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ORIGINAL ARTICLE

Long-term outcomes of twins based on gestational age at delivery

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ABSTRACT

Objective: Prematurity is associated with adverse outcomes. However, there are less data regarding long-term outcomes of twins based on gestational age at delivery. Our objective was to identify the association between gestational age at delivery and long-term outcomes in twins.

Study design: All patients with a twin pregnancy ≥24 weeks delivered by a single Maternal Fetal Medicine practice from 2005 to 2014 were surveyed regarding pediatric outcomes at or after 2 years of life. We excluded twins with aneuploidy or major fetal anomalies. The survey was mail-based, with phone follow-up for nonresponses or for clarification. Using logistic regression analysis, we compared long-term outcomes between twins born in four gestational age groups: 24 to 27–6/7 weeks, 28 to 31–6/7 weeks, 32 to 35–6/7 weeks, and 36 weeks or later.

Results: Six hundred fifty-three twin deliveries met inclusion criteria and 425 (65.1%) mothers responded. Mean age at the time of survey completion was 6.0 ± 2.4 years. Earlier gestational age was significantly associated with neonatal death (14, 2, 0, and 0% in the four groups, respectively, $p < .001$). Prematurity was associated with a composite of major adverse outcomes (death; cerebral palsy; necrotizing enterocolitis; chronic renal, heart, or lung disease) (14, 7, 4, and 2% in the four groups, $p = .036$), as well as minor adverse outcomes (learning disability; need for speech, occupational, or physical therapy) (83, 69, 54, and 38%, $p < .001$).

Conclusions: Long-term morbidity in twin pregnancies is inversely related to gestational age at delivery. However, for twins born after 28 weeks, neonatal death and severe long-term morbidity are rare.

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Introduction

Complications arising from prematurity are the leading cause of morbidity and mortality in twin pregnancies. Among twin pregnancies, 59% deliver prior to 37 weeks and 11% prior to 32 weeks [1]. Extreme prematurity, defined as birth at or before 28 weeks of gestation, has been associated with the highest rate of infant mortality and severe impairment [2,3]. All preterm infants are at an increased risk of major and minor morbidities, both in the short and long term [4].

Published data indicate that gestational age at delivery is predictive of long-term outcomes. A large cohort study undertaken in 2004 demonstrated an association between infection in the neonatal period of premature and low-birth weight infants and adverse neurodevelopmental outcomes at 18–22 months and found higher rates of cerebral palsy, and lower scores on the Bayley Scales of Infant Development [5]. Another study serially assessed preterm infants until 18 months utilizing established developmental milestones, and found delay of visual and social skills [6]. A separate study completed in 2014, utilizing a secondary analysis of a large-scale longitudinal study of infants born in the United Kingdom, assessed long-term disease burden on infants born between 32 and 37 weeks' gestation as compared with infants born after 37 weeks. The study assessed growth, hospital admissions, asthma, use of prescription drugs, and parental rating of their children's health. Outcomes measured at 3 and 5 years of age demonstrated a dose response relationship between increasing level of prematurity and poor outcomes [7]. However, each of the above studies was predominantly focused on singleton births, and systematic reviews demonstrate that the impact of gestational age on outcomes may diminish over time [8]. It is not clear that data from singleton births can be directly extrapolated to twins, nor that the effects measured by standardized prospective

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studies well represent the clinical outcomes of middle childhood prioritized by families. There are few studies of twins specifically that correlate long-term outcomes to gestational age at delivery groupings, which would be useful in counseling patients around the time of delivery. To address these gaps in understanding critical to effective family counseling of twin pregnancies, we sought to specifically assess long-term outcomes of twins that are clinically meaningful to parents.

The objective of this study was to quantify associations between gestational age at delivery and long-term health outcomes valued by parents, specifically for twins.

