Mortality and Morbidity of VLBW Infants With Trisomy 13 or Trisomy 18

WHAT'S KNOWN ON THIS SUBJECT: Infants with trisomy 13 (T13) or trisomy 18 (T18) are known to have poor survival. Little is known about how very low birth weight (VLBW) impacts survival and morbidities among infants with T13 or T18.

WHAT THIS STUDY ADDS: We examined the risks of mortality and neonatal morbidities for VLBW infants with T13 or T18 compared with VLBW infants with trisomy 21 and VLBW infants without birth defects in a 16-year cohort from the Neonatal Research Network.

abstract

OBJECTIVE: Little is known about how very low birth weight (VLBW) affects survival and morbidities among infants with trisomy 13 (T13) or trisomy 18 (T18). We examined the care plans for VLBW infants with T13 or T18 and compared their risks of mortality and neonatal morbidities with VLBW infants with trisomy 21 and VLBW infants without birth defects.

METHODS: Infants with birth weight 401 to 1500 g born or cared for at a participating center of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network during the period 1994–2009 were studied. Poisson regression models were used to examine risk of death and neonatal morbidities among infants with T13 or T18.

RESULTS: Of 52 262 VLBW infants, 38 (0.07%) had T13 and 128 (0.24%) had T18. Intensity of care in the delivery room varied depending on whether the trisomy was diagnosed before or after birth. The plan for subsequent care for the majority of the infants was to withdraw care or to provide comfort care. Eleven percent of infants with T13 and 9% of infants with T18 survived to hospital discharge. Survivors with T13 or T18 had significantly increased risk of patent ductus arteriosus and respiratory distress syndrome compared with infants without birth defects. No infant with T13 or T18 developed necrotizing enterocolitis.

CONCLUSIONS: In this cohort of liveborn VLBW infants with T13 or T18, the timing of trisomy diagnosis affected the plan for care, survival was poor, and death usually occurred early. *Pediatrics* 2014;133:226–235

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KEY WORDS

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Trisomy 18 (T18) and trisomy 13 (T13) are the second and third most commonly diagnosed autosomal trisomies among liveborn infants after trisomy 21 (T21).¹ The previous literature on infants with T13 or T18 has addressed mainly the operative interventions, management, and survival of these infants.^{2–6} Few studies have examined the dual risks of very low birth weight (VLBW) and T13 or T18. Boghossian et al published a descriptive report from the Vermont Oxford Network examining neonatal interventions, neonatal morbidities, and in-hospital mortality among VLBW infants with major chromosomal anomalies including T13 and T18.⁷ We undertook the current study to expand on these findings.

Data from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN) were used to (1) examine timing of trisomy diagnosis and plan for care among VLBW infants with T13 or T18 and (2) compare neonatal characteristics, delivery room interventions, and risk of in-hospital morbidities and mortality among VLBW infants with T13 or T18 to VLBW infants with T21 and VLBW infants with no major birth defects.

METHODS

Infants born January 1, 1994 through December 31, 2009 and cared for at NRN hospitals were studied. The NRN is a network of NICUs at academic centers in the United States and a data coordinating center, which was formed to conduct research to improve care for high-risk infants.⁸ From 1994 through 2007, all VLBW infants (401–1500 g) born at or admitted to an NRN center within 14 days of birth were included in a registry maintained by the NRN. Eligibility criteria changed in January 2008 to include inborn infants with birth weight (BW) 401 to 1000 g or gestational age (GA) 22 to 28 weeks or infants enrolled

in another NRN study. Infants enrolled based on GA or other criteria with BW outside 401 to 1500 g were excluded from this report to maintain consistency over the study period. Trained research nurses entered maternal demographic, pregnancy, and delivery information, and infant data collected from birth to hospital discharge, death, or 120 days. The institutional review board at each center approved the registry and the additional medical record review undertaken in this study. Neonatal information included BW, GA, gender, race, mode of delivery, delivery room interventions, final status, and cause of death. Small for GA (SGA) was defined as BW <10th percentile.⁹ Neonatal morbidities diagnosed during the hospital stay were recorded for infants surviving >12 hours including respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), Bell's Stage $\geq$ IIA necrotizing enterocolitis,¹⁰ severe intraventricular hemorrhage (grade 3 or 4), periventricular leukomalacia, retinopathy of prematurity defined for infants still hospitalized at 28 days, bronchopulmonary dysplasia (BPD) defined as need for supplemental oxygen at 36 weeks' postmenstrual age (PMA), and late-onset sepsis defined by positive blood culture after 72 hours of age and intent to treat with antibiotics for $\geq$ 5 days. Weight, length, and head circumference were measured at 36 ± 1 weeks PMA.

