Acta Genet Med Gemellol 33:87-95 (1984)

TWIN RESEARCH 4 – Part A: Biology and Obstetrics
Proceedings of the Fourth International Congress on Twin Studies (London 1983)

Malformations in Twins and Their Siblings, Norway, 1967-79

G.C. Windham, T. Bjerkedal
Medical Birth Registry of Norway, Norwegian Health Services, Department of Social Affairs, Oslo

Abstract. During 1967-79 the population-based Medical Birth Registry of Norway registered 7,660 twin pairs (1% of births) born to 7,596 mothers, who gave birth to 6,608 additional infants (twin siblings). The total rate of malformations among twins (278.1/10,000) was not significantly different than among singletons (302.1/10,000), nor among twin siblings (314.8/10,000). By specific type of defect, twins had significantly higher rates than singletons of central nervous system (CNS) defects (Rate Ratio = 1.8) and cardiovascular defects (RR = 1.5). The twins also had a significantly low rate of congenital hip dislocation (RR = 0.4), which may explain the relatively low incidence of malformations in twins. Like-sex (LS) twins had a slightly higher rate of malformations than unlike-sex (US) twins (RR = 1.1), as well as a higher rate of CNS defects (RR = 3.0). The siblings also had a significantly increased rate of CNS defects compared to singletons (RR = 1.9), but not of cardiovascular defects (RR = 0.9). The results indicate that twins have elevated rates of at least some congenital malformations. The observations about CNS defects suggest common factors that can lead to either like-sex twinning, CNS defects, or both. The increased frequency of cardiovascular defects in twins appears to be associated with the biologic conditions of twinning.

Key words: Twinning, Congenital malformations, Ascertainment

INTRODUCTION

Twin studies have traditionally been used to separate the relative contibution of genetic and environmental factors in elucidating etiology of disease. The value of these studies for congenital malformation research derives from the tenet that all twins share relatively similar prenatal environments, and that monozygotic (MZ) twins in addition share identical genotypes whereas dizygotic (DZ) twins are no more similar genetically than other siblings. One of the most important methodologic concerns in such twin studies is ob-

taining unselected cases in numbers great enough for analyses of events as rare as malformations [3].

Few large studies have been conducted to measure the incidence of malformations in twins compared to singletons, but some [5, 6] have reported higher rates among twins, specifically among MZ or like-sexed twins. Furthermore, some investigators [6, 7] have suggested that the twinning phenomeon itself is etiologically associated with defects, either as a casual influence, or as an additional result of disruptive factors in-utero.

Studying the incidence of birth defects in the siblings of twins may aid in distinguishing whether an association between defects and twins is due to the twinning process or whether there are familial factors, either genetic or environmental, that increase susceptibility to malformations and twinning. The siblings also provide a comparison group that is more similar to the twins demographically than the total population may be. This study thus examines the incidence of malformations in twins, their siblings and singletons of the same population, using the large number of unselected twins in the Medical Birth Registry (MBR) of Norway.

MATERIALS AND METHODS

Data for the study was obtained from the national Medical Birth Registry (MBR) of Norway, which has been in existence since 1967 [1]. The registry consists of mandatory reports of all livebirths and stillbirths of 16 weeks gestation or more, made by the attending midwives and physicians. The reported information includes demographics about the fetus and the parents, as well as mother's health before and during pregnancy, circumstances surrounding the delivery, and condition of the newborn.

Of the almost 800,000 births registered in 1967-79, 1.9% were reported to be twin individuals. Zygosity is not routinely determined at birth, so like-sex (LS) versus unlike-sex (US) pair status was used as a substitute in the analysis. Of the 15,320 twins, 69.8% were LS and 30.0% were US (0.2% were of unknown pair type).

All Norwegian residents are assigned a unique personal identification number which is recorded in the MBR for newborns and their parents. Using the mother's identification number, the twins siblings born in 1967-79 could be extracted from the registry. The 7,660 twin pairs were born to 7,596 mothers who gave birth to 6,608 additional siblings within the study period. The sibships may not be complete, but there should be little bias in selection by this method and the data were analyzed as a combined group of siblings, separate from twins. In calculating malformation rates for sibs of like-sex versus unlike-sex twin pairs, only the siblings in families with 1 pair of twins were included. This excluded 50 sibs in families with more than 1 pair of twins, and 17 in families with unknown pair type.