Materials and methods

Institutional Review Board approval was obtained from Biomedical Research Alliance of New York Institutional Review Board. We conducted a survey of all patients with twin pregnancies delivered by a single Maternal Fetal Medicine practice between June 2005 and March 2014. Mail-based surveys were sent to the mothers of these twins in April 2016. Births after March 2014 were excluded to ensure that children would be as least 2 years old at the time of the survey. If clarification of answers was needed, responders were contacted via phone or email. Nonresponses were followed up via phone or email as well, and patients who declined to participate were not contacted again. The survey questions were intended to be easily answerable by parents, and were designed to address outcomes clinically relevant to parents considering long-term outcomes of twins (Figure 1).

For this analysis, we included all live births delivered at 24-0/7 weeks of gestation or greater, which enabled us to analyze whether there was a dose-response relationship between long-term outcomes and increasing prematurity. We excluded pregnancies that resulted in intrauterine fetal demise of either twin, and twin pregnancies with major fetal anomalies or genetic abnormalities discovered before or after birth.

There were two primary outcomes for this study: a composite of major adverse outcomes (death; cerebral palsy; necrotizing enterocolitis; chronic renal, heart, or lung disease), and a composite of minor adverse outcomes (learning disability; need for speech, occupational, or physical therapy). We also analyzed each individual outcome on the survey. For the outcomes related to when each infant began crawling, walking, and speaking, we adjusted the results for prematurity up to 2 years of life. For example, if a child began walking at 18 months, but was born at 32 weeks (8 weeks, or 2 months, early), we adjusted the result by 2 months.

STUDY SURVEY

Your Name: _____

Date of twin delivery: _____

Date of survey (today's date): _____

Please fill out as much information as you can.

**NOTE: ALL AGES REFER TO YOUR CHILD'S AGE FROM HIS/HER ACTUAL DATE OF BIRTH (NOT THE ADJUSTED AGE FROM THE ORIGINAL DUE DATE)

	Twin A (older twin)	Twin B (younger twin)
Birth weight		
Gender	Male / Female	Male / Female
Was your baby in the NICU? If yes, for how many days?	Yes / No	Yes / No
Has your child ever been diagnosed with or treated for:		
Colic	Yes / No	Yes / No
Asthma / Reactive airways	Yes / No	Yes / No
Any other chronic lung disease	Yes / No	Yes / No
Gastrointestinal reflux	Yes / No	Yes / No
Kidney (renal) disease	Yes / No	Yes / No
Heart (cardiac) disease	Yes / No	Yes / No
Necrotizing enterocolitis (NEC)	Yes / No	Yes / No
Cerebral palsy	Yes / No	Yes / No
Any learning disability	Yes / No	Yes / No
Difficulty with hearing	Yes / No	Yes / No
Diabetes	Yes / No	Yes / No
High blood pressure	Yes / No	Yes / No
Has your child ever required:		
Speech Therapy	Yes / No	Yes / No
Occupational Therapy ("OT")	Yes / No	Yes / No
Physical Therapy ("PT")	Yes / No	Yes / No
AT OR AFTER the age of 2 years, has your pediatrician ever had any concerns regarding your child's:		
Height (too short)	Yes / No	Yes / No
Weight (too light)	Yes / No	Yes / No
Weight (too heavy)	Yes / No	Yes / No
Vision	Yes / No	Yes / No
Hearing	Yes / No	Yes / No
Motor skills	Yes / No	Yes / No
	Twin A (older twin)	**Twin B (younger twin)**
Please list any operations your child has undergone:		
Please list any medications your child takes regularly:		
Is your child allergic to any foods? If yes, which foods?	Yes / No	Yes / No
Has your child ever been evaluated or treated by a psychologist or psychiatrist?	Yes / No	Yes / No
Does your child wear glasses?	Yes / No	Yes / No
At what age (in months) did your child start crawling?		
At what age (in months) did your child start walking?		
At what age (in months) did your child say his or her first word?		
If your child is school-age, what grade is he/she in (nursery, pre-k, kindergarten, 1st, 2nd, etc)		

Figure 1. Study survey.

Infants were divided into four cohorts, based on gestational age at delivery: (a) 24-0/7 to 27-6/7 weeks gestation, (b) 28-0/7 to 31-6/7 weeks gestation, (c) 32-0/7 to 35-6/7 weeks gestation, and (d) 36 weeks' gestation or greater. Gestational age was determined by last menstrual period, and confirmed by ultrasound in

Table 1. Baseline characteristics of the twin pregnancies*, based on gestational age at delivery.