Collection of major birth defects changed during the study period. From 1994 through 1997, information was recorded in text fields in response to questions about pulmonary, cardiac, neurologic, and gastrointestinal (GI) malformations and a general question about syndromes and major malformations. Beginning in 1998, major birth defects were entered using codes from a predefined list in the study manual of operations. T13, T18, and T21 had predefined codes. Major defects not listed

were described in text fields. Text fields and birth defect codes were reviewed to identify infants with T13, T18, or T21. Infants with T13, T18, or T21 who had co-occurring anomalies were included only in the appropriate trisomy group. Medical records of infants with T13 or T18 were retrospectively reviewed, if available, to look for documentation of when the diagnosis of trisomy was first suspected and when it was confirmed by genetic testing. Plans for initial care in the delivery room and for subsequent care were recorded if noted in the record. For infants who survived to discharge, plans based on poor prognosis, such as hospice care, were also recorded.

Infants were classified into the following groups: T13, T18, T21, other major birth defect, and no major birth defect. All infants were included in the denominator for prevalence estimates and in models described subsequently. Analyses focused on comparisons between infants with T13 and T18, and between each of these groups and infants with T21 or with no major birth defect. Patients with suspected but not proven T13 (2 patients) or T18 (11 patients), multiple chromosomal abnormalities (1 patient with both T13 and 4p deletion), chromosome 18 translocation (2 patients), and a defect recorded as "triploidy trisomy 18" (1 patient) were excluded from the T13 and T18 groups and instead included with other major birth defects. Patients with known mosaic or partial T13 or T18 (described in Supplemental Table 6) were included in prevalence estimates but excluded from the trisomy groups for the primary analysis. Statistical significance for unadjusted comparisons was determined using the Fisher's exact or χ^2 test for categorical variables or the *t* test for continuous variables. Kaplan-Meier survival curves were used to estimate time to death distributions with statistical

significance between groups determined by the log-rank test.

Poisson regression models with robust variance estimators¹¹ were first used to assess factors associated with an increased risk for the outcome T13 or the outcome T18. A second set of models was used to assess risk of death and morbidity outcomes for infants with T13 or T18 compared with infants with T21 and infants with no major birth defect. Models comparing death and morbidity outcomes included a birth defect group indicator (T13, T18, T21, other major birth defect, no major birth defect) to allow for pairwise contrasts. Covariates included are noted in table footnotes. Adjusted relative risks (RR), 95% confidence intervals (CI), and Score or Wald χ^2 tests are reported on the basis of parameter and variance estimates from these models. In this exploratory study, *P* values were not adjusted for multiple comparisons and are presented largely for descriptive purposes.

RESULTS

Prevalence of T13 and T18

From 1994 through 2009, 52 262 VLBW infants were cared for at 22 NRN centers. A major birth defect was reported for 5%. Overall, 38 (0.07%) VLBW infants were identified with T13, of whom 12 had full T13 and 2 had mosaic T13; the other 24 were presumed to have full T13. T18 was reported for 128 infants (0.24%), of whom 58 had full T18, 2 had mosaic T18, and 1 had partial T18; the other 67 were presumed to have full T18 (Supplemental Table 7). The final analysis included 36 infants with T13 and 125 infants with T18 (Table 1).

Risks of T13 and T18

Risk of T13 was reduced for infants from multiple births compared with singletons. Risk of T18 increased significantly with

TABLE 1 Characteristics of VLBW Infants With T13 or T18 Compared With Other VLBW Infants in the NRN Born 1994–2009

Characteristic, <i>N</i> (%) or Mean (SD)	Group			
	T13, <i>n</i> = 36	T18, <i>n</i> = 125	T21, <i>n</i> = 139	No Birth Defect, <i>n</i> = 49 600
Maternal age (y), mean (SD)	28 (7.7)	32 (8.3)**v13	31 (7.9)*v13	27 (6.7)***v18
<25	15 (42)	30 (24)*v13	34 (24)	19 992 (40)***v18
25–29	6 (17)	19 (15)	24 (17)	11 694 (24)
30–34	3 (8)	23 (18)	32 (23)	10 367 (21)
35–39	10 (28)	25 (20)	29 (21)	5953 (12)
40+	2 (6)	28 (22)	20 (14)	1563 (3)
Multiple birth	1 (3)	15 (12)	22 (16)*v13	12 512 (25)**v13,***v18
BW (g), mean (SD)	1105 (269)	1101 (291)	1032 (296)	994 (303)*v13,***v18
401–750	2 (6)	20 (16)	31 (22)	13 276 (27)*v13,***v18
751–1000	12 (33)	23 (18)	26 (19)	11 860 (24)
1001–1250	10 (28)	34 (27)	44 (32)	11 698 (24)
1251–1500	12 (33)	48 (38)	38 (27)	12 766 (26)
GA (wk), mean (SD)	30 (3.0)	32 (3.8)***v13	29 (3.6)*v13,***v18	28 (3.0)***v13,***v18
<25	2 (6)	4 (3)	22 (16)***v18	8953 (18)***v13,***v18
25–28	8 (22)	22 (18)	34 (24)	21 802 (44)
29+	26 (72)	99 (79)	83 (60)	18 826 (38)
SGA	19 (53)	98 (79)**v13	55 (40)***v18	9558 (19)***v13,***v18
Male gender	17 (47)	47 (38)	61 (44)	25 312 (51)*v18
Maternal race				
Black	13 (37)	27 (22)	38 (28)	20 071 (41)***v18
White	21 (60)	86 (70)	96 (70)	26 990 (55)
Other	1 (3)	9 (7)	4 (3)	2095 (4)
Maternal Hispanic ethnicity	5 (15)	40 (33)*v13	27 (20)*v18	7942 (17)***v18
Apgar at 1 min $\leq$ 3	17 (50)	83 (66)	41 (30)*v13,***v18	15 938 (33)*v13,***v18
Apgar at 5 min $\leq$ 3	14 (41)	44 (35)	16 (12)***v13,***v18	5705 (12)***v13,***v18

