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Major Chromosomal Anomalies among Very Low Birth Weight Infants in the Vermont Oxford Network

Nansi S. Boghossian, MPH, PhD^a, Jeffrey D. Horbar, MD^{b,c}, Joseph H. Carpenter, MS^b, Jeffrey C. Murray, MD^a, Edward F. Bell, MD^a, and for the Vermont Oxford Network

^aDepartment of Pediatrics, University of Iowa, Iowa City, Iowa

^bVermont Oxford Network, Burlington, Vermont

^cDepartment of Pediatrics, University of Vermont, Burlington, Vermont

Abstract

Objective—To examine prevalence, characteristics, interventions and mortality of VLBW infants with trisomy 21 (T21), trisomy 18 (T18), trisomy 13 (T13) or triploidy.

Study design—Infants with birth weight 401–1500 g admitted to centers of the Vermont Oxford Network during 1994–2009 were studied. A majority of the analyses are presented as descriptive data. Median survival times and their 95% CIs were estimated using the Kaplan-Meier approach.

Results—Of 539509 VLBW infants, 1681 (0.31%) were diagnosed with T21, 1416 (0.26%) with T18, 435 (0.08%) with T13, and 116 (0.02%) with triploidy. Infants with T18 were the most likely to be growth restricted (79.7%). Major surgery was reported for 30.4% of infants with T21, 9.2% with T18, 6.4% with T13, and 4.8% with triploidy. Hospital mortality occurred among 33.1% of infants with T21, 89.0% with T18, 92.4% with T13, and 90.5% with triploidy. Median survival time was 4 days (95% CI, 3–4) among infants with T18 and 3 days (95% CI, 2–4) among both infants with T13 and infants with triploidy.

Conclusion—In this cohort of VLBW infants, survival among infants with T18, T13 or triploidy was very poor. This information can be used to counsel families.

Keywords

neonatal mortality; neonatal morbidity; premature; preterm; very low birth weight; birth defect; trisomy 21; Down syndrome; trisomy 18; Edward syndrome; trisomy 13; Patau syndrome; triploidy

INTRODUCTION

Trisomy 21 (T21), trisomy 18 (T18), and trisomy 13 (T13) represent the most commonly diagnosed autosomal trisomies in live-born infants.¹ Previous literature described extensively the physical features, associated anomalies, management, and survival of these infants.^{2–8} However, a majority of the published articles addressed survival and interventions among term or near-term infants or were limited by small numbers of patients.

Address correspondence to Nansi S. Boghossian, MPH, PhD, Epidemiology Branch Division of Epidemiology, Statistics & Prevention Research *Eunice Kennedy Shriver* National Institute of Child Health & Human Development, 6100 Executive Blvd Room 7B03C, Bethesda, MD 20892-7510. nansi.boghossian@nih.gov Telephone: 301 435 7597. Fax: 301 402 2084.

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Very-low-birth-weight (VLBW) infants with chromosomal anomalies have different challenges, as VLBW newborns are known to be at a higher risk of mortality and several neonatal morbidities. We used data from the Vermont Oxford Network (VON) to examine the frequency, associated anomalies, interventions, mortality, and neonatal morbidities of VLBW infants with T21, T18, T13, or triploidy.

METHODS

Data were collected prospectively by US and international Neonatal Intensive Care Units (NICUs) participating in the VON. VON is a nonprofit voluntary collaboration of health care professionals dedicated to improving the outcomes of high-risk newborn infants. The use of the VON database for research was approved by the Committee for Human Research at the University of Vermont. Eligibility criteria for the centers participating in the VON database included from 1994–1995, infants with birth weight 501–1500 g; and from 1996–2009, infants with birth weight 401–1500 g. Accordingly, depending on the birth year, infants with birth weight 401–1500 or 501–1500 g, born between January 1, 1994 and December 31, 2009, at one of the VON participating centers or transferred to one of the study centers within the first 28 days after birth were studied. Participating centers followed a consistent set of rules for identifying and collecting data for eligible infants as outlined in the VON's *Manual of Operations*.⁹

Neonatal information, including demographic measures and major birth defects, was collected for all eligible infants. Data on neonatal morbidities diagnosed during the hospital stay were collected for infants admitted to the NICU and included respiratory distress syndrome, pneumothorax, patent ductus arteriosus (PDA), early bacterial sepsis (positive blood and/or cerebrospinal fluid culture before day 3 of life), coagulase-negative staphylococcus sepsis (after day 3 of life), late bacterial sepsis (after day 3 of life), nosocomial infection (after day 3 of life), fungal infection (after day 3 of life), necrotizing enterocolitis (NEC), gastrointestinal perforation, severe intraventricular hemorrhage (grades 3–4), periventricular leukomalacia, retinopathy of prematurity (ROP), severe ROP (stages 3–5), and chronic lung disease at 36 weeks' corrected gestational age (GA). Small for gestational age (SGA) was defined by birth weight below the 10th percentile.¹⁰

Major birth defects were entered according to a predefined list in the *Manual of Operations* or as a text field for defects considered lethal or life threatening by the reporting unit. Chromosomal anomalies including T21, T18, and T13 had predefined codes. Prior to 2008, triploidy was recorded in text fields in response to a general question about other major chromosomal anomalies. In 2008, triploidy was also assigned a predefined code. Specific surgery codes were added in 2006. Before 2006, a general question asked if any major surgical procedure was conducted in the operating room. This excluded PDA ligation, NEC surgery, and ROP surgery, as they were collected as individual questions. Other changes in the collection of variables are noted in table footnotes as appropriate. Worth noting is that chromosomal microarray analysis was not considered in the current study.

To identify all infants with T21, T18, T13 or triploidy, relevant text fields were reviewed. Additionally, among infants with T21, T18, T13, or triploidy, surgery codes specific for certain types of birth defects were reviewed to identify infants with associated lesions that had not been recorded elsewhere. Final discharge status and length of hospital stay (LOHS), defined as the sum of stay at all hospitals before the first discharge to home, death, or first birthday, whichever occurred first, were assessed for all infants.

