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The Effect of Plurality and Gestation on the Prevention or Postponement of Infant Mortality: 1989–1991 Versus 1999–2001

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Abstract

Advances in perinatal technology that improved survival may have also resulted in prolonged death from the neonatal to the postneonatal period for some infants. The objectives of this study were to determine if the medical advances that occurred in the 1990s benefited infants of multiple births more than their singleton counterparts, and if these changes prevented or postponed mortality for the smallest and most immature infants. The study population included live births of 22 to 43 weeks' gestation from the 1989–1991 and 1999–2001 US Birth Cohort Linked Birth/Infant Death Data Sets. Odds ratios were calculated to evaluate the change in risk by plurality, gestation, and to compare the change to that for singletons. Neonatal and infant mortality rates declined for all pluralities; postneonatal mortality increased for births at less than 26 weeks, but declined at later gestations. In general, the risk of death for twins and triplets compared to singletons decreased, and the improvement in survival was greater for multiples during the early neonatal period and overall. Infant mortality rates improved by 28% for singletons, 32% for twins and triplets during the 1990s, although for the most premature infants, some deaths were postponed from the early to the late neonatal period.

In 2004 there were 139,494 infants in multiple pregnancies born in the United States, the highest number ever recorded (Martin et al., 2006). Multiple pregnancies have risen dramatically since 1980, with a 93% increase in twins and a 544% increase in triplet and higher order births (quadruplets and quintuplets). This contemporary trend of increasing multiple pregnancies has been reported in many industrialized nations, including Japan, Sweden, Finland, Denmark, Canada, Australia, Austria, Israel, the Netherlands, and the United Kingdom (Gissler & Tiitinen, 2001; Imaizumi, 1997). It is estimated that approximately one-fourth of the rise in multiple births is due to the long-term trend of childbearing at older maternal ages, while for three-fourths is attributable to the use of assisted reproductive technologies (ART; Centers for Disease Control, 2000; Jewell & Yip, 1995; Reynolds et al., 2003; Wilcox et al., 1996). Although infants of multiple births comprise only 3% of all live births, they are disproportionately represented among preterm (less than 37 weeks, 16%), very preterm (less than 32 weeks, 22%), low birthweight (32%), and very low birthweight (27%) infant populations (Martin et al., 2003). The average birthweight and gestational age is 3316 g at 38.7 weeks for singletons, compared to 2333 g

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at 35.2 weeks for twins, 1700 g at 32.1 weeks for triplets, 1276 g at 29.7 weeks for quadruplets, and 1103 g at 28.4 weeks for quintuplets (Martin et al., 2006). National vital statistics are increasingly being reported separately as singletons versus multiples because of the effect of the latter on estimates of low birthweight and prematurity (Blondel et al., 2002; Centers for Disease Control, 1999; Friede et al., 1987).

Advances in perinatal technology that have dramatically increased the survival of very low birthweight infants may have also resulted in prolonging the time to death with a postponement of mortality from the neonatal to the postneonatal period (Friede et al., 1987; Gould et al., 2000). In an assessment of infant mortality among very low birthweight infants in California, Gould et al. (2000) concluded that although the average time to death was significantly increased in very low birthweight infants weighing greater than 750 g between 1987 and 1993, advances in perinatal technology dramatically decreased overall very low birthweight mortality. Analyses of infant mortality rates in New York City between 1988 and 1989 and between 1992 and 1993 concluded that the declines between these two periods were attributable to improvements in birthweight-specific death rates and not to a positive shift in the birthweight distribution of the population (Racine et al., 1998). The objectives of this study were to determine if the medical advances that occurred in the 1990s benefited infants of multiple births more than their singleton counterparts, and if these changes prevented or postponed mortality for the smallest and most immature infants.