Information was missing in the groups shown for maternal age: 31 infants; multiple birth: 2; GA: 19; SGA: 33; male gender: 3; race: 449; Hispanic ethnicity: 1683; Apgar at 1 min: 686; Apgar at 5 min: 679. The numbers in the table do not include 2362 infants with other birth defects but no trisomy.

* $P \leq .05$, ** $P \leq .01$, *** $P \leq .001$ by *t* test (means for maternal age, BW, GA), Mantel-Haenszel χ^2 test (categorical maternal age, BW, GA), or the general association χ^2 test. Pairwise comparisons were performed between infants with T13 versus T18, T21, and no birth defects, and between infants with T18 versus T21 and no birth defects. For each significant result, a “v13” or “v18” indicates the comparison group.

maternal age and decreased for infants born to African American compared with white mothers. Males and infants from multiple births were at reduced risk for T18 compared with females and singletons (Supplemental Table 8).

Timing of Diagnosis and Plan for Care

Medical records were reviewed for 24 infants (67%) with T13 and 90 infants (72%) with T18. Where timing was known, the diagnosis was suspected prenatally for 14/21 (67%) infants with T13 and for 36/82 (44%) infants with T18 (Table 2). When the diagnosis was confirmed before birth, the plan was to withhold intensive care in the delivery room for a greater percent of infants with

T13 than with T18 (89% vs 39%, $P = .005$) (Table 2). Provision of care in the delivery room varied according to whether the trisomy was confirmed prenatally or postnatally. Full intensive care was received in the delivery room for 1 infant with T13 (11%) when the diagnosis was confirmed prenatally, whereas 9 (90%) of the 10 infants with T13 confirmed after birth received full intensive care, $P = .001$. Similarly, full intensive care was planned for only 4% of infants with T18 confirmed prenatally, but 95% of those confirmed after birth received full intensive care in the delivery room, $P < .001$. For infants with T13 or T18, the plan for subsequent care in the hospital also varied by timing of trisomy confirmation. Full intensive care (20%) or limited care (30%) was planned

TABLE 2 Timing of Diagnosis and Plan for Care Among a Subset of VLBW Infants With T13 or T18 in the NRN Born 1994–2009

	T13, <i>n</i> = 24, <i>n</i> (%)	T18, <i>n</i> = 90, <i>n</i> (%)	<i>P</i> ^a
Diagnosis first suspected			.09
Prenatally	14 (67)	36 (44)	
Postnatally ^b	7 (33)	46 (56)	
Unknown	3	8	
Diagnosis confirmed by genetic testing			.17
Prenatally	9 (47)	24 (29)	
Postnatally	10 (53)	58 (71)	
Unknown	3	8	
Genetic testing not done	2	0	
Trisomy confirmed before birth	<i>n</i> = 9	<i>n</i> = 24	
Cesarean delivery	0 (0)	7 (29)	.15
Plan for initial care in delivery room			.005
Full intensive care	1 (11)	1 (4)	
Limited care and/or DNR	0 (0)	13 (57)	
Any or all intensive care withheld or withdrawn	8 (89)	9 (39)	
Unknown		1	
Plan for subsequent care			.03
Full intensive care	0	0	
Limited care and/or DNR	0 (0)	8 (40)	
Any or all intensive care withheld or withdrawn	9 (100)	12 (60)	
Unknown		4	
Trisomy confirmed after birth	<i>n</i> = 10	<i>n</i> = 58	
Cesarean delivery	6 (60)	44 (76)	.44
Delivery room care provided			.49
Full intensive care	9 (90)	53 (95)	
Limited care and/or DNR	0 (0)	2 (4)	
Any or all intensive care withheld or withdrawn	1 (10)	1 (2)	
Unknown		2	
Plan for care in hospital			.70
Full intensive care	2 (20)	6 (11)	
Limited care and/or DNR	3 (30)	16 (29)	
Any or all intensive care withheld or withdrawn	5 (50)	33 (60)	
Unknown		3	

DNR, do not resuscitate.

