556
  15. Weissman A, Talmon R, Jakobi P. The outcome of abdominally delivered triplets and twins: a matched case-control study. *Eur J Obstet Gynecol Reprod Biol*. 1998;79(2):123–125
  16. Kaufman GE, Malone FD, Harvey-Wilkes KB, Chelmow D, Penzias AS, D'Alton ME. Neonatal morbidity and mortality associated with triplet pregnancy. *Obstet Gynecol*. 1998;91(3):342–348
  17. Sutcliffe AG, Derom C. Follow-up of twins: Health, behaviour, speech, language outcomes and implications for parents. *Early Hum Dev*. 2006;82(6):379–386
  18. Petterson B, Nelson KB, Watson L, Stanley F. Twins, triplets, and cerebral palsy in births in Western Australia in the 1980s. *BMJ*. 1993;307(6914):1239–1243
  19. Saygan-Karamursel B, Teksam O, Aksu T, Yurdakok M, Onderoglu L. Perinatal outcomes of spontaneous twins compared with twins conceived through intracytoplasmic sperm injection. *J Perinat Med*. 2006;34(2):132–138
  20. Bower C, Hansen M. Assisted reproductive technologies and birth outcomes: overview of recent systematic reviews. *Reprod Fertil Dev*. 2005;17(3):329–333
  21. Minakami H, Sayama M, Honma Y, et al. Lower risks of adverse outcome in twins conceived by artificial reproductive techniques compared with spontaneously conceived twins. *Hum Reprod*. 1998;13(7):2005–2008
  22. Zaib-un-Nisa S, Ghazal-Aswad S, Badrinath P. Outcome of twin pregnancies after assisted reproductive techniques: a comparative study. *Eur J Obstet Gynecol Reprod Biol*. 2003;109(1):51–54
  23. el-Jallad MF, Abu-Heijja AT, Ziadeh S, Obeidat A. Is the second-born twin at high risk? *Clin Exp Obstet Gynecol*. 1997;24(4):226–227
  24. Hall JG. Twinning. *Lancet*. 2003;362(9385):735–743

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