Neonatal characteristics, delivery room (DR) interventions, surgeries, in-hospital morbidity outcomes and mortality were examined for all infants with T21, T18, T13, or triploidy. In

some tables, infants without chromosomal anomalies are also included for comparison purposes. A majority of the analyses are presented as descriptive data. Median survival times and their 95% CIs were estimated using the Kaplan-Meier approach. The Cochran-Armitage trend test was also used to examine trends in mortality rates across the study period. All analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

A total of 539509 VLBW infants were born or cared for at one of the 915 institutions participating in VON between 1994 and 2009, of which 456279 (84.6%) infants were cared for at US centers. VLBW infants with major birth defects accounted for 25,634 (4.8%) with chromosomal anomalies reported for 5257 (0.97%) infants. Table 1 ([online](#)) shows the frequency of VLBW infants with T21 (1681, 0.31%), T18 (1416, 0.26%), T13 (435, 0.08%) or triploidy (116, 0.02%) in the VON cohort. A majority of these infants were cared for at US centers (range 83.0%–87.9%). No significant differences were noted in the percentage of triploidy cases before and after the triploidy code was added in 2008. Nine infants with suspected, but not proved T21, T18, or T13 and 24 infants with T21, T18, or T13 plus other associated chromosomal anomalies were excluded from subsequent analyses.

Infant Characteristics

Infants with T18 were more likely to be growth restricted than infants in the other groups (Table 2). Worth noting are the lower percentages of multiple births among infants with the more severe chromosomal anomalies (multiple births: 17.0% of infants with T21, 0.86% of infants with triploidy). Among T18 or T13 multiples, a shift towards a higher distribution of females was also noted (T13 multiples: 57.6% females; T18 multiples: 67.6% females) (data not shown).

Co-Occurring Birth Defects and Surgeries

A total of 583 (34.7%), 574 (40.5%), 168 (38.6%), and 35 (30.2%) infants with T21, T18, T13, or triploidy, respectively, had one or more associated structural malformations (Table 3; [online](#)). Congenital heart defects (CHDs) were most commonly reported for infants with T21, and gastrointestinal defects were the most prevalent type of birth defect among infants with T18 or T13.

Among DR survivors, major surgery was reported for 30.4% of infants with T21, 9.2% of infants with T18, 6.4% of infants with T13, and 4.8% of infants with triploidy (Table 4). After examining the surgery-specific codes added in 2006, the most common procedures involved the abdomen. Only 3 (0.70%) infants with T18 and 1 (0.76%) infant with T13 had heart surgery. As expected, procedures among infants with triploidy were very rare; 4 (4.8%) infants were reported to have had major surgery. The types of surgeries were available for 2 infants; 1 had omphalocele repair and 1 had PDA ligation.

Interventions and Discharge Characteristics

Cesarean-section delivery was performed for >50% of infants with chromosomal anomalies. Any type of DR intervention among infants with a chromosomal anomaly ranged between 66.6% for infants with T13 and 80.8% for infants with T21, and 90.9% of infants without a chromosomal anomaly had DR interventions. When NICU interventions among DR survivors were examined, the percentages of infants receiving any type of respiratory support were comparable among the groups. Infants with T18, T13, or triploidy were more likely to be discharged on oxygen and a monitor and were more likely to have received no enteral feeding before discharge or death compared to infants with T21 and infants without a chromosomal anomaly (Table 5).

Mortality and Survival

In-hospital mortality was 33.1% for infants with T21, 89.0% for infants with T18, 92.4% for infants with T13, and 90.5% for infants with triploidy. Mortality was highest among infants with the lowest GA and was >95% among infants with T18, T13, or triploidy with a GA \geq 29 weeks (Table 6). No significant trends in mortality rates were noted in any group across the study period (P value trend-test >0.05). Among the 153 infants with T18 (including 5 reported to be mosaic), 33 infants with T13 (including 1 reported to be mosaic), and 11 infants with triploidy (including 1 reported to be mosaic diploid/triploid) discharged home, the median LOHS was 33 days (25–75%, 13–58), 45 days (25–75%, 31–77) and 43 days (25–75%, 20–72) with a mean (SD) discharge weight of 1732 (673) g, 1992 (748) g, and 1838 (666) g, respectively. The median survival time was 4 days (95% CI, 3–4) among infants with T18 and 3 days (95% CI, 2–4) among both infants with T13 and infants with triploidy. By 1 week of life, 67.4% of infants with T18 and 73.1% of infants with T13 had died.

Morbidities

Table 7 ([online](#)) shows the outcomes of DR survivors among the 4 groups of infants with chromosomal anomalies and among infants without chromosomal anomalies. Approximately 50% of infants with T21 had a PDA with 19.8% treated with indomethacin and 9.4% having a surgical ligation. Infections and sepsis rates were lower among infants with T18, T13, or triploidy in comparison with infants with T21 and infants without chromosomal anomalies, reflecting the higher rates of early mortality among the former groups of infants. NEC surgery was performed for 6 (0.56%) infants with T18 and 4 (1.4%) infants with T13. Cranial imaging and ROP examination were more likely obtained for infants with T21 and infants without a chromosomal anomaly than among the other groups of infants. ROP surgery was performed among 10 (0.67%) infants with T21 and 2 (0.19%) infants with T18. Chronic lung disease was more common among infants with T18, T13, or triploidy than among infants with T21 and infants without a chromosomal anomaly, with steroid administration being more common among infants in the 2 latter groups.