	24 0/7 to 27 6/7 weeks $N = 14$	28 0/7 to 31 6/7 weeks $N = 44$	32 0/7 to 35 6/7 weeks $N = 246$	≥36 0/7 weeks $N = 546$	p value
Gestational age at delivery (w)	26.8 ± 1.1	30.5 ± 1.0	34.5 ± 1.1	37.2 ± 0.8	<.001
Birthweight (g)	924 ± 172	1446 ± 394	2098 ± 377	2627 ± 377	<.001
Gender					.341
Male	35.7%	59.1%	46.7%	53.5%	
Female	64.3%	40.9%	53.3%	46.6%	
Maternal age (y)	36.2 ± 6.6	34.9 ± 4.8	35.1 ± 6.5	33.7 ± 6.3	.202
Maternal prepregnancy body mass index (kg/m^2)	22.3 ± 1.2	23.0 ± 4.0	23.0 ± 4.0	23.6 ± 4.8	.496
Chorionicity					.178
Monochorionic	0%	18.2%	17.1%	9.8%	
Dichorionic	100%	81.8%	82.9%	90.2%	
In vitro fertilization	85.7%	77.3%	68.3%	64.7%	.107
Egg donor	14.3%	9.1%	14.6%	10.2%	.437
White race	85.7%	72.7%	86.2%	92.0%	.006
Maternal preeclampsia	0.0%	18.2%	23.1%	8.9%	.018
Maternal gestational diabetes	0.0%	9.1%	11.7%	8.8%	.900
Antenatal corticosteroid exposure	100%	86.4%	61.8%	15.6%	<.001
Mode of delivery					<.001
Vaginal	21.4%	11.4%	33.7%	41.8%	
Cesarean	78.6%	88.6%	66.3%	58.2%	
5-minute Apgar score <7	0%	2.3%	0.8%	0.6%	.413

*Reported rates are per pregnancy (gestational age at delivery, maternal age, maternal prepregnancy body mass index, chorionicity, *in vitro* fertilization, egg donor, white race, maternal preeclampsia, maternal gestational diabetes, antenatal corticosteroid exposure) or per child (birthweight, gender, mode of delivery, 5-minute Apgar score <7).

all patients. Until 14 weeks' gestation, ultrasound was used to redate pregnancies with a discrepancy greater than 5 days. After 14 weeks, a discrepancy greater than 7 days was corrected. Twin gestations resulting from *in vitro* fertilization (IVF) had their gestational ages determined based on recorded IVF dating.

Baseline characteristics of the pregnancies were compared between the four groups. For this analysis, we used chi-square for trend and one-way analysis of variance (ANOVA). For the characteristics that would be the same for twin pairs (gestational age at delivery, maternal age, maternal prepregnancy body mass index, chorionicity, IVF conception, donor egg, maternal race, maternal preeclampsia, maternal gestational diabetes, antenatal corticosteroid exposure), we compared the characteristics per pregnancy, not per child. For the characteristics unique to each twin (birth weight, gender, 5-minute Apgar score), we compared the characteristics per child. For long-term childhood outcomes, we compared all outcomes per child using ordinal logistic regression. For this analysis, the long-term outcomes were independent variables and the gestational age groupings were ordinal categorical dependent variables, with robust clustering to control for nonindependence of observations given that two twins were born to one mother [9]. A p-value of <.05 was considered significant.

Results

There were 653 twin deliveries 24 weeks or greater who met inclusion criteria. We received responses from 425 mothers, for a response rate of 65.1%. Therefore, this study included 425 twin pairs, or 850 children. There were no significant differences between responders and nonresponders in regards to maternal age, IVF, chorionicity, prepregnancy body mass index, gestational age at delivery, preeclampsia, gestational diabetes, birthweight of the larger or smaller twins, or steroid exposure (data not shown). Responders were more likely to be white (89 versus 80%, $p = .002$). Also, the age of the children of responders was younger than nonresponders (6.0 versus 6.6 years, $p = .001$), which was not unexpected given the greater difficulty in reaching women via survey who delivered longer ago.