Methods

The data sets for this study included the Birth Cohort Linked Birth/Infant Death Data Set for 1989–1991 and 1999–2001, the earliest and most recent years for which plurality-specific data are available. The methodology takes advantage of two existing data sources: state-linked files for the identification of linked birth and infant death certificates, and National Center for Health Statistics (NCHS) natality and mortality computerized statistical files, the source of computer records for the two linked certificates. All states link infant death certificates to their corresponding birth certificates for legal and statistical purposes. When the birth and death of an infant occur in different states, copies of the records are exchanged by the state of death and the state of birth in order to affect a link. In addition, if a third state is identified as the state of residence at the time of birth or death, that state is also sent a copy of the appropriate certificate by the state where the birth or death occurred. The NCHS natality and mortality files, produced annually, include statistical data from birth and death certificates that are provided to NCHS by States under the Vital Statistics Cooperative Program. The data have been coded according to uniform coding specifications, have passed rigid quality control standards, have been edited and reviewed, and are the basis for official US birth and death statistics. To initiate processing, NCHS obtains matching birth certificate numbers from states for all infant deaths that occurred in their jurisdiction. This information is used to extract final, edited mortality and natality data from the NCHS natality and mortality statistical files. Individual birth and death records are selected from their respective files and linked into a single statistical record, thereby establishing a national linked record file. After the initial linkage, NCHS returns to the states where the deaths occurred with computer lists of unlinked infant death certificates for follow-up linking. If the birth occurred in a state different from the state of death, the state of birth identified on the death certificate is contacted to obtain the linking birth certificate. State additions and corrections are incorporated, and a final, national linked file is produced.

Three-year periods were chosen to dampen year-to-year fluctuations. The data were limited to live-born infants of 20 to 43 weeks' gestation. To reduce implausible birthweight-gestational age combinations, the data was cleaned in the following manner: for each week of gestation the upper range for birth-weight was defined using the gender-specific 97th

percentile for singletons (Kramer et al., 2001) and the lower limit as the 5th percentile for triplets (Min et al., 2004). The data was grouped by weeks of gestation as 22–23, 24–25, 26–28, 29–32, 33–36, 37–40, and 41–43, and as less than 26 weeks versus 26 weeks or greater. Plurality of each infant was categorized as singletons, twins, and triplets. Infant mortality was defined as neonatal (0–27 days, including early, 0–6 days and late, 7–27 days), postneonatal (28–364 days, including early, 28–167 days and late, 168–364 days), and infant (0–364 days) according to NCHS definitions (Kochanek et al., 2004).

The analyses included three aspects. First, plurality-specific neonatal, postneonatal, and infant mortality rates were calculated overall and by gestation periods for 1989–1991 and 1999–2001 and compared using χ^2 analyses. Second, the plurality-specific odds ratios and 95% confidence intervals of neonatal, postneonatal, and infant death compared to the risk for singletons within each time period (1989–1991 and 1999–2001) was calculated, overall and for births at less than 26 weeks and births at 26 weeks or greater. Third, within each plurality the change in the risk of early and late neonatal and postneonatal mortality, and in overall infant mortality from 1989–1991 to 1999–2001 for all gestations and for births at less than 26 weeks and 26 weeks or greater was calculated. The odds ratios for twins and triplets were then compared to the singleton odds ratios to evaluate if the change in risk (improvement in survival) had been greater or lesser for multiples than for singletons.

Results

The study population for 1989–1991 and 1999–2001 included 11,310,423 and 11,172,265 live births, and 83,527 and 60,558 infant deaths, respectively. Between the two time periods, there was a shift to older maternal ages, higher maternal education, and a decrease in smoking during pregnancy overall and for each plurality, as well as a decrease in postmaturity (Table 1). The plurality- and gestation-specific mortality rates are given in Table 2. Overall, the neonatal and infant mortality rates declined significantly overall and at each gestation period; postneonatal mortality increased for births at less than 26 weeks, but declined for births at later gestations. The greatest declines in mortality rates were among births at 26 to 36 weeks.