^a *P* value for a difference between infants with T13 and T18 by Fisher's exact test.^b Diagnosis suspected postnatally on day 1 of life for all 7 infants with T13 and for 32 of 46 infants with T18. Diagnosis for T18 also suspected postnatally for 10 infants at 2 to 6 d of life, and for 1 infant each at ages 11, 17, and 40 d. Age of postnatal diagnosis was missing for 1 infant with T18.

for infants whose diagnosis was confirmed after birth, but neither was planned for infants whose trisomy was confirmed before birth, *P* = .03. Full intensive care was planned for 11% of infants with T18 confirmed after birth but for no infants whose T18 was confirmed before birth, *P* = .26.

Delivery, Interventions, and Ventilator Support

The percent of infants delivered by cesarean delivery did not vary significantly between groups (Table 3). Generally, the birth resuscitation methods examined were used less frequently for infants with T13 compared with

infants with T18. Chest compression was used more frequently for infants with T18 than for infants with T21 and infants with no birth defect. A smaller proportion of infants with T13 received ventilator support and surfactant therapy than did infants with T21 and infants with no birth defect. Among survivors past 12 hours, the percentage of infants with T13 and with T18 who underwent surgery was smaller than among those with T21.

Co-occurring Birth Defects and Surgeries

A co-occurring major birth defect was reported for 24 (67%) of the 36 infants

with T13 and 93 (74%) of the 125 infants with T18. Congenital heart defects were most frequent, reported for 13 (36%) with T13 and 78 (62%) with T18 (Supplemental Tables 9 and 10).

Surgical procedures were reported for 3 infants with T13 and 5 infants with T18. All survived ≥ 3 days. One infant with T13, atrial septal defect, and intestinal malrotation underwent Ladd's procedure before dying on day 5 of life. Two infants with T13 and GI anomalies had GI procedures: small and large bowel diversion and subsequent stoma takedown and reanastomosis for 1 who survived to discharge on day 83; tracheoesophageal fistula repair for the other infant who also had a tracheostomy, release of tongue-lip adhesion, and central line placement and survived to discharge on day 110. All 5 infants with T18 who underwent surgery died before hospital discharge. PDA surgery was reported for 2 of the 5 infants, of whom 1 had interrupted aortic arch and a ventricular septal defect (VSD) and died on day 49, and the other had a VSD and died on day 27. Another infant with T18, tetralogy of Fallot, pulmonary atresia, and cleft palate had a tracheostomy before dying on day 10. The fourth infant had proximal esophageal atresia, underwent esophageal atresia repair and gastrostomy, and died on day 17. The fifth infant had meningomyelocele, microcephaly, and VSD and underwent myelomeningocele repair but died on day 4.

Infant Characteristics

Infants with T18 were more likely to be SGA than were infants in the other groups (Table 1). A greater percentage of infants with T18 were female and had white mothers compared with infants without birth defects. The proportion of infants with T18 with Hispanic mothers was greater than among infants with T13, T21, or no birth defect.

TABLE 3 Delivery and Interventions for VLBW Infants With T13 or T18 Compared With Other VLBW Infants in the NRN Born 1994–2009

Intervention, n (%) ^a	Group			
	T13, n = 36	T18, n = 125	T21, n = 139	No Birth Defect, n = 49 600
Cesarean delivery	17 (47)	79 (63)	76 (55)	28 852 (58)
Delivery room resuscitation				
Oxygen	21 (58)	95 (76) ^{*v13}	124 (89) ^{***v13,***v18}	45 392 (92) ^{***v13,***v18}
Bag and mask ventilation	19 (53)	81 (65)	83 (60)	31 851 (64)
Chest compression	4 (11)	17 (14)	5 (4) ^{**v18}	3717 (8) ^{**v18}
Intubation	10 (28)	61 (49) ^{*v13}	53 (38)	26 671 (54) ^{**v13}
Drugs	4 (11)	5 (4)	3 (2) ^{v13}	2733 (6)
Mechanical ventilation ^b	14 (39)	77 (62) ^{*v13}	94 (68) ^{**v13}	34 964 (71) ^{***v13,v18}
Surfactant therapy	9 (25)	48 (38)	60 (43) ^{*v13}	29 321 (59) ^{***v13,***v18}
Infants born 1998–2009	n = 15	n = 64	n = 100	n = 36 336
who survived >12 h				
Any surgery ^c	3 (20)	4 (6)	49 (49) ^{*v13,***v18}	6704 (18) ^{*v18}

^a Information was missing in the groups shown for cesarean delivery: 59; delivery room oxygen: 67; delivery room bagging and mask: 91; delivery room chest compression: 83; delivery room intubation: 72; delivery room drugs: 84; mechanical ventilation: 14; surfactant: 59.