DISCUSSION

VLBW infants represent 1.5% of annual births in the US.¹¹ For 2009, data collected by the VON database represented approximately 70% of the VLBW population born in the United States. The prevalence of the major chromosomal anomalies per 10000 live births in this population was: 31.2 for T21, 26.2 for T18, 8.1 for T13, and 2.2 for triploidy. The rates for the trisomies are much higher than those based on all US births, with recent estimates for T21, T18, and T13 per 10000 live births being: 13.5, 2.5, and 1.2, respectively.¹ As this study was based on VLBW newborns, the elevated rates reflect the high proportions of growth restriction among these infants. This was especially the case for infants with T18, of whom 80% had low birth weight for gestational age (ie, SGA) consistent with previous findings.^{2,12} The higher rates are also consistent with the general observation that infants with significant abnormalities are more likely to be born prematurely and to be SGA.^{13,14}

In general, infants with a chromosomal anomaly were less likely to receive any type of DR intervention than infants without a chromosomal anomaly. For infants with T13 or T18, DR resuscitation rates were 65% and 74%, respectively. In contrast, a recent survey found that at the mother's request, 44% of U.S. neonatologists would consider resuscitating a preterm infant with confirmed T18 and a known CHD,¹⁵ and the most recent American Academy of Pediatrics neonatal resuscitation guidelines excluded T18 but included T13 in the list of conditions for which resuscitation is not indicated.¹⁶ We did not, however, have information on when the diagnosis of the chromosomal anomaly was suspected and when it was

confirmed. In particular, we had no information about whether the diagnosis had been made prenatally, which might have affected both parent and medical team views on the mode of delivery and resuscitation. Beyond the DR, the use of respiratory support in the NICU among infants with T18 or T13 was as common as among infants without chromosomal anomalies, and major surgeries were performed on 9.2% of infants with T18 and 6.4% of infants with T13.

Median survival times for VLBW infants with T18 or T13 in our cohort were similar to some previous reports^{3,7,17} but lower than others.^{4,5} By 1 week of age, 67.4% of infants with T18 and 73.1% of infants with T13 had died. This is higher than the previously reported estimates from more recent studies (T18: range 40–63%; T13: 50–58%).^{3,4,5,7,18} At 1 year of age, 3 (0.21%) infants with T18 were still hospitalized. Others have reported 1-year survival among these infants to range between 0–8%.^{3,4,5,7,18,19,20} Our mortality rates, however, might have been confounded by withholding medical treatment from these infants given the dual risks of major chromosomal anomaly and VLBW. Although offering intensive management for infants with T21 is standard treatment,^{21,22} the decision to implement or continue invasive or other life-sustaining procedures among infants with T18 or T13 is a complex decision dependent on input from the family, family supporters, involved healthcare workers and sometimes bioethicists and/or independent guardians of the infant. Although some have indicated that cardiac surgery is not appropriate for these infants as they die of conditions unrelated to their cardiac defects,^{5,20,23} others have argued that cardiac surgery and the related intensive treatment are ethically acceptable as they can alleviate their symptoms and prolong their survival.^{6,24,25,26} An extensive body of literature addresses the challenges created by the birth of infants with T18 or T13, whether treatment is in their best interest or whether it is “medically futile” extending their suffering and pain given their profound neurodevelopmental disability and reduced life span.²⁷ These difficult choices and their timing cannot be derived from algorithms based on empiric outcome data alone. We offer the findings in this study as one facet of the information that can help families and the health care community with these agonizing decisions.

Our study had several limitations. The age at surgery for infants in the VON cohort was not available, and thus the duration of postoperative survival for infants with T18 or T13 could not be established. Data on long-term follow-up beyond hospital discharge were not available, and the duration of survival for 10.8% of infants with T18, 7.6% of infants with T13, and 9.5% of infants with triploidy could not be examined. Some of these infants, given their short LOHS and their very low weight at discharge, were likely discharged home to die with comfort care only. In addition to the previously mentioned mosaic cases, we cannot exclude the possibility of other infants with mosaicism influencing survival in the VON cohort. The associated malformations among infants with chromosomal anomalies were, in general, likely to have been under-reported, as several hospitals consider these chromosomal anomalies to be a complete report and do not list other congenital anomalies separately. For example, among VLBW infants with T21 in our study, the rate of CHD was 20%, whereas most studies of T21 report a 40–55% CHD rate.²⁸ The large sample size in our study makes our findings generalizable to a diverse group of NICUs with varying care practices. Such information is useful to health care providers in counseling families of VLBW infants affected with these chromosomal anomalies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ABBREVIATIONS

CHD	congenital heart defect
CI	confidence interval
DR	delivery room
GA	gestational age
LOHS	length of hospital stay
NEC	necrotizing enterocolitis
NICU	Neonatal Intensive Care Unit
PDA	patent ductus arteriosus
ROP	retinopathy of prematurity
SGA	small for gestational age
T13	trisomy 13
T18	trisomy 18
T21	trisomy 21
VLBW	very-low-birth-weight
VON	Vermont Oxford Network

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TABLE 1

Frequency and distribution of major types of chromosomal anomalies among VLBW infants in the Vermont Oxford Network born 1994–2009

Type of Chromosomal Anomaly	Including Infants with Other Chromosomal Anomalies	Excluding Infants with Other Chromosomal Anomalies
	N (%) ¹	N (%) ²
Trisomy 21	1690 (0.31)	1681 (0.31)
Trisomy 18	1430 (0.27)	1416 (0.26)
Trisomy 13	443 (0.08)	435 (0.08)
Triploidy	116 (0.02)	116 (0.02)

¹ 7 infants had T21 and other chromosomal anomaly including: 2 with triple X syndrome, 3 with Klinefelter's syndrome, 1 with DiGeorge syndrome and 1 with 3p deletion; 2 infants had T21 and T18; 7 infants had T18 and other chromosomal anomaly including: 3 with triple X syndrome, 1 with Klinefelter's syndrome, 1 with trisomy 6, 1 with Wolf-Hirschhorn syndrome and 1 with partial trisomy 20q and partial monosomy 20p; 5 infants had T18 and T13; 3 infants had T13 and other chromosomal anomaly including: 1 with triple X syndrome, 1 with DiGeorge syndrome, and 1 with ring chromosome 15.

² Numbers exclude infants with associated chromosomal anomalies. Numbers include mosaic cases: 2 infants with T21, 5 with T18, 1 with T13, 1 with triploidy/diploidy.