The odds ratios and 95% confidence intervals representing the change in the risk of death between 1989–1991 and 1999–2001 by plurality and gestation are given in Table 3. For all infant deaths (0–364 days after birth), survival significantly improved for every plurality overall and for births less than 26 weeks and 26 weeks or greater. During the neonatal period, the greatest improvements occurred during the early neonatal period (0–6 days), significant for every plurality and in all gestation categories, whereas in the late neonatal period (7–27 days) significant improvements only occurred for singletons overall and for singletons and twins born at 26 weeks or greater. Both early and late postneonatal survival improved overall for all pluralities, as well as for singletons at less than 26 weeks and 26 weeks or greater. For twins and triplets, late postneonatal survival improved among births at less than 26 weeks, early postneonatal survival improved for births at 26 weeks or greater. For twins born at 26 weeks or greater, late postneonatal survival also improved significantly. The plurality-specific change in risk of death between 1989–1991 and 1999–2001 compared to the change for singletons is also given in Table 3. For all infant deaths (0–364 days after birth) significantly greater improvements in survival occurred among twins overall, among both pluralities at both less than 26 weeks and 26 weeks or greater. During the early neonatal period (0–6 days), greater improvements occurred among twins and triplets overall and at both earlier and later gestations, but during the late neonatal period (7–27 days) only among twins for births 26 weeks or greater. During the postneonatal period, significantly greater improvements occurred in the early period (28–167 days) for both twins and triplets

for births at 26 weeks or greater, and during the late period (168–364 days) only for twins born at 26 weeks or greater.

Discussion

This population-based study of all live births in the United States between 1989–1991 and 1999–2001 documents the substantial improvement in survival among all infants that has been achieved during the past decade. This improvement has been greater for twins and triplets than for singletons and greater during the early versus late neonatal period. Despite this encouraging progress, the continuing rise in multiple births has important public health implications. In 2002, nearly one out of every five neonatal deaths was an infant born from a multiple pregnancy (MacDorman et al., 2005), and an estimated 19% of all NICU days are associated with multiple pregnancies (Ross et al., 1999). The 2004 prematurity rate of 12.5% represents the highest level in 25 years, and the low birthweight rate of 8.1% has also risen to a new peak (Martin et al., 2006). These figures fall far short of the United States' 2010 Health People 2010 Objectives of 7.6% for prematurity and 5.0% for low birthweight. Although infants of multiple births contribute disproportionately to both of these adverse outcomes, this increase in prematurity and low birth-weight is also occurring among singleton births.

During the 1990s, clinical studies reported that postponement of infant death for infants with birthweights of less than 1000 g had increased from two days in 1991 to 10 days in 2001 (Meadow et al., 1996, 2004). Our findings indicate that this postponement has occurred primarily from the early to the late neonatal period, and only among births at less than 26 weeks—the smallest and most premature infants. This has also been the infant population which demonstrated the greatest improvement in survival during this time period: a 38% improvement for singletons, 54% for twins, and 52% for triplets. Although survival rates have improved dramatically during the 1990s, studies have shown that this improvement has slowed or even ceased during the late 1990s, particularly among the smallest infants (Horbar et al., 2002; Meadow et al., 2004).

The survival prognosis of infants born at the threshold of viability remains problematic. Data from the National Institute of Child Health and Human Development Neonatal Centers in 1995–1996 indicated neonatal survival rates of 30% at 23 weeks, 52% at 24 weeks, and 76% at 25 weeks, which is comparable with the results reported in this study (Lemons et al., 2001). However, the incidence of moderate or severe neurodevelopmental disability in survivors is high, ranging from 30 to 50% by 18 to 30 months of age (Emsley et al., 1998; Tudehope et al., 1995; Wood et al., 2000). The potential spectrum of long-term health consequences of prematurity evident in early childhood through young adulthood includes visual impairment (Ley et al., 2004; Martin et al., 2004; O'Connor et al., 2004), alterations in renal structure and function (Amann et al., 2004; Rodriguez-Soriano et al., 2005), neurobehavioral deficits (Anderson et al., 2003; Breslau et al., 2004; O'Keefe et al., 2003), impaired motor development (Evensen et al., 2004; Hediger et al., 2002), and chronic health conditions (Hack et al., 2005), particularly if also born small for gestational age.

The use of vital statistics data has limitations. First, there is the potential for misclassification of gestational age. We have attempted to minimize this error by cleaning the data to eliminate implausible birthweight-gestational age combinations, but it is still possible that some remain despite this effort. Second, because of the intracluster correlation of mortality risk for infants born in a multiple versus singleton pregnancy, the risk of death for these infants is acknowledged to be greater, beyond that due to lowered birthweight and younger gestational age (Huang et al., 2003; Johnson & Zhang, 2002). The annual linked birth and death files are reported as individual births, although NCHS has released a

matched multiple birth file that links multiple births to the same mother; this matched file is only available for births between 1995 and 2000, which includes only a portion of the time period evaluated in the current study. Despite these limitations, the use of multi-year, population-based data provides the best available data for evaluating national trends in live births.