^b Includes conventional and high-frequency ventilation.

^c PDA surgery, surgery for necrotizing enterocolitis, and other major surgeries were included. Complete surgery information was prospectively collected beginning 1998 for infants who survived >12 h. Additional surgery information was collected for infants with T13 and T18 by retrospective medical record review when records were available (see Methods), including those born before 1998. One infant with T18 born before 1998 who had PDA surgery is not included. Information was missing for 7 infants with no birth defect.

* $P \leq .05$, ** $P \leq .01$, *** $P \leq .001$ by the χ^2 test. Pairwise comparisons were performed between infants with T13 versus T18, T21, and no birth defects, and between infants with T18 versus T21 and no birth defects. For each significant result, a “v13” or “v18” indicates the comparison group.

Mortality

Approximately 90% of VLBW infants with T13 (89%) or T18 (91%) died during the initial hospitalization (Table 4). Differences in timing of death are reflected in the survival curves for each group (Fig 1). Median age at death was 1 day (interquartile range 1–5) for infants with T13 and 4 days (interquartile range 1–9) for infants with T18.

Infants with T18 had >4 times the risk of death before discharge than infants with T21 (RR: 4.06; 95% CI: 2.87–5.75) and >9 times the risk compared with infants with no birth defect (RR: 9.24; 95% CI: 7.10–12.02; Table 5). Risk of death was similarly elevated for infants with T13 compared with each of these groups.

No information about status after the birth hospitalization was available for the 4 infants with T13 who survived to discharge. One with BW of 990 g was discharged on day 110. Two of the 4 infants with T13 were discharged from the hospital on oxygen, with 1 also on a cardiorespiratory monitor. Of the 11

infants with T18 who survived to discharge, status after discharge was known for 2. One infant with T18 and BW of 946 g was discharged on day 22 to hospice care at home with tube feedings but died after discharge (date unknown). The other infant stayed in the hospital for 15 days; was discharged to hospice care at home with tube feedings, oxygen, and a monitor; and died during the month after discharge. Seven of the remaining 9 infants with T18 who survived the hospital stay were discharged to hospice care (6 in the home; 1 in a facility) with 5 on nasogastric or nasojejunal tube feedings, 1 with gastrostomy feedings, and 3 on oxygen and with 2 of these also on a monitor. Final status of these patients is unknown. Special discharge instructions and final status are unknown for the remaining 2 infants with T18 who survived to discharge.

Morbidities Among Infants Who Survived >12 Hours

PDA was more frequent with T18 than with T13 (Tables 4 and 5). Risk of PDA

was increased both for infants with T13 and those with T18 compared with infants without birth defects. Infants with T13 or T18 were also at increased risk for RDS compared with infants with T21 and infants with no birth defect. Among infants with T13 or T18 evaluated at 36 weeks, risk of BPD was increased compared with infants with T21 and infants with no birth defect (Table 5). Only 5 infants with T13 had measurements taken at 35 to 37 weeks PMA. These infants weighed less and had smaller head circumference on average than infants with no birth defect (Table 4). Similarly, infants with T18 weighed less, were shorter, and had smaller head circumference than infants with T21 and infants with no birth defect.

DISCUSSION

Among VLBW infants with T13 or T18 born and/or cared for at NRN centers over a 16-year period, timing of trisomy diagnosis influenced the level of care received at birth and subsequently in the hospital. When the trisomy was detected prenatally, provision of full intensive care at delivery was planned for only 1 (11%) infant with T13 and 1 (4%) infant with T18; the plan for subsequent care included either withholding all intensive care (100% of infants with T13; 60% of infants with T18) or providing limited care only (40% of infants with T18). In contrast, at least 90% of infants with T13 or T18 diagnosed postnatally were actively resuscitated at birth, and 2 (20%) infants with T13 and 6 (11%) infants with T18 had full intensive care planned subsequently. In the most recent American Academy of Pediatrics neonatal resuscitation guidelines, T13 but not T18 was included in the examples of conditions for which resuscitation is typically withheld.¹² McGraw and Perlman reported that 44% of US neonatal providers would consider resuscitating a 36-week infant prenatally

TABLE 4 In-Hospital Mortality, Morbidities, and Growth Measurements in VLBW Infants With T13 or T18 Compared With Other VLBW Infants in the NRN Born 1994–2009