TABLE 2

Characteristics of VLBW infants with T21, T18, T13 and triploidy in the Vermont Oxford Network born 1994–2009

Characteristic, N (%) or Mean (SD) [†]	Group			
	T21 N=1681	T18 N=1416	T13 N=435	Triploidy N=116
Antenatal steroids	944 (56.9)	425 (30.2)	166 (38.2)	52 (45.6)
Female	790 (47.0)	806 (57.0)	240 (55.3)	67 (58.3)
Multiple births	285 (17.0)	140 (9.9)	33 (7.6)	1 (0.86)
Race				
Black	227 (13.6)	232 (16.5)	82 (18.9)	12 (10.3)
Hispanic	341 (20.4)	305 (21.6)	109 (25.2)	13 (11.2)
White	972 (58.0)	726 (51.5)	218 (50.3)	87 (75.0)
Asian ²	80 (5.0)	93 (7.0)	12 (2.9)	3 (2.8)
Native American ²	13 (0.82)	17 (1.3)	3 (0.73)	1 (0.93)
Other	42 (2.5)	37 (2.6)	9 (2.1)	0 (0.0)
Small for gestational age	769 (45.8)	1128 (79.7)	201 (46.2)	68 (58.6)
Apgar-1min ³	383 (23.0)	878 (62.9)	264 (61.5)	67 (58.3)
Apgar-5min ³	206 (12.3)	451 (32.5)	160 (37.3)	44 (38.3)
Inborn	1368 (81.4)	1157 (81.7)	376 (86.4)	100 (86.2)
Birth weight (grams)				
Mean (SD)	1070 (316)	1102 (287)	1088 (316)	889 (295)
Range	401–1500	405–1500	401–1500	410–1440
401–500	102 (6.1)	39 (2.7)	25 (5.7)	12 (10.3)
501–600	100 (6.0)	59 (4.2)	25 (5.7)	14 (12.1)
601–700	98 (5.8)	62 (4.4)	21 (4.8)	14 (12.1)
701–800	91 (5.4)	84 (5.9)	25 (5.7)	9 (7.8)
801–900	106 (6.3)	116 (8.2)	22 (5.1)	8 (6.9)
901–1000	129 (7.7)	130 (9.2)	39 (9.0)	14 (12.1)
1001–1100	159 (9.5)	158 (11.2)	35 (8.1)	16 (13.8)
1101–1200	171 (10.2)	146 (10.3)	47 (10.8)	6 (5.2)
1201–1300	216 (12.8)	170 (12.0)	53 (12.2)	14 (12.1)
1301–1400	242 (14.4)	207 (14.6)	59 (13.6)	5 (4.3)
1401–1500	267 (15.9)	245 (17.3)	84 (19.3)	4 (3.4)
Gestational age (weeks)				
Mean (SD)	29.4 (3.8)	31.8 (3.6)	29.6 (3.4)	29.6 (3.9)
Range	19–40	17–41	21–37	18–38
15–23	163 (9.7)	33 (2.3)	37 (8.5)	8 (6.9)
24–26	187 (11.1)	88 (6.2)	39 (9.0)	15 (12.9)
27–29	430 (25.6)	226 (16.0)	111 (25.5)	28 (24.1)
30–32	548 (32.6)	409 (28.9)	171 (39.3)	40 (34.5)
33–41	351 (20.9)	659 (46.6)	77 (17.7)	25 (21.6)

¹SD= standard deviation. Information was missing in the groups shown for mode of delivery: 2 infants; antenatal steroids: 32; sex: 4; race: 14; SGA: 4; GA: 3; Apgar-1 min: 39; Apgar-5 min: 44.

²Variable added in 1997, thus the denominator excludes infants born prior to 1997. Prior to 1997, Asian race and Native American race coded in Other race category.

TABLE 3

Frequency and distribution of associated birth defects among infants with T21, T18, T13 and triploidy in the Vermont Oxford Network Database born 1994–2009

Category, N (%)	Group			
	T21 [‡] N=1681	T18 ^{##} N=1416	T13 ^{###} N=435	Triploidy N=116
Central Nervous System Defects (CNS)	29 (1.7)	88 (6.2)	38 (8.7)	15 (12.9)
Anencephaly	--	3 (0.21)	--	--
Meningomyelocele	1 (0.06)	36 (2.5)	4 (0.92)	9 (7.8)
Hydranencephaly	--	2 (0.14)	--	--
Congenital hydrocephalus	21 (1.2)	18 (1.3)	5 (1.1)	5 (4.31)
Holoprosencephaly	2 (0.12)	8 (0.56)	24 (5.5)	2 (1.7)
Other lethal or life-threatening CNS defects [†]	5 (0.41)	29 (2.9)	7 (2.3)	3 (3.8)
Congenital Heart Defects (CHD)	340 (20.2)	256 (18.1)	82 (18.9)	8 (6.9)
Truncus arteriosus	1 (0.06)	1 (0.07)	2 (0.46)	--
Transposition of the great vessels	--	8 (0.56)	2 (0.46)	1 (0.86)
Tetralogy of Fallot	44 (2.6)	48 (3.4)	21 (4.8)	3 (2.6)
Single ventricle	2 (0.12)	12 (0.85)	1 (0.23)	--
Double outlet right ventricle	10 (0.59)	68 (4.8)	15 (3.4)	1 (0.86)
Complete atrioventricular canal	222 (13.2)	26 (1.8)	6 (1.4)	--
Pulmonary atresia	6 (0.36)	7 (0.49)	8 (1.8)	1 (0.86)
Tricuspid atresia	--	3 (0.21)	--	--
Hypoplastic left heart syndrome	5 (0.30)	32 (2.3)	11 (2.5)	--
Interrupted aortic arch	4 (0.24)	13 (0.92)	9 (2.1)	--
Total anomalous pulmonary venous return	2 (0.12)	2 (0.14)	1 (0.23)	1 (0.86)
Other lethal or life-threatening CHD [†]	71 (5.8) [*]	77 (7.8) [*]	12 (3.9)	2 (2.6)
Gastrointestinal (GI) Defects	191 (11.4)	277 (19.6)	89 (20.5)	14 (12.1)
Cleft palate	9 (0.54)	40 (2.8)	61 (14.0)	11 (9.5)
Tracheoesophageal fistula	13 (0.77)	130 (9.2)	8 (1.8)	--
Esophageal atresia	13 (0.77)	98 (6.9)	3 (0.69)	--
Duodenal atresia	131 (7.8)	3 (0.21)	1 (0.23)	1 (0.86)
Ileal atresia	2 (0.12)	1 (0.07)	--	--
Atresia of large bowel or rectum	1 (0.06)	--	--	--
Imperforate anus	10 (0.59)	18 (1.3)	6 (1.4)	--
Omphalocele	4 (0.24)	68 (4.8)	19 (4.4)	2 (1.7)
Gastroschisis	1 (0.06)	6 (0.42)	2 (0.46)	--
Other lethal or life-threatening GI defects [†]	25 (2.0)	8 (0.81)	2 (0.65)	--
Genitourinary (GU) Defects	22 (1.3)	20 (1.4)	10 (2.3)	2 (1.7)
Bilateral renal agenesis	1 (0.06)	2 (0.14)	1 (0.23)	--
Bilateral polycystic, multicystic, or dysplastic kidneys	2 (0.12)	7 (0.49)	4 (0.92)	1 (0.86)
Obstructive uropathy with congenital hydronephrosis	14 (0.83)	6 (0.42)	2 (0.46)	1 (0.86)
Exstrophy of the bladder	--	--	1 (0.23)	--