Conclusion

Medical advances in the 1990s resulted in reductions in infant mortality by 28% for singletons, 32% for twins and triplets. For births at less than 26 weeks, 94% of the improvement in survival occurred within the early neonatal period, compared to 34% of the improvement for births at 26 weeks or greater. Because of their greater risk for adverse growth and developmental sequelae, the improved survival of smaller and more immature infants has major public health implications

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Table 1

Characteristics of the Study Population by Plurality, 1989–1991 and 1999–2001

Characteristic	Singletons			Twins			Triplets			All Pluralities*		
	1989–1991	1999–2001	1989–2001	1989–1991	1999–2001	1989–2001	1989–1991	1999–2001	1989–2001	1989–1991	1999–2001	1989–2001
(<i>N</i> , mothers)**	11,039,476	10,814,840	131,550	27.7 (5.6)	169,222	2616	6327	11,173,642	26.4 (5.7)	10,990,389	27.2 (6.2)	
Maternal age in years: mean (<i>SD</i>)	26.4 (5.7)	27.1 (6.2)	27.7 (5.6)	29.2 (6.2)	29.8 (4.8)	32.0 (5.2)						
Maternal age groups (%)												
< 20	12.8	11.9	7.7	6.0	2.5	1.2						
20–34	78.4	75.0	80.6	73.4	80.5	68.8						
> 34	8.8	13.1	11.8	20.6	16.9	30.0						
Maternal race (%)												
White	79.3	78.8	78.0	79.1	88.0	89.4						
Black	16.3	15.2	18.8	16.6	9.9	7.3						
Other	4.5	5.9	3.3	4.3	2.1	3.3						
Maternal Education in yrs (%)												
12	63.9	54.1	59.6	44.6	44.1	26.6						
13–15	19.2	21.5	20.5	22.5	20.6	22.8						
16	16.9	24.3	19.9	32.8	35.3	50.5						
Primipara (%)	41.6	41.0	20.5	22.0	18.6	21.6						
Married (%)	72.3	66.7	73.9	73.4	88.6	91.8						
Smoker (%)	12.4	9.3	11.7	7.6	6.1	2.4						
<i>N</i> , infants, live-born	11,039,476	10,814,840	263,099	338,444	7848	18,981						
<i>N</i> , infant deaths	75,321	52,995	7714	6751	492	812						
Birthweight (grams)	3337 (545)	3314 (536)	2434 (635)	2378 (614)	1821 (573)	1729 (540)						
Gestational categories (weeks; %)												
22–23	0.1	0.1	0.8	0.8	2.2	2.1						
24–25	0.1	0.1	1.0	1.1	2.9	2.9						
26–28	0.3	0.3	2.4	2.5	6.7	8.1						
29–32	0.8	0.9	7.9	9.0	25.1	31.7						
33–36	6.8	7.4	34.7	42.8	51.0	47.7						
37–40	67.5	73.9	48.6	41.2	11.1	6.6						

Characteristic	Singletons			Twins		Triplets		All Pluralities*	
	1989–1991	1999–2001	1989–1991	1989–1991	1999–2001	1989–1991	1999–2001	1989–1991	1999–2001
	24.3	17.3	4.7	2.6	1.1	1.0	23.8	16.8	
41–43									

Note:

* Singleton, twins, and triplets.

** The numbers of mothers were calculated based on the number of infants per pregnancy, but because some multiple pregnancies may have included fetal deaths, this is only an estimate.