Cases were selected with malformations corresponding to 8th Revision ICD codes 740-759 (congenital anomalies), 551-553 (abdominal hernias), plus cardiac murmurs and positive Ortolani test of the hip. Malformation rates in twins were compared to rates in their siblings and in the singleton population, using a chi-square with 1 degree of freedom to test for significant differences. Total malformation rates count each case once, but different specific malformation groups may include the same individual more than once if he has more than one malformation coded. Malformation rates were adjusted for maternal age (5-year intervals) and parity (1, 2, 3, 4+) differences by the indirect standardization method, with total population rates used as the standard.

RESULTS

Demographics

The percentage of twins in the popultation (1.9%) and the percentage like-sexed (69.8%) were both in accordance with commonly reported rates from other countries. Over the study period the rate of twinning remained fairly constant. The mothers of twins had an average of 1.9 deliveries, which is comparable to the rate in the total population. Of the 6,608 twin sibs, 70.7% had 1 LS pair and 28.3% had 1 US pair as siblings (the remaining 1% were described in "Materials").

The maternal age distribution for twin births was significantly higher than for population births, whereas the maternal age distribution for siblings was similar to the population. Also, twin and their siblings were born at higher parities than population newborns, but their parity distribution is complicated by counting 1 twin delivery as two births.

Malformations

Rates. Overall, twins had a rate of congenital malformations of 278.1 per 10,000 births which did not deviate significantly from the rate of 302.1/10,000 among singletons (Table 1). LS twins had a slightly higher rate than total and US twins. The twin siblings (Table 2) had an even higher rate (314.8/10,000), which was not significantly different from the singleton (Rate Ratio = 1.0) or the twin (RR = 1.1) rates. Siblings of US twins had a slightly higher rate than siblings of LS twins (RR = 1.2).

By malformation type (Table 1) twins had significantly higher rates than singletons of central nervous system (CNS) and cardiovascular (CV) defects, with rate ratios of 1.8 and 1.5 respectively. LS twins had higher rates than US twins of CNS (RR = 3.0), but not of CV defects (RR = 0.9). The excess of CNS defects was due primarily to an increased frequency of hydrocephaly as well as a smaller increase of anencephaly. Most of the excess cardiovascular defects were listed as "unspecified", no doubt due to incomplete diagnostic work-up at the time of registration. In addition, the rate of congenital hip dislocation and Ortolani test positive was significantly lower among twins (RR = 0.4), both LS and US, than singletons.

The siblings of twins (Table 2) also had a significantly higher rate of CNS defects than singletons (RR = 1.9), comparable to the twin rate (RR = 1.1). Siblings of LS and US twins had similar rates of CNS defects (RR = 1.1), so the CNS rate of siblings varied more from the rates in their twin sibs in sibships with US twins (RR = 2.5) versus LS twins (RR = 0.9).

Maternal Age and Parity. Twins had fewer malformation cases than expected from the population rate, but indirect adjustment for maternal age did not alter the rate ratio between either LS or US twins and the population. In contrast to singletons, twins do not have the highest age-specific malformation rate among births to mothers 40 years or older. Adjusting for parity also did not alter the rate ratios appreciably. Nor did similar adjustment of the twin sibling rates alter their rate ratio comparisons to singletons.

Concordance. Among LS twin pairs affected by any malformation, 19.5% had both twins of the pair affected compared to 6.4% among US pairs. Counting only pairs with both twins affected by defects in the same specific category, 16.0% of LS pairs and 3.6% of US pairs were concordant (Table 3).

TABLE 1 - Rate of Malformations (per 10,000 Individuals) in Singletons Compared to Twins - Norway, 1967-79