Category, N (%)	Group			
	T21 [‡] N=1681	T18 ^{‡‡} N=1416	T13 ^{‡‡‡} N=435	Triploidy N=116
Other lethal or life-threatening GU defects ¹	5 (0.41)	5 (0.51)	2 (0.65)	--
Other Coded Categories of Birth Defects	51 (3.0)	76 (5.4)	17 (3.9)	2 (1.7)
Skeletal dysplasia	3 (0.18)	12 (0.85)	4 (0.92)	1 (0.86)
Congenital diaphragmatic hernia	1 (0.06)	49 (3.5)	8 (1.8)	--
Hydrops fetalis ²	35 (2.1)	4 (0.28)	3 (0.69)	--
Oligohydramnios sequence ³	10 (0.59)	10 (0.71)	2 (0.46)	1 (0.86)
Inborn error of metabolism	4 (0.24)	--	--	--
Myotonic dystrophy ⁴	--	1 (0.07)	--	--
Tracheal agenesis or atresia ⁵	--	2 (0.67)	--	--
Hemoglobin Barts	1 (0.25)	--	--	--
Pulmonary Birth Defects	1 (0.25)	2 (0.67)	1 (1.1)	--
Congenital cystic adenomatoid malformation of the lung ⁵	--	1 (0.34)	--	--
Other lethal or life-threatening pulmonary malformation ⁵	1 (0.25)	1 (0.34)	1 (1.1)	--
Other Lethal or Life-Threatening Birth Defects	42 (2.5)	44 (3.1)	11 (2.5)	11 (9.5)

Numbers and frequencies shown in bolded font represent the number of infants with a certain malformation. Subsequent numbers represent the number of defects. An infant can be included more than once in the same organ system. Example an infant with a duodenal atresia and other GI defect is included in both categories.

¹Variable added in 2002; to be considered as lethal or life threatening, a birth defect must either: 1) be the primary cause of death or 2) be treated prior to discharge with specific surgical or medical therapy to correct a major anatomic defect or a life threatening physiologic dysfunction.

²Hydrops fetalis with anasarca and one or more of the following: ascites, pleural effusion, pericardial effusion.

³Oligohydramnios sequence including all 3 of the following: 1) Oligohydramnios documented by antenatal ultrasound 5 or more days prior to delivery, 2) evidence of fetal constraint on postnatal physical exam and 3) postnatal respiratory failure requiring endotracheal intubation and assisted ventilation.

⁴Requiring endotracheal intubation and assisted ventilation.

⁵Variable added in 2008.

[‡]583 (34.7%) infants with T21 had one or more additional structural malformations: 469 (27.9%), 94 (5.6%), 13 (0.77%) and 7 (0.42%) infants had 1, 2, 3, and 4 additional malformations respectively. Among infants with additional structural malformations, CHD and GI defects occurred together in 47 (8.1%) infants, 9 (1.5%) infants had heart and CNS defects.

^{‡‡}574 (40.5%) infants with T18 had one or more additional structural malformations: 336 (23.7%), 165 (11.7%), 50 (3.5%) and 23 (1.6%) infants had 1, 2, 3, and 4 additional malformations respectively. Among infants with additional structural malformations, CHD and GI defects occurred together in 74 (12.9%) infants, 24 (4.2%) infants had CHD and CNS defects and 25 infants (4.4%) had GI and CNS defects.

^{‡‡‡}168 (38.6%) infants had one or more additional structural malformations: 99 (22.8%), 47 (10.8%), 12 (2.8%) and 10 (2.3%) infants had 1, 2, 3, and 4 additional malformations respectively. Among infants with additional structural malformations, CHD and GI defects occurred together in 32 (19.0%) infants, 16 (9.5%) infants had heart and CNS defects and 18 infants (10.7%) had GI and CNS defects.

^{*}The majority of CHDs in this group are attributed to ventricular septal defect (VSD) with or without atrial septal defect (ASD).

TABLE 4

Types of surgeries among VLBW delivery room survivors with T21, T18 and T13 in the Vermont Oxford Network born 2006–2009