Outcome, <i>n</i> (%) or Mean (SD)/median	Group			
	T13	T18	T21	No Birth Defect
	<i>n</i> = 36	<i>n</i> = 125	<i>n</i> = 139	<i>n</i> = 49 600
Survived to discharge	4 (11)	11 (9)	86 (62)	40 238 (81)
Died ^a	32 (89)	114 (91)	53 (38)	9362 (19)
Died by time of death ^b				
≤12 h	19 (53)	38 (30)	13 (9)	3602 (7)
>12–24 h	2 (6)	3 (2)	0 (0)	396 (<1)
>1–3 d	3 (8)	23 (18)	2 (1)	1058 (2)
4–7 d	6 (17)	28 (22)	4 (3)	748 (2)
8–14 d	1 (3)	12 (10)	10 (7)	930 (2)
15–28 d	1 (3)	5 (4)	6 (4)	1094 (2)
29+ days	0 (0)	5 (4)	18 (13)	1531 (3)
Infants who survived >12 h	<i>n</i> = 17	<i>n</i> = 87	<i>n</i> = 126	<i>n</i> = 45 998
PDA	7 (41)	62 (71) ^{*v13}	75 (60)	14 887 (32) ^{***v18}
NEC	0 (0)	0 (0)	20 (16) ^{***v18}	3567 (8) ^{***v18}
RDS	14 (82)	71 (82)	84 (67) ^{*v18}	35 215 (77)
Infants who survived >3 d	<i>n</i> = 12	<i>n</i> = 61	<i>n</i> = 124	<i>n</i> = 44 541
Late-onset sepsis	1 (8)	4 (7)	34 (27) ^{***v18}	10 621 (24) ^{**v18}
Infants who had a cranial sonogram within 28 d ^c	<i>n</i> = 13	<i>n</i> = 60	<i>n</i> = 112	<i>n</i> = 42 999
Severe IVH	0 (0)	3 (5)	15 (13)	5142 (12)
Infants who had a late cranial sonogram ^d	<i>n</i> = 11	<i>n</i> = 45	<i>n</i> = 104	<i>n</i> = 40 115
PVL	0 (0)	1 (2)	4 (4)	1699 (4)
Infants with sufficient information to include in analysis ^e	<i>n</i> = 11	<i>n</i> = 47	<i>n</i> = 101	<i>n</i> = 40 090
Severe IVH or PVL	0 (0)	4 (9)	15 (15)	5925 (15)
Infants still in the hospital at 28 d who had a ROP examination	<i>n</i> = 2	<i>n</i> = 4	<i>n</i> = 77	<i>n</i> = 31 419
ROP	0 (0)	1 (25)	22 (29)	15 154 (48)
ROP stage ≥3	0 (0)	0 (0)	1 (1)	3565 (11)
Infants alive at 36 wk PMA	<i>n</i> = 5	<i>n</i> = 13	<i>n</i> = 98	<i>n</i> = 39 241
BPD ^f	3 (60)	8 (62)	38 (39)	11 066 (28) ^{**v18}
Infants with growth measurements at 36 wk PMA, Mean (SD) ^g	<i>n</i> = 5	<i>n</i> = 29	<i>n</i> = 87	<i>n</i> = 31 920
Wt, g	1569 (447)	1264 (211)	1765 (486) ^{***v18}	1943 (393) ^{*v13,***v18}
Length, cm	40 (3.7)	38 (2.7)	41 (2.9) ^{***v18}	42 (2.9) ^{***v18}
Head circumference, cm	29 (1.9)	28 (1.6)	29 (1.8) ^{**v18}	31 (1.7) ^{*v13,***v18}
Length of hospital stay, d, ^h Median (25th–75th percentile)	1 (1–5)	4 (1–8)	60 (20–100)	54 (30–84)

IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

Information was missing for infants in the groups shown for PDA: 26 infants; NEC: 19; RDS: 75; late-onset sepsis: 38; IVH: 33; PVL: 23; ROP: 5; ROP stage 3+: 22; BPD: 1489. Most infants with missing information were among those with no major birth defect.

^a Cause of death was coded as congenital malformation for all infants with T13 and T18 and for 49% of infants with T21. Among the 9362 infants with no birth defects who died, death was most frequently attributed to immaturity (34%), RDS alone or with other complications (23%), and sepsis and/or NEC (19%).

^b Percents are among all infants including survivors. Timing of death was missing for 3 infants with no major birth defect.

^c Severe IVH was defined as grade 3 or 4. For infants born 1994 through 1997, IVH was diagnosed based on the cranial sonogram with the most severe results; for infants born 1998 through 2009, the most severe sonogram taken within 28 d of birth was used.

^d For infants born 1994 through 1997, PVL was diagnosed based on a cranial sonogram taken at ≥2 wk of life; for infants born 1998 through 2009, PVL was determined based on a sonogram taken within 28 d of birth and/or a sonogram taken closest to 36 wk PMA (specified as after 28 d beginning in 2006).

^e Percents were based on infants with nonmissing IVH and PVL outcomes, except that a diagnosis of either condition was sufficient to set the outcome to yes. Most infants who could not be evaluated were born 1994 through 1997 and had a sonogram showing no IVH but who did not have a sonogram at ≥2 wk so that PVL information was missing.