There were 14 (1.6%) children born at 24 to 27-6/7 weeks, 44 (5.2%) children born at 28 to 31-6/7 weeks, 246 (28.9%) children born at 32 to 35-6/7 weeks, and 546 (64.2%) children born at 36 weeks or greater. The mean age of the children at the time of survey completion was 6.0 ± 2.4 years and did not differ between the four groups (7.1 ± 2.4 years, 6.0 ± 2.8 years, 6.0 ± 2.4 years, 5.9 ± 2.4 years, respectively, $p = .62$).

Baseline characteristics of the four groups are shown in Table 1. As expected, the birth weights, exposure to steroids, and mode of delivery differed between the four groups. Earlier gestational age at delivery was associated with higher rates of maternal preeclampsia, which was likely due to preeclampsia being the indication for preterm delivery. White race was associated with later gestational ages at delivery. There were no differences in other characteristics such

Table 2. Long-term outcomes of twins, based on gestational age at delivery.

	24 0/7 to 27 6/7 weeks $N = 14$	28 0/7 to 31 6/7 weeks $N = 44$	32 0/7 to 35 6/7 weeks $N = 246$	≥36 0/7 weeks $N = 546$	p^* value
Neonatal death	14%	2%	0%	0%	<.001
Composite Major (Death, CP, NEC Chronic renal/heart/lung disease)	14%	7%	4%	2%	.036
Composite Minor (Learning disability, Speech therapy, OT, PT)	83%	69%	54%	38%	<.001
Has either twin been diagnosed with or treated for:					
Colic	17%	5%	6%	9%	.343
Asthma/Reactive airways	17%	7%	10%	8%	.519
Any other chronic lung disease	0%	2%	2%	0%	.025
Gastrointestinal reflux	50%	27%	22%	15%	.005
Kidney (renal) disease	0%	0%	1%	0%	.305
Heart (cardiac) disease	0%	0%	1%	1%	.566
Necrotizing enterocolitis (NEC)	0%	5%	0%	0%	<.001
Cerebral palsy	0%	0%	0%	0%	NA
Any learning disability	8%	5%	11%	9%	.836
Difficulty with hearing	0%	7%	4%	3%	.169
Diabetes	0%	0%	0%	0%	NA
High blood pressure	0%	0%	0%	0%	NA
Has your child ever required:					
Speech Therapy	67%	54%	36%	27%	<.001
Occupational Therapy (OT)	75%	41%	35%	21%	<.001
Physical Therapy (PT)	83%	56%	31%	20%	<.001
At or after the age of 2 years, has your pediatrician ever had any concerns regarding your child's:					
Height (too short)	0%	2%	6%	3%	.309
Weight (too light)	8%	20%	10%	6%	.017
Weight (too heavy)	0%	0%	2%	2%	.391
Vision	17%	27%	12%	10%	.118
Hearing	0%	7%	4%	3%	.363
Motor skills	8%	17%	12%	8%	.065
Has your child undergone any operations	58%	36%	18%	22%	.516
Does your child take any medications	0%	8%	11%	9%	.753
Is your child allergic to any foods	8%	13%	11%	7%	.068
Has your child ever been evaluated or treated by a psychologist or psychiatrist?	17%	21%	10%	12%	.706
Does your child wear glasses?	25%	14%	9%	12%	.671
Age when both twins were crawling (months, corrected for gestational age at delivery)	8.20	6.42	6.65	7.40	.003
Age when both twins were walking (months, corrected for gestational age at delivery)	13.20	11.96	12.40	12.78	.118
Age when both twins said their first word (months, corrected for gestational age at delivery)	17.45	12.18	12.33	12.43	.947

*Ordinal logit regression with robust clustering to control for nonindependence of observations given that two twins were born to one mother.

as maternal age, body mass index, gestational diabetes, chorionicity, IVF, donor egg, nor in the children's genders or 5-minute Apgar scores.