Type of Surgery ¹ , N (%)	Group		
	T21 N=653	T18 [‡] N=429	T13 ^{‡‡} N=131
Open Heart or Vascular Procedures	38 (5.8)	3 (0.70)	1 (0.76)
S502 Repair of coarctation of the aorta	2 (0.31)	1 (0.23)	--
S504 Repair or palliation of congenital heart disease	33 (5.1)	2 (0.47)	1 (0.76)
S500 Other open heart or vascular surgery requiring general or spinal anesthesia	5 (0.77)	--	--
Abdomen	137 (21.0)	28 (6.5)	7 (5.3)
S301 Rectal biopsy with or without anoscopy	10 (1.5)	1 (0.23)	--
S302 Laparoscopy (diagnostic, with/without biopsy)	3 (0.46)	--	--
S303 Laparotomy (diagnostic or exploratory, with/without biopsy)	37 (5.7)	2 (0.47)	2 (1.5)
S304 Fundoplication	10 (1.5)	1 (0.23)	--
S307 Jejunostomy, ileostomy, enterostomy, colostomy for intestinal diversion	26 (4.0)	2 (0.47)	3 (2.3)
S308 Small bowel resection with or without primary anastomosis	24 (3.7)	2 (0.47)	2 (1.5)
S309 Large bowel resection	5 (0.77)	--	--
S310 Duodenal atresia/stenosis/web repair	48 (7.4)	--	--
S312 Excision of Meckel's diverticulum	2 (0.31)	1 (0.23)	1 (0.76)
S313 Drainage of intra-abdominal abscess (not as primary treatment for NEC)	1 (0.15)	--	--
S314 Surgery for meconium ileus	2 (0.31)	1 (0.23)	--
S315 Excision of omphalomesenteric duct or duct remnant	1 (0.15)	--	--
S317 Omphalocele repair (primary or staged)	--	1 (0.23)	1 (0.76)
S318 Lysis of adhesions	4 (0.61)	--	--
S319 Repair of imperforate anus (with or without vaginal, urethral, or vesicle fistula)	2 (0.31)	--	--
S320 Pull through for Hirschsprung's disease (any technique)	2 (0.31)	--	--
S325 Repair of diaphragmatic hernia	1 (0.15)	2 (0.47)	--
S327 Gastrostomy/jejunostomy tube	48 (7.4)	22 (5.1)	1 (0.76)
S328 Upper endoscopy (stomach or duodenum, with or without biopsy)	3 (0.46)	--	--
S329 Colonoscopy/sigmoidoscopy (with or without biopsy)	1 (0.15)	--	--
S330 Takedown of ostomy and/or reanastomosis of bowel (small or large bowel) ²	4 (0.77)	1 (0.30)	--
S331 Ladd's or other procedure for correction of malrotation ²	5 (0.97)	1 (0.30)	--
S332 Appendectomy ²	10 (1.9)	1 (0.30)	--
S333 Primary peritoneal drainage for NEC, suspected NEC or intestinal perforation	11 (1.7)	1 (0.23)	1 (0.76)
S336 Liver biopsy done during laparotomy or laparoscopy (includes wedge or needle techniques) ³	1 (0.27)	--	--
S300 Other abdominal surgery requiring general or spinal anesthesia	11 (1.7)	1 (0.23)	--
Thorax	25 (3.8)	11 (2.6)	4 (3.1)
S201 Tracheal resection	1 (0.15)	--	--
S203 Tracheoesophageal atresia and/or fistula repair	6 (0.92)	8 (1.9)	1 (0.76)
S204 Thoracoscopy (with or without pleuridesis or pleurectomy)	1 (0.15)	1 (0.23)	--
S205 Thoracotomy (with or without pleural or lung biopsy)	3 (0.46)	1 (0.23)	--

Type of Surgery ¹ , N (%)	Group		
	T21 N=653	T18 [‡] N=429	T13 ^{‡‡} N=131
S210 Bronchoscopy (with or without biopsy)	18 (2.8)	1 (0.23)	1 (0.76)
S211 Esophagoscopy (with or without biopsy)	--	--	1 (0.76)
S200 Other thoracic surgery requiring general or spinal anesthesia	2 (0.31)	--	1 (0.76)
Genitourinary	7 (1.1)	4 (0.93)	1 (0.76)
S410 Inguinal hernia repair	7 (1.1)	3 (0.70)	1 (0.76)
S411 Orchiopexy	1 (0.29)	--	--
S400 Other genitourinary surgery requiring general or spinal anesthesia	--	1 (0.23)	--
Central Nervous System	6 (0.92)	2 (0.47)	--
S901 Ventriculoperitoneal or other ventricular shunt	4 (0.61)	1 (0.23)	--
S902 External ventricular drain	1 (0.15)	--	--
S903 Ventricular drain with reservoir placement or removal	2 (0.31)	--	--
S904 Meningocele or myelomeningocele repair	1 (0.15)	2 (0.47)	--
S900 Other central nervous system surgery requiring general or spinal anesthesia	1 (0.15)	--	--
Skin or soft tissue surgery requiring general or spinal anesthesia	2 (0.31)	--	--
Head and Neck	14 (2.1)	6 (1.4)	1 (0.76)
S101 Tracheostomy/Tracheotomy	11 (1.7)	5 (1.2)	1 (0.76)
S103 Ophthalmologic surgery other than laser or cryosurgery for ROP	2 (0.31)	--	--
S100 Other head and neck surgery requiring general or spinal anesthesia	1 (0.15)	1 (0.23)	--
Diagnostic or Interventional Cardiac Catheterization	10 (1.5)	1 (0.23)	--
S601 Diagnostic cardiac catheterization	8 (1.2)	--	--
S602 Interventional catheterization with balloon septostomy	--	1 (0.23)	--
S604 Interventional catheterization with pulmonary valvuloplasty	1 (0.15)	--	--
S600 Other interventional catheterization whether or not anesthesia was required	2 (0.31)	--	--
	N=1515	N=1106	N=302
Any major surgery*	453 (30.4)	99 (9.2)	19 (6.4)

For a complete list of surgeries collected refer to the VON Manual of Operations. Numbers and frequencies shown in bolded font represent the number of infants with a certain surgery. Subheadings of surgeries represent the number of procedures. Example an infant with S303, S307 and S308 abdominal surgeries is included only once in bolded font and in each surgery category code accordingly.

¹ Surgery specific codes added in 2006 unless otherwise stated.

² Variable added in 2007.

³ Variable added in 2008.

* Includes data collected from 1994–2009 on: infants with any of the above surgery codes (surgery specific codes added in 2006), NEC surgery, ROP surgery, surgical PDA ligation and infants with any major surgery conducted before the addition of the surgery specific codes in 2006. Surgeries S410 and S411 are not counted as major surgeries.

[‡] Infants with T18 and/or multiple procedures and/or open heart or vascular procedures included: 1 infant with S303, S307, S308, S312, S327, S330, S331, S332, S410, S101 and NEC surgery with an initial LOHS of 91 days, transferred to a non-VON center for other surgeries and was still hospitalized as of first birthday; infant with S502 procedure had a LOHS of 4 days and died; two infants with S504 procedure, 1 had a LOHS of 124 days and died and the second a LOHS of 103 days with missing data on discharge status; 1 infant with S327, S410, S101 with LOHS 303 days discharged alive.