^f As shown are infants still in the hospital or discharged/transferred at 36 wk PMA with sufficient information to determine BPD status. BPD was defined as receiving supplemental oxygen at 36 wk PMA, or discharged/transferred on oxygen before 36 wk. All 5 infants with T13 and 11 of 13 infants with T18 were still in the hospital at 36 wk; 81% of infants with T21 and 68% of infants with no birth defect were still in the hospital. One infant with T18 was discharged from the hospital at 35 wk PMA, not on oxygen; the other infant was transferred at 34 wk PMA on oxygen and discharged from the hospital at 38 wk. Results were similar in the subset of infants still in the hospital at 36 wk.

^g As shown are infants who have at least one 36 wk measurement. In this group of infants, information was missing for weight for 37; length for 3462; head circumference for 1500.

^h The significantly shorter lengths of stay for infants with T13 and T18 reflect the higher mortality rates in these groups. The 4 infants with T13 who survived to discharge stayed in the hospital 36, 58, 83, and 110 d. Length of hospital stay ranged from 7 to 49 d (median: 29 d) for the 11 infants with T18 who were discharged from the hospital.

* $P \leq .05$, ** $P \leq .01$, *** $P \leq .001$ by the χ^2 or the t test (means for weight, length, head circumference). Pairwise comparisons were performed between infants with T13 versus T18, T21, and no birth defects, and between infants with T18 versus T21, and no birth defects. For each significant result, a “v13” or “v18” indicates the comparison group.

diagnosed with T18 and a congenital heart defect, with maternal preference being the main reason (70%) to initiate resuscitation.¹³ Intensive management

was planned for fewer of our VLBW infants with prenatal diagnosis of T13 or T18; however, we had no information on the counseling parents might have

received and the degree of accord in the decision-making between the care providers and parents. With the dual risks of VLBW and trisomy, more parents

FIGURE 1

Estimated proportion survived to discharge by birth defect group among VLBW infants in the NRN born 1994 through 2009. Differences in the survival distributions were significant ($P < .001$ by the log-rank test). No statistically significant difference was found between the survival curves for infants with T13 compared with infants with T18. Survival rates at 28 days were as follows: no major birth defect: 84%; T21: 75%; T18: 11%; T13: 11%. The last death before discharge occurred at 27 days among infants with T13; 4 infants were discharged alive after hospital stays of 36 to 110 days. Among infants with T18, the infant who remained in the hospital longest died on day 52; 11 infants were discharged alive after hospital stays of 7 to 49 days.

TABLE 5 Risk of Morbidities and Mortality for VLBW Infants With T13 or T18 Compared With Other VLBW Infants in the NRN Born 1994–2009

Outcome	Adjusted RR (95% CI) ^a		
	T13 vs T18	T13 vs T21	T13 vs No Birth Defect
PDA	0.48 (0.27–0.85)	0.83 (0.47–1.45)	1.97 (1.15–3.36)
RDS	0.77 (0.58–1.01)	1.41 (1.09–1.83)	1.44 (1.14–1.82)
Late-onset sepsis	1.08 (0.12–9.45)	0.44 (0.06–3.15)	0.69 (0.10–4.83)
BPD	0.80 (0.41–1.54)	3.58 (2.01–6.39)	6.44 (3.77–10.99)
Mortality	0.93 (0.59–1.46)	3.76 (2.42–5.84)	8.55 (5.87–12.47)
	T18 vs T13	T18 vs T21	T18 vs No Birth Defect
PDA	2.10 (1.18–3.72)	1.74 (1.33–2.26)	4.12 (3.36–5.05)
RDS	1.30 (0.99–1.71)	1.84 (1.53–2.20)	1.88 (1.62–2.16)
Late-onset sepsis	0.92 (0.11–8.08)	0.41 (0.15–1.11)	0.64 (0.25–1.67)
Severe IVH	NA	0.71 (0.22–2.28)	1.15 (0.39–3.38)
Severe IVH or PVL	NA	0.98 (0.35–2.73)	1.34 (0.53–3.38)
ROP	NA	1.08 (0.14–8.32)	0.93 (0.12–7.03)
BPD	1.25 (0.65–2.42)	4.49 (2.86–7.05)	8.07 (5.45–11.96)
Mortality	1.08 (0.69–1.70)	4.06 (2.87–5.75)	9.24 (7.10–12.02)

^aRelative risks and CIs from a modified Poisson regression model fit to each outcome that included study center, GA (<23, 23–24, 25–28, 29–32, 33+), SGA, male sex, maternal race (white, black, other), maternal ethnicity (Hispanic, non-Hispanic), and birth defect group (T13, T18, T21, other birth defect, no birth defect). No infants with T13 survived and were diagnosed with IVH, IVH/PVL or ROP. NA, not applicable.

may have been comfortable limiting medical care.