Table 2
Neonatal, Postneonatal, and Infant Mortality Rates by Plurality and Gestation, 1989–1991 vs. 1999–2001

Plurality	Neonatal (NNMR)*			Postneonatal (PNMR)**			Infant (IMR)***			Per cent change, 1999–2001 vs. 1989–1991			
	1989–1991	1999–2001	1989–1991	1989–1991	1999–2001	1989–1991	1989–1991	1999–2001	NNMR	PNMR	IMR	p value	
All gestations													
Singletons	3.74	2.81	3.09	2.09		6.82	4.90		–24.9	–32.4	–28.2	< .0001	
Twins	22.08	15.18	7.24	4.77		29.32	19.95		–31.3	–34.1	–32.0	< .0001	
Triplets	51.35	36.67	11.34	6.11		62.69	42.78		–28.6	–46.1	–31.8	< .0001	
22–23 weeks													
Singletons	804.77	721.81	31.37	34.63		836.14	756.44		–10.3	+10.4	–9.5	< .0001	
Twins	884.24	773.60	10.35	31.34		894.59	804.94		–12.5	+202.8	–10.0	< .0001	
Triplets	958.58	816.83	5.92	19.80		964.50	836.63		–14.8	—	–13.3	< .0001	
24–25 weeks													
Singletons	434.28	299.04	60.18	63.76		494.46	362.81		–31.1	+5.9	–26.6	< .0001	
Twins	553.81	336.68	60.56	66.67		614.37	403.35		–39.2	+10.1	–34.3	< .0001	
Triplets	552.17	381.13	47.83	34.48		600.00	415.61		–31.0	—	–30.7	< .0001	
26–28 weeks													
Singletons	153.48	89.97	45.79	33.15		199.27	123.11		–41.4	–27.6	–38.2	< .0001	
Twins	181.12	88.03	45.12	25.52		226.24	113.54		–51.4	–43.4	–49.8	< .0001	
Triplets	128.11	48.99	49.71	24.17		177.82	73.15		–61.8	–51.4	–58.9	< .0001	
29–32 weeks													
Singletons	40.19	26.15	17.82	11.36		58.01	37.51		–34.9	–36.3	–35.3	< .0001	
Twins	24.44	13.43	15.06	8.09		39.50	21.52		–45.0	–46.3	–45.5	< .0001	
Triplets	13.72	8.15	11.18	4.49		24.90	12.64		–40.6	–59.8	–49.2	< .0001	
33–36 weeks													
Singletons	6.92	5.00	6.42	4.03		13.34	9.04		–27.7	–37.2	–32.2	< .0001	
Twins	4.99	2.85	6.07	3.25		11.06	6.10		–42.9	–44.8	–44.8	< .0001	
Triplets [§]	4.03	3.05	5.85	2.38		9.88	5.44		–24.3	–44.9	–44.9	< .0001	
37–40 weeks													
Singletons	1.34	0.97	2.53	1.63		3.87	2.60		–27.6	–35.6	–32.8	< .0001	
Twins	2.15	1.88	3.98	2.27		6.13	4.15		–12.6	–43.0	–32.3	< .0001	

Neonatal (NNMR) *		Postneonatal (PNMR) **		Infant (IMR) ***		Per cent change, 1999–2001 vs. 1989–1991	
Plurality	1989–1991	1999–2001	1989–1991	1999–2001	1989–1991	1999–2001	<i>p</i> value
41–43 weeks							
Singletons	1.29	0.87	2.28	1.52	3.57	–32.6	–33.1 < .0001
Twins	3.68	2.03	5.07	2.93	8.75	–44.8	–43.3 < .0001

Note:

* Neonatal mortality rate, deaths during days 0–27 after birth, per 1000 live births.

** Postneonatal mortality rate, deaths during days 28–364 after birth, per 1000 live births.

*** Infant mortality rate, deaths during days 0–364 after birth, per 1000 live births.

§ Includes triplets born 33–36 weeks and later. Rates in italics are based on small numbers (less than 20 in the numerator) and should be interpreted with caution. — Indicates difference in rates not calculated because of small numbers.