^{††}Infants with T13 and and/or multiple procedures and/or open heart or vascular procedures included: 1 infant with S303, S307, S308, S210 and S101 with a LOHS of 66 days and died; 1 infant with S303, S307, S308, and S211 with a LOHS of 110 days discharged alive; 1 infant with S327 and S203 with a LOHS of 66 days and died; 1 infant with S504 procedure with a LOHS of 168 days discharged alive (also had PDA ligation).

TABLE 5

Interventions and discharge characteristics among VLBW Infants with T21, T18, T13, triploidy and infants without chromosomal anomalies in the Vermont Oxford Network born 1994–2009

Type of Intervention/ Discharge Characteristic, N (%)	Group					No Chromosomal Anomaly* N=533916
	T21 N=1681	T18 N=1416	T13 N=435	Triploidy N=116		
Delivery Room (DR) Interventions						
Cesarean section delivery	1200 (71.5)	910 (64.3)	239 (54.9)	71 (61.2)		353451 (66.2)
Oxygen given	1331 (79.5)	1049 (74.2)	282 (64.8)	82 (70.7)		472540 (88.7)
Face mask ventilation	705 (42.1)	820 (58.1)	208 (47.8)	66 (56.9)		299449 (56.2)
Endotracheal tube ventilation	577 (34.5)	678 (48.0)	185 (42.5)	58 (50.0)		292586 (54.9)
Epinephrine given	34 (2.0)	94 (6.6)	13 (3.0)	4 (3.4)		20449 (3.8)
Cardiac compression	55 (3.3)	132 (9.3)	31 (7.1)	5 (4.3)		31869 (6.0)
DR surfactant ¹	232 (16.6)	136 (11.7)	47 (13.1)	23 (24.7)		127194 (29.8)
Any type of DR intervention	1352 (80.8)	1070 (75.7)	289 (66.6)	84 (72.4)		484409 (90.9)
Surfactant at any time	614 (36.6)	513 (36.3)	169 (39.2)	52 (45.2)		336310 (63.1)
NICU Interventions among DR Survivors						
Oxygen	N=1515	N=1106	N=302	N=85	N=512537	
Conventional ventilation	1300 (85.8)	990 (89.5)	272 (90.1)	76 (89.4)	457574 (89.3)	
High frequency ventilation	915 (60.4)	774 (70.0)	232 (76.8)	65 (76.5)	350303 (68.4)	
Any type of ventilation	275 (18.2)	233 (21.1)	65 (21.5)	24 (28.2)	117314 (22.9)	
High flow nasal cannula ²	937 (61.8)	804 (72.7)	240 (79.5)	68 (80.0)	363565 (70.9)	
Nasal IMV or nasal SIMV ²	288 (44.2)	75 (17.5)	16 (12.2)	1 (3.7)	91487 (45.0)	
Inhaled nitric oxide ³	75 (11.5)	21 (4.9)	4 (3.1)	0 (0.0)	27632 (13.6)	
Nasal CPAP ⁴	43 (11.7)	10 (4.3)	5 (7.4)	2 (16.7)	4987 (4.7)	
Early nasal CPAP ⁵	719 (47.5)	259 (23.4)	55 (18.2)	13 (15.3)	317674 (62.0)	
Any type of respiratory support	283 (49.1)	117 (53.9)	29 (60.4)	3 (42.9)	82441 (35.6)	
Discharge Characteristics among DR Survivors	N=1515	N=1106	N=302	N=85	N=512537	
Oxygen at discharge ⁶	608 (40.2)	704 (63.8)	212 (70.2)	64 (75.3)	135996 (26.6)	

Type of Intervention/ Discharge Characteristic, N (%)	Group				
	T21 N=1681	T18 N=1416	T13 N=435	Triploidy N=116	No Chromosomal Anomaly* N=533916
Monitor at discharge ⁶	752 (52.8)	698 (68.2)	210 (74.5)	59 (75.6)	223776 (46.7)
Enteral feeding at discharge ⁷					
None	258 (23.3)	547 (72.5)	169 (80.1)	44 (77.2)	46776 (13.4)
Human milk only	74 (6.7)	43 (5.7)	14 (6.6)	2 (3.5)	30905 (8.8)
Formula only	435 (39.3)	122 (16.2)	24 (11.4)	6 (10.5)	160202 (45.8)
Human milk with fortifier or formula	340 (30.7)	42 (5.6)	4 (1.9)	5 (8.8)	111724 (32.0)

* Excludes 336 infants with missing information on birth defects. Information was missing in the chromosomal anomaly groups shown for oxygen: 9 infants; face mask ventilation 10; endotracheal tube ventilation: 10; epinephrine: 9; cardiac compression: 10; DR surfactant: 5; any type of DR intervention: 10; surfactant at any time: 10; discharge oxygen: 6; discharge monitor: 5; enteral feeding: 19; high frequency vent: 1; high flow nasal cannula: 1; nasal IMV: 2. Missing information not reported for infants in the no chromosomal anomaly group.

¹ Variable added in 2000.

² Variable added in 2006; IMV: intermittent mandatory ventilation; SIMV: synchronized intermittent mandatory ventilation.

³ Variable added in 2008.

⁴ CPAP: continuous positive airway pressure. For the purpose of this definition, nasal IMV and SIMV are both considered forms of nasal CPAP.

⁵ Variable added in 2002, coded if nasal CPAP yes and if before endotracheal tube ventilation.

⁶ Variable added in 1997; for infants who died before discharge, item is checked yes if the infant received supplemental oxygen or was on an apnea monitor or cardio-respiratory monitor at any time on the day of death.

⁷ Variable added in 2002; based on enteral feedings received during the 24 hour period prior to discharge, transfer or death and is not applicable if infant died in the DR.