Parents and care providers face complex and challenging decisions regarding the management of infants with T13 and T18. Although provision of intensive care for infants with T21 has

been standard for decades, this has not been the case for infants with T13 and T18. Despite the higher prevalence of serious birth defects with T13 and T18 compared with T21, only 20% of infants with T13 and 6% of infants with T18 underwent surgery, compared with

49% of infants with T21. Many care providers label the diagnoses of T13 and T18 as “lethal” and advocate providing palliative care only.^{14,15} More recently however, a more active approach has been called for by some.^{16–18} This approach includes engaging the parents in the choice of care options, avoiding language that assumes outcome and that presumes a family's view of quality of life for their children, and informing parents of the possibility of long-term survival.^{17,19} Several recent studies have contributed to altering the conventional picture of infants with these diagnoses. Two studies showed that, contrary to the expectations of care providers, parents of children with T13 or T18 who belong to support groups report having an enriching family experience, regardless of their children's length of survival.^{16,20} Baty et al reported that individuals with T13 or T18 are generally severely or profoundly handicapped but may continue to make modest developmental progress.²¹ A more recent study using data from a US national inpatient database showed that children with T13 or T18 receive substantial inpatient medical care, and a significant number live >1 year.²²

Although 90% of our VLBW infants with T13 or T18 died before hospital discharge, this finding is confounded by the limited medical management received by most of our patients. Survival was shorter for infants whose T13 or T18 was diagnosed prenatally compared with those diagnosed postnatally (T13, 1 vs 3 days; T18, 1 vs 5 days; data not shown). Kosho et al reported that patients with T18 who received intensive treatment including respiratory support, GI surgery and pharmacologic treatment of heart defects survived longer, with 1-year survival of 25% and median survival time of 152 days.³ Although cardiac surgery has been shown to prolong survival in infants with T13 or

T18 and a congenital heart defect, the role of cardiac surgery for these infants remains controversial.^{3,5,18,23–28}

The risks of PDA, RDS, and BPD were increased among infants with T13 or T18 compared with infants without birth defects. Our study and the majority of other studies cited here provide little information on the quality of life experienced by the surviving infants with T13 or T18. We have no data on overall resource utilization or on the difference in resource consumption between infants with prenatal versus postnatal diagnosis.

CONCLUSIONS

The intensity of delivery room care for VLBW infants with T13 or T18 varied depending on the timing of trisomy diagnosis. For the majority of infants, the plan for subsequent care was to withdraw care or to provide comfort care only. This practice influenced the timing of death and rates of survival to discharge. Median age at death was 1 day for VLBW infants with T13 and 4 days for those with T18. Despite the limited medical management received by most T13 and T18 infants, 11% of VLBW infants with T13 and 9% with T18 survived to hospital discharge. These data can be used to inform care providers and policy makers and to counsel affected families.

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(Continued from first page)

ABBREVIATIONS

BPD—bronchopulmonary dysplasia
 BW—birth weight
 CI—confidence interval
 GA—gestational age
 GI—gastrointestinal
 NRN—Neonatal Research Network
 PDA—patent ductus arteriosus
 PMA—postmenstrual age
 RDS—respiratory distress syndrome
 RR—relative risk
 SGA—small for gestational age
 T13—trisomy 13
 T18—trisomy 18
 T21—trisomy 21
 VLBW—very low birth weight
 VSD—ventricular septal defect

Dr Boghossian participated in the conception and design of the study including the analysis plan, participated in the interpretation of the data, wrote the first and subsequent drafts of the manuscript, and helped to revise it critically for important intellectual content. Ms Hansen helped to design the analysis plan; was responsible for the data management and analysis; performed the analysis with guidance from Drs Boghossian, Bell, and Das; and helped to revise the manuscript critically for important intellectual content. Dr Bell participated in the conception and design of the study including the analysis plan, participated in the interpretation of the data, and revised the manuscript critically for important intellectual content. Dr Stoll participated in the design of the study, chaired the committee responsible for designing and managing the study from which the data were drawn, participated in the interpretation of the data, and helped to revise the manuscript critically for important intellectual content. Drs Murray, Carey, Adams-Chapman, Shankaran, Walsh, Laptook, and Faix participated in the conception and design of the study, participated in the interpretation of the data, and reviewed the manuscript critically for important intellectual content. Ms Newman and Ms Hale participated in the conception of the study, participated in the acquisition and interpretation of the data, and reviewed the manuscript critically for important intellectual content. Dr Das participated in the design of the study and the plan for data analysis, was responsible for the data management and participated in the analysis, and helped to revise the manuscript critically for important intellectual content. Ms Wilson, Ms Hensman, Ms Grisby, Ms Collins, Ms Vasil, Ms Finkle, Ms Maffett, Ms Ball, Ms Lacy, and Ms Bara participated in the acquisition of data and reviewed the manuscript critically for important intellectual content. Dr Higgins participated in the design of the study, participated in the interpretation of the data, and helped to revise the manuscript critically for important intellectual content.

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