Malformation category [a]	Singletons			Twins						
				Total		Like-sex		Unlike-sex		
	N	Rate	RR [b] T/S	N	Rate	N	Rate	N	Rate	RR [c] LS/US
HERNIA	568	7.3	1.2	14	9.1	12	11.2	2	4.4	2.5
CNS	1147	14.8	1.8*	41	26.8	35	32.7	5	10.9	3.0*
EEFN	424	5.5	0.9	8	5.2	7	6.5	1	2.2	3.0
CV	1876	24.2	1.5*	54	35.2	37	34.6	17	37.0	0.9
CL/P	1430	18.4	1.2	33	21.5	22	20.6	11	24.0	0.9
RESP/DG	632	8.2	0.9	11	7.2	10	9.4	1	2.2	4.3
G-U	2813	36.3	1.0	58	37.9	44	41.1	14	30.5	1.3
LIMB	6472	83.5	1.0	130	84.8	83	77.6	47	102.4	0.8
HIP	7117	91.8	0.4*	59	38.5	39	36.5	20	43.6	0.8
OTHER	866	11.2	1.1	19	12.4	18	16.8	1	2.2	7.6*
MULTIPLE	423	5.5	1.3	11	7.2	8	7.5	0	0	–
DOWN	780	10.1	0.8	12	7.8	8	7.5	4	8.7	0.9
Total diagnoses	24,548	316.6	0.9	450	293.7	323	302.0	123	267.9	1.1
Individuals	23,424	302.1	0.9	426	278.1	306	286.1	117	254.8	1.1
Population	775,405			15,320		10,694		4,592		

a Abbreviations and codes listed in Appendix. One individual may only appear in each category once, but may appear in up to 3 different categories.
b Rate ratio of twins compared to singletons.
c Rate ratio of Like-sex Twins to Unlike-sex Twins (17 pairs were of unknown sex).
* $P < 0.05$ for Chi-square, 1 degree of freedom.

TABLE 2 - Rate of Malformations (per 10,000 Individuals) in Siblings of Twins - Norway 1967-79

Malformations category [a]	Siblings of LS twins		Siblings of LS twins		Siblings of Total twins [b]		RR [c]	RR [d]
	N	Rate	N	Rate	N	Rate		
HERNIA	8	17.1	1	5.4	10	15.1	2.1	1.7
CNS	14	30.0	5	26.8	19	28.8	1.9*	1.1
EEFN	1	2.1	1	5.4	2	3.0	0.5	0.6
CV	9	19.3	6	32.1	15	22.7	0.9	0.6
CL/P	6	12.8	8	42.8	14	21.2	1.2	1.0
RESP/DG	3	6.4	2	10.7	5	7.6	0.9	1.1
G-U	17	36.4	2	10.7	19	28.8	0.8	0.8
LIMB	36	77.0	15	80.3	52	78.7	0.9	0.9
HIP	40	85.6	21	112.5	62	93.8	1.0	2.4*
OTHER	4	8.6	2	10.7	6	9.1	0.8	0.7
MULTIPLE	3	6.4	4	21.4	7	10.6	1.9	1.5
DOWN	2	4.3	2	10.7	4	6.1	0.6	0.8
Total diagnoses	143	305.9	69	369.6	215	325.4	1.0	1.1
Individuals	138	295.3	67	358.9	208	314.8	1.0	1.1
Population	4674		1867		6608			

a Abbreviations and codes listed in Appendix. One individual may appear in each category once, but may appear in up to 3 different categories.
b Siblings of LS and US twins only in families with 1 pair of known-sex twins. Total includes all sibs of all twins.
c Rate ratio of rate in total sibs compared to singletons.
d Rate ratio of rate in sibs compared to twins.
* $P < 0.05$ for Chi-square, 1 degree of freedom.

TABLE 3 - Concordance Rates of Same Malformation Category in Sibships, by Twins and Siblings Norway, 1967-79

Malformation category [a]	LS twin pairs		US twin pairs		T-S [b]	S-S	Total Sibships	
	N	%	N	%	N	N	N	%
HERNIA	2	20.0	0	0	1	0	3	14.3
CNS	3	9.4	0	0	1	0	3[c]	5.4
EEFN	1	16.7	0	0	0	0	1	11.1
CV	4	12.1	0	0	0	0	4	6.2
CL/P	3	15.8	0	0	0	0	3	6.8
RESP/DG	0	0	0	0	0	0	0	0
G-U	9	18.2	0	0	0	0	9	13.2
LIMB	9	12.2	2	4.4	3	2	16	9.6
HIP	6	18.2	2	11.1	1	2	11	10.0
OTHER	1	5.9	0	0	0	0	1	4.0
MULTIPLE	2[d]	33.3	0	0	0	0	2	5.6
DOWN	1	14.3	0	0	0	0	1	6.3
Total	41	16.0	4	3.6	6	4	54	9.9

a Abbreviations and codes listed in Appendix.
b T-S indicates twin-sib concordances, S-S indicates 2 sibs (no twins).
c One sibship has 2 concordant twins, plus 2 sibs, all concordant for hydrocephaly.
d Two pairs of conjoined twins in multiple category.