The survey responses of long-term outcomes are shown in Table 2. Earlier gestational age was significantly associated with neonatal death, which was as frequent as 14% in the 24-0/7 to 27-6/7 group, 2% at 28 to 31-6/7 weeks, and 0% after 32 weeks ($p < .001$). Both composite primary outcomes were significantly associated with gestational age at delivery. The composite of major adverse outcomes was 14% in the 24-0/7 to 27-6/7 group 7% in the 28-0/7 to 31-6/7 group, 4% in the 32-0/7 to 35-6/7 group, and 2% in the twins born 36 weeks or later ($p = .036$). The composite of minor adverse outcomes was 83% in the 24-0/7 to 27-6/7 group, 69% in the 28-0/7 to 31-6/7 group, 54% in the 32-0/7 to 35-6/7 group, and 38% in the twins born 36 weeks or later ($p < .001$).

There were three neonatal deaths in the cohort. The first was a twin born at 30 6/7 weeks to a healthy, nulliparous, mother with a IVF quadruplet pregnancy who underwent multifetal pregnancy reduction to dichorionic twins. Twin A had severe fetal growth restriction with a birthweight of 520 g. She was delivered by cesarean due to preterm labor and breech presentation. She received antenatal corticosteroids within a week of delivery. The baby died after birth due to complications from prematurity and fetal growth restriction. The second and third neonatal deaths were born at 25 1/7 weeks to the same mother. She was nulliparous, had a prior uterine septum resection, and had a IVF dichorionic pregnancy. The twins were delivered vaginally due to preterm labor and they both died from prematurity within a week after birth. She received antenatal corticosteroids within a week of delivery.

Gastrointestinal reflux (GERD) was the most common medical condition reported and was significantly higher with earlier gestational ages at delivery (50% in the 24-0/7 to 27–6/7 group with reduced percentages

in each subsequent group to 15% in the twins born >36 weeks). The rates of severe disease such as cardiac, chronic lung or renal disease, diabetes, hypertension and cerebral palsy were low in all groups.

Additional services such as speech, occupational and physical therapy were commonly reported in the cohort and significantly higher in twins born at earlier gestational ages. For example, for twins born at 24-0/7 to 27-6/7 weeks, the likelihoods of requiring speech, occupational, and physical therapy were 67, 75, and 83%, respectively, whereas for twins born at 36 weeks or greater, the likelihoods were only 27, 21, and 20%, respectively ($p < .001$ across the four groups for all three outcomes).

In regards to the reported concerns of the children's pediatricians, the only one that differed significantly across the four groups was a concern over the child being too small. There were no differences in the likelihood of undergoing an operation, wearing glasses, taking medications, having allergies to foods, and being evaluated by a mental health professional.

After correcting for gestational age at delivery, twins born at 24-0/7 to 27-6/7 weeks crawled at the latest age. There were no differences across the four groups in regards to the age at which the child started walking or speaking.

Discussion

In this study, we found a significant association between gestational age at delivery and long-term outcomes in twins at an average age of 6 years old. In the cohort born under 28 weeks, there was a mortality rate of 14%, which was significantly higher than the 2% rate at 28–32 weeks, and 0% thereafter. In the cohort of twins born under 28 weeks, a composite of major adverse outcomes were reported in 14% of participants, while a composite of minor adverse outcomes were reported in as high as 83% of participants.

The data obtained from this study have practical implications for both medical professionals and caregivers. The data demonstrate that twins born prematurely are more likely to have GERD, require supplementary physical, occupational, and speech therapy, and tend to raise concerns over their smaller size. Obstetricians, pediatricians, and neonatologists can utilize this information to better understand and explain the risks and outcomes of varying degrees of prematurity in terms that parents can easily understand. Moreover, this understanding of the long-term risks of varying degrees of prematurity increases a patient's ability to give informed consent for prophylaxis against, and treatment for preterm labor. Pediatricians can utilize this data to more specifically screen twins, and to subsequently implement necessary treatment regimens to minimize and eliminate possible negative outcomes. This data can also be used to reassure primary caregivers, and to enable them to monitor children for outcomes like GERD, physical and linguistic delay, and growth, and implement treatment regimens outlined by professionals.