Table 3

The Odds Ratios and 95% Confidence Intervals (CIs) of Neonatal, Postneonatal, and Infant Death for Twins or Triplets Compared to Singletons

	Neonatal deaths (0–27 days)			Postneonatal deaths (28–364 days)			Infant deaths (0–364 days)					
	1989–1991			1999–2001			1989–1991			1999–2001		
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
All gestations												
Singletons	1.00		1.00		1.00		1.00		1.00		1.00	
Twins	6.02	5.86–6.19	5.46	5.30–5.62	2.40	2.29–2.51	2.32	2.21–2.44	4.40	4.30–4.51	4.49	4.38–4.61
Triplets	14.44	13.06–15.97	13.49	12.50–14.56	3.89	3.16–4.80	3.04	2.53–3.65	9.74	8.89–10.67	10.27	9.57–11.02
< 26 weeks												
Singletons	1.00		1.00		1.00		1.00		1.00		1.00	
Twins	1.66	1.55–1.77	1.22	1.16–1.29	1.11	0.94–1.31	1.11	0.98–1.26	1.64	1.53–1.76	1.22	1.15–1.29
Triplets	1.88	1.51–2.35	1.52	1.33–1.73	0.93	0.51–1.70	0.64	0.43–0.95	1.79	1.42–2.25	1.38	1.21–1.57
26 weeks												
Singletons	1.00		1.00		1.00		1.00		1.00		1.00	
Twins	3.82	3.66–3.98	3.25	3.10–3.41	2.25	2.14–2.36	1.97	1.86–2.08	2.97	2.88–3.07	2.57	2.48–2.67
Triplets	6.29	5.23–7.57	5.05	4.31–5.92	3.53	2.82–4.42	2.54	2.06–3.13	4.80	4.16–5.54	3.72	3.28–4.22

Table 4

The Odds Ratios and 95% Confidence Intervals (CIs) Representing the Change in Risk of Neonatal, Postneonatal, and Infant Death Between 1989–1991 and 1999–2001 by Plurality and Gestation

	Neonatal			Postneonatal			All Infant Deaths		
	Early (0–6 days)			Late (7–27 days)			Late (168–364 days)		
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR
All gestations									
Singleton	0.71	0.70–0.72	0.90	0.88–0.92	0.67	0.66–0.68	0.70	0.68–0.72	0.72
Twin	0.64	0.61–0.66	0.95	0.89–1.01	0.66	0.62–0.70	0.64	0.57–0.71	0.67
Triplet	0.63	0.57–0.71	1.18	0.96–1.45	0.53	0.42–0.66	0.54	0.32–0.90	0.67
< 26 weeks									
Singleton	0.56	0.55–0.57	1.12	1.07–1.18	0.84	0.79–0.90	0.75	0.66–0.86	0.62
Twin	0.41	0.39–0.43	1.03	0.92–1.14	0.88	0.77–1.01	0.62	0.45–0.86	0.46
Triplet	0.44	0.38–0.51	1.26	0.86–1.85	0.78	0.40–1.54	0.19	0.04–0.98	0.48
< 26 weeks									
Singleton	0.65	0.64–0.66	0.81	0.79–0.83	0.65	0.64–0.66	0.69	0.67–0.71	0.68
Twin	0.56	0.53–0.59	0.69	0.63–0.75	0.57	0.53–0.61	0.59	0.52–0.67	0.59
Triplet	0.45	0.35–0.57	0.83	0.62–1.12	0.44	0.34–0.58	0.61	0.35–1.08	0.52
Comparison to singleton ORs *									
All gestations									
Singleton	1.00		1.00		1.00		1.00		1.00
Twin	0.90	0.87–0.93	1.05	0.99–1.12	0.99	0.93–1.04	0.91	0.81–1.01	0.94
Triplet	0.90	0.82–0.98	1.31	1.11–1.55	0.79	0.64–0.97	0.77	0.52–1.15	0.93
< 26 weeks									
Singleton	1.00		1.00		1.00		1.00		1.00
Twin	0.73	0.69–0.77	0.91	0.82–1.01	1.04	0.91–1.20	0.83	0.61–1.12	0.74
Triplet	0.78	0.64–0.83	1.12	0.71–1.17	0.93	0.69–1.58	0.25	0.26–2.59	0.77
26 weeks									
Singleton	1.00		1.00		1.00		1.00		1.00
Twin	0.86	0.81–0.91	0.85	0.78–0.93	0.88	0.82–0.94	0.86	0.76–0.97	0.87
Triplet	0.68	0.55–0.85	1.03	0.81–1.31	0.68	0.54–0.86	0.89	0.58–1.36	0.77

Note: Odds ratios < 1 denote improvement in survival

* The plurality-specific change in risk of death between 1989–1991 and 1999–2001 compared to the change for singletons.