APPENDIX

Malformations Included, Their Abbreviations and ICD Codes (1965)

Abbreviation	Malformation	ICD Codes (1965)
HERNIA	Abdominal hernias, including gastroschisis	550-553
CNS	Central Nervous System	740-743
EEFN	Eye, Ear, Face and Nose	744-745
CV	Cardiovascular system and systolic murmurs	746-747
		778.7[a]
CL/P	Cleft lip and/or palate	749.0-.2
RESP/DG	Respiratory/Digestive system	748
		750-751
G-U	Genitourinary system	752-753
LIMB	Limb and foot	754-755
		except 755.6
HIP	Congenital dislocation of hip plus	755.6
	Ortolani test positive	778.5[a]
OTHER	Other; bone, skin, endocrine glands etc.	756-758
MULTIPLE	Multiple; plus conjoined twins, chromosomal	759
	defects and "monsters"	except 759.3
DOWN	Down syndrome	759.3

a Codes specific for Medical Birth Registry.

https://doi.org/10.1017/S0001566000007558 Published online by Cambridge University Press

By specific malformation groups, urogenital defects and hip dislocation had the highest concordance rates. Only the respiratory/digestive system group had no concordant pairs. If the 2 pairs of conjoined twins are excluded, the LS concordance rate would be reduced slightly to 15.2%.

Familial Malformation Incidence. Of the 7596 sibships with twins, 553 (7.3%) had at least one member (including twins) affected with a malformation, which falls between the expected percent in sibships consisting of 2 deliveries (5.9%) and that in sibships of 3 independent births (8.7%). Of these 553 affected sibships, 54 had 2 cases (including concordant twins) registered in the same malformation category (Table 3). Counting twins as 1 delivery (ie, as 1 case rather than 2), there were 25 sibships with 2 affected deliveries or 0.3% of the total number of sibships. In comparison, 0.1% of sibships would be expected to have 2 malformation cases, assuming independent events and an average of 2 deliveries per mother. Of these 25, 10 had both defects in the same category. One sibship included both concordant twins and sibs; the 2 twins (1 pair) and 2 sibs all had hydrocephaly.

Sixty-four (0.8%) sibships contained more than 1 pair of twins, which is eighty times the expected 0.01% based on independent chances of 2 deliveries both being twin pairs. The sibships were comprised of 23 with 2 LS pairs, 13 with 2 US pairs, 27 with 1 US and 1 LS pair (plus one with 2 LS and 1 US pair), which indicates a nonrandomness of US twinning. These multipair sibships had malformation rates of 333.3/10,000 LS twins compared to 92.5/10,000 US twins. None of these sibships had a case in each of the 2 twin pairs.

DISCUSSION

Use of data from the population-based Medical Birth Registry should have ensured identification of all twins and their siblings born during the study period. Notification of all births and malformations is mandatory in Norway, so reporting of malformations in twins should not be biased by the pair status of the twins nor their concordance. However, it is possible that twins receive different clinical attention than singletons, affecting ascertainment, but this may be a problem in any surveillance study. Unfortunately, reporting at birth does not identify all malformations, as some are diagnosed later in life; however, this is presumably equally true for twins, siblings, and singletons. Because twins are frequently born at high parities, some of their older sibs may have been excluded because they were born before the study period, but adjustment for maternal age and parity did not effect the results.

The finding that the rate of total malformations in twins is similar to that in singletons is not in accordance with some studies [5, 6]. However, the definition of malformations and ascertainment methods differ between studies, making comparisons difficult. For example, the large register-based study in Atlanta [5] which found an increase of malformations in twins, recorded malformations up to 1 year of age. If twin births were considered the unit of observation in our study, so that twin pairs rather than individuals comprised the denominator, the rate of malformations in twin deliveries (4.9%) would have been significantly higher than in singletons (3.0%).

Twins were observed to have a significant increase of central nervous system and cardiovascular defects compared to singletons. The increase in CNS defects was greater in LS than US twins. A number of studies of twins have noted increased rates of the CNS

group of defects [6, 8], as well as of specific CNS defects including hydrocephaly [3, 5]. A few studies [3, 6] have also noted increases in congenital heart defects among twins.