In addition to helping doctors and parents prepare for adverse outcomes, these data can be used to reassure parents. Overall, the likelihood of severe adverse outcomes was low, particularly for twins born after 28 weeks. Despite the need for short-term intensive care, most premature twins had relatively few significant long-term consequences of prematurity. It should be noted that all twins were under the care of Maternal Fetal Medicine specialists and delivered at a tertiary care center with 24-hour level IV neonatal intensive care unit (NICU) coverage. It is unclear if long-term outcomes would differ for twins born under different care paradigms.

Large population-based studies have consistently shown that long-term neurodevelopmental outcomes are worse for twins than singletons; however, this is largely due to the different weight and gestational age distributions at birth [10]. Long-term outcome data should ideally be stratified by gestational age at delivery, as this would be more useful as a predictive tool for parents and healthcare providers. However, data on long-term outcomes of prematurity by gestational age are principally limited to singletons. We are unaware of any prior studies comparing long-term outcomes in a large cohort of twins, based on gestational age at delivery. Higher rates of short-term morbidity and mortality have been established for babies born from a singleton gestation before 37 weeks' gestation as compared with those born at term [11,12]. A large cohort study or preterm infants published in 2004 demonstrated an association between infection in the neonatal period and adverse neurodevelopmental outcomes at 18–22 months including higher rates of cerebral palsy, and lower scores on the Bayley Scales of Infant Development [5]. Another study serially assessed preterm infants until 18 months utilizing established developmental milestones, and found delay of visual and social skills [6]. A separate study completed in 2014, utilizing secondary analysis of a large scale longitudinal study of infants born in the United Kingdom, assessed long-term disease burden on infants born between 32 and 37 weeks' gestation compared to infants born after 37 weeks. The study assessed growth, hospital admissions, asthma, use of

prescription drugs, and parental rating of their children's health. Outcomes measured at 3 and 5 years of age demonstrated a dose response relationship between increasing level of prematurity and poor outcomes, including classification as underweight, shorter stature, and higher rates of medication for asthma [7]. Boyle et al. based their findings on a secondary analysis of a pre-existing database, not built by the researchers who conducted the analysis, with no distinction between singleton and twin gestations. Thus, our study enhances the data obtained from that study as we report outcomes in a large population composed exclusively of twins.

Our study was a mail-based survey geared towards nonmedical professionals, which has its strengths and its limitations. First, the mean age of children surveyed in the study was 6 ± 2 years which provides long-term outcome data. As a retrospective study based on parent report, the possibility of recall bias exists. Among our cohort, 66.5% of surveys were completed and returned, a strong-rate of return for this study design. Only 14/653 (2.1%) women specifically declined to participate, while the rest simply could not be reached due to outdated contact information. This response rate is relatively good, but not perfect, and so may have introduced selection bias. However, we did not find any differences in pregnancy or delivery characteristics between responders and nonresponders, aside from a small difference in maternal race. The survey itself was geared towards parents, and included outcomes that are not typically measured by researchers but are clinically relevant to parents when considering the health of their children. Examples include whether the child wears glasses, whether the child required additional therapy, whether the child was diagnosed with a learning disability, and at what age the child started walking. We believe this is a significant strength of our study as it presents data that parents can understand. However, we did not use a validated clinical tool for the evaluation of the children which limits the precision of our findings. Finally, since the rates of severe outcomes were low, we did not have enough power to estimate the effect fetal growth restriction, twin-to-twin transfusion (TTTS), and chorionicity had on these outcomes at early gestational ages.

As they stand, our findings are useful in guiding both obstetrical and pediatric counseling. This data combined with prior studies demonstrate that the classification of infants as preterm versus full term is inadequate to predict long-term outcomes in premature twins. Rather a classification system based on gestational age at birth may be more useful when considering outcomes, and implementing interventions during the prenatal, postnatal, and early childhood periods. Further studies, specifically prospective studies with enrollment occurring at birth, and serial objective neurodevelopmental assessments are needed to confirm these data. In conclusion, long-term morbidity in twin pregnancies is inversely related to gestational age at delivery. However, for twins born after 28 weeks, neonatal death and severe long-term morbidity are rare.

Disclosure statement

No potential conflict of interest was reported by the authors.

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