TABLE 6

Discharge status, timing of death and mortality by birth weight and gestational age among VLBW infants with T21, T18, T13 and triploidy in the Vermont Oxford Network born 1994–2009

Outcome, N (%)	Group			
	T21 N=1681	T18 N=1416	T13 N=435	Triploidy N=116
Final discharge status				
Died	550 (33.1)	1259 (89.0)	402 (92.4)	105 (90.5)
Home	1111 (66.8)	153 (10.8)	33 (7.6)	11 (9.5)
Still hospitalized at 1 st birthday	2 (0.12)	3 (0.21)	0 (0.0)	0 (0.0)
DR Death	166 (9.9)	310 (21.9)	133 (30.6)	31 (26.7)
Died by time of death (days)				
1	189 (34.4)	469 (37.3)	167 (41.5)	40 (38.1)
2–3	21 (3.8)	224 (17.8)	70 (17.4)	24 (22.9)
4–7	29 (5.3)	261 (20.7)	81 (20.1)	17 (16.2)
8–28	120 (21.9)	218 (17.3)	67 (16.7)	18 (17.1)
>28	190 (34.6)	86 (6.8)	17 (4.2)	6 (5.7)
Birth weight (grams) mortality				
750	287 (82.0)	203 (98.1)	81 (100)	45 (100)
751–1000	109 (40.8)	272 (96.1)	74 (97.4)	23 (88.5)
1001–1250	84 (19.3)	358 (93.2)	91 (87.5)	26 (89.7)
1251–1500	70 (11.5)	426 (78.7)	156 (89.7)	11 (68.8)
Gestational age (weeks) mortality				
15–23	158 (97.5)	33 (100)	37 (100)	8 (100)
24–26	120 (65.6)	87 (98.9)	38 (97.4)	15 (100)
27–29	138 (32.3)	219 (96.9)	107 (96.4)	27 (96.4)
30–32	92 (17.0)	381 (93.2)	154 (90.1)	38 (95.0)
33–41	41 (11.7)	538 (81.8)	66 (85.7)	17 (68.0)

Information was missing on discharge status: 18 T21 infants, 1 T18; gestational age: 2 T21 infants, 1 T18; timing of death: 1 T21 infant, 1 T18.

TABLE 7

Outcomes of delivery room survivors among VLBW infants with T21, T18, T13, triploidy and infants without chromosomal anomalies in the Vermont Oxford Network born 1994–2009

Outcome, N (%)	Group				
	T21 N=1515	T18 [‡] N=1106	T13 ^{‡‡} N=302	Triploidy ^{‡‡‡} N=85	No chromosomal anomaly N=512537
Respiratory distress syndrome	792 (52.3)	620 (56.2)	191 (63.7)	58 (69.0)	371985 (72.6)
Pneumothorax	60 (4.0)	45 (4.1)	19 (6.3)	11 (13.1)	26631 (5.2)
PDA	753 (49.7)	468 (42.6)	129 (43.0)	27 (32.1)	181686 (35.5)
Indomethacin	299 (19.8)	100 (9.1)	23 (7.6)	5 (5.9)	153845 (30.1)
Ibuprofen for PDA [†]	36 (9.9)	5 (2.1)	5 (7.4)	--	13722 (12.9)
Surgical PDA ligation	142 (9.4)	23 (2.1)	5 (1.7)	1 (1.2)	38552 (7.5)
Early bacterial sepsis	24 (1.6)	10 (0.91)	2 (0.67)	--	11837 (2.3)
Coagulase-negative staph sepsis	154 (10.6)	17 (2.4)	6 (3.1)	--	62953 (13.0)
Late bacterial sepsis	143 (9.8)	27 (3.9)	11 (5.7)	1 (1.9)	53659 (11.1)
Nosocomial infection	258 (17.8)	33 (4.7)	14 (7.3)	1 (1.9)	99761 (20.6)
Fungal infection ²	21 (1.5)	2 (0.3)	--	--	11904 (2.5)
NEC	135 (8.9)	18 (1.6)	9 (3.0)	--	33541 (6.6)
NEC surgery ³	63 (4.2)	6 (0.56)	4 (1.4)	--	16232 (3.2)
Gastrointestinal perforation ⁴	40 (3.1)	9 (1.0)	4 (1.6)	--	9905 (2.4)
Cranial imaging	1306 (86.3)	665 (60.2)	203 (67.2)	57 (67.1)	469049 (91.6)
Intraventricular hemorrhage (grades 1–4)	274 (21.0)	82 (12.3)	37 (18.3)	14 (24.6)	123206 (26.3)
Severe intraventricular hemorrhage (grades 3–4)	86 (6.6)	25 (3.8)	16 (7.9)	2 (3.5)	43661 (9.3)
Cystic periventricular leukomalacia	35 (2.6)	9 (1.3)	1 (0.50)	3 (5.3)	16141 (3.4)
ROP examination performed	901 (59.5)	110 (10.0)	42 (13.9)	11 (12.9)	351400 (68.6)
ROP	213 (23.7)	14 (12.7)	3 (7.1)	2 (18.2)	143119 (40.8)
Severe ROP	24 (2.7)	2 (1.8)	1 (2.4)	--	32964 (9.4)
ROP surgery	10 (0.67)	2 (0.19)	--	--	22028 (4.4)
Chronic lung disease	459 (37.6)	199 (65.7)	38 (74.5)	9 (56.2)	116158 (26.6)
Steroids for chronic lung disease	164 (10.8)	25 (2.3)	3 (1.0)	3 (3.5)	72290 (14.2)

Information was missing in the chromosomal anomaly groups shown for respiratory distress syndrome: 6 infants; pneumothorax: 3; PDA: 10; indomethacin: 8; ibuprofen: 4; surgical PDA ligation: 1; early sepsis: 9; coagulase-negative staph sepsis: 51; late bacterial sepsis: 50; nosocomial infection: 50; NEC: 3; cranial imaging: 3; intraventricular hemorrhage: 2; ROP examination: 6; ROP: 3; steroids for chronic lung disease: 5.

[†]Infants with T18 and procedures: ROP surgery, 1 infant with LOHS 195 days and 1 with LOHS 93 days (also had PDA ligation); PDA ligation, LOHS median 49 days (25–75%: 18–93) range (3–138); NEC surgery, LOHS of infants 5, 6, 29, 49, 91, 157 days.

^{††}Infants with T13 and procedures: PDA ligation, LOHS of infants 19, 20, 53, 72, 168 days; NEC surgery, LOHS of infants 66, 84, 85, 110 days.

^{†††}Infants with triploidy and procedures: PDA ligation with a LOHS of 90 days.

¹Variable added in 2008.

²Variable added in 1996.

³Variable added in 1995.

⁴Variable added in 2000.