Of particular importance in this study is the observation that the siblings of twins had a significantly higher rate than singletons of CNS defects, but not of CV defects. The sibling total malformation and CNS rates were similar to those of twins. The concordance of CNS defects was lower than that of total defects and only one sibship had both twin and sib CNS cases.

The only defect category that was significantly decreased in twins compared to both siblings and total singletons was congenital hip dislocation. This represents a deficit of a relatively large number of malformation cases, and was not found in the Atlanta study [5]. If it is due to biased reporting (lack of) among twins, because they are receiving more critical attention for example, this deficit may explain the relatively low rate of total malformations found among twins.

Other studies [5, 8] have found that if a defect is increased in twins it is often more frequent in LS or MZ than in US or DZ twins. The observation of higher concordance rates in LS versus US twins also suggests LS twins have a stronger association with malformations. However, a recent report from England [2] found a nonsignificant difference of 5.3% affected in MZ twins versus 3.7% in DZ twins, similar to our findings regarding total malformation rates in LS versus US twins. Furthermore, they found no difference in rates between monochorionic or dichorionic pairs so they concluded the monochorionic placenta is not causal in the contribution of twinning to malformation occurrence.

CONCLUSIONS

The answer to whether malformations are more frequent among twins may vary by the definition of malformations included, the methods of ascertainment and even the prevalence of the various defects in different areas [8]. However, a growing amount of evidence suggests that at least some malformations are increased in twins. This might conceivably be due to common factors leading to twins and/or malformations, or to disruptions caused by the twinning process giving rise to malformations.

The results of this study support a specific association between CNS defects and LS twins, as has been suggested elsewhere [4, 9]. Concordance rates are not high, so the association does not appear to be entirely genetic, but perhaps associated with factors affecting MZ twinning. The observation that CNS defects are also increased in twin siblings indicates that the twinning process is not causal, but there may be common familial factors that, depending on when they are present, can lead to MZ twinning, CNS defects, or both.

Cardiovascular defect rates were elevated in twins, but not in their siblings, indicating that the excess is specific to twinning. It seems most likely that the increased frequency of these types of defects among twins is associated with the unique biologic conditions of twinning, including the shared intrauterine environment as well as the risk of being born preterm.

Acknowledgments. We thank Rolv Skjaerven of the Medical Birth Register for the preparation of the original data, and Bjorn Almaas and Rune Siland of the Medical Epidemiologic Data Service, supported by the Norwegian Research Council of Sciences and Humanities, for assistance with data management. The study was in part funded by the Borregaard A.S. Research Fund.

REFERENCES

1. Bjerkedal T (1981): The Medical birth registry of Norway. In Mednick SA, Baert AE (eds): Prospective longitudinal research: An empirical basis for the primary prevention of psychosocial disorders. Oxford: Oxford University Press, p 58-60.
2. Corney G, MacGillivray I, Campbell DM, Thompson B, Little J. Congenital anomalies in twins. Presented at International Workshop on Twin Pregnancies, April 1982, Paris.
3. Hay S, Wehrung DA (1970): Congenital malformations in twins. Am J Hum Genet 22:662-678.
4. James WH (1976): Twinning and anencephaly. Ann Hum Biol 3:401-409.
5. Layde PM, Erickson JD, Falek A, McCarthy BJ (1980): Congenital malformations in twins. Am J Hum Genet 32:69-78.
6. Myrianthopoulos NC (1978): Congenital malformations: The contribution of twin studies. Birth Defects 14:151-165.
7. Schinzel AAGL, Smith DW, Miller JR (1979): Monozygotic twinning and structural defects. J Pediatr 95:921-930.
8. Windham GC, Sever LE (1982): Neural tube defects among twin births. Am J Hum Genet 34: 988-998.
9. Windham GC, Bjerkedal T, Sever LE (1982): The association of twinning and neural tube defects: The association of twinning and neural tube defects: Studies in Los Angeles, California and Norway. Acta Genet Med Gemellol 31:165-172.

Correspondence: Dr. T. Bjerkedal, Medical Birth Registry, Institute of Preventive Medicine, University of Oslo, Gydas vei 8, Oslo, Norway.