ORIGINAL ARTICLE

Cerebral palsy in twins: a national study

P O D Pharoah, T S Price, R Plomin

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See end of article for authors' affiliations

Correspondence to: Dr Pharoah, Department of Public Health, University of Liverpool, Liverpool L69 3GB, UK; p.o.d.pharoah@liv.ac.uk

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Background: Cerebral palsy is more common in twins than singletons. Among twins, if one twin suffers a fetal death or dies in infancy, the prevalence of cerebral palsy in the surviving co-twin is considerably increased, and those from like-sex pairs are particularly at high risk.
Aim: To compare birthweight specific cerebral palsy prevalence in like-sex and unlike-sex twins where both twins survive infancy and to provide a comparative and composite picture of cerebral palsy prevalence according to whether a co-twin died or where both twins survived.
Methods: Parents of twins born in England and Wales in 1994 and 1995 completed a booklet with open ended questions asking whether their twins had any medical, physical, visual, genetic, or chromosomal problems. Any mention of cerebral palsy, hemiplegia, diplegia, or quadriplegia allowed the child to be included as a case of cerebral palsy. Birthweight specific prevalence rates of cerebral palsy were determined for like and unlike-sex twins in birthweight groups < 1000 g, 1000–1499 g, 1500–1999 g, 2000–2499 g, and ⩾ 2500 g.
Results: When both twins survived infancy, like-sex were at greater risk of cerebral palsy than unlike-sex twins, but the difference was not statistically significant. If both twins survived infancy, the birthweight specific prevalence of cerebral palsy was significantly less than if the co-twin had died.
Conclusions: Among the generality of twins, like-sex compared with unlike-sex twins are at greater risk of cerebral palsy particularly if one twin suffers a fetal or infant death. Although it is not possible to subdivide the twins according to zygosity, it is postulated that monozygosity and, specifically, monochorionicity may be the crucial feature that leads to the higher prevalence of cerebral impairment among like-sex twins.

Twins are at greater risk of cerebral palsy than singletons.[1–4] In part this is attributable to the higher proportion of very preterm births in twins with their higher risk of hypoxic ischaemic cerebral impairment. However, comparison of birthweight specific prevalence rates in twins and singletons shows that the greatest disparity in rates occurs among those of normal birth weight—that is, those weighing ⩾ 2500 g.[3] Among twins, the surviving twin of a co-twin that suffered fetal or infant death is at high risk and particularly so if the twins are of like sex.[1 5–7] We report here the birthweight specific cerebral palsy prevalence rates among twins born in England and Wales during 1994 and 1995 according to whether they were of like or unlike sex and whether the co-twin suffered a fetal or infant death or if both survived.

METHODS

All registered twin births in 1994 and 1995, according to whether they were of like or unlike sex, birthweight group (< 1000 g, 1000–1499 g, 1500–1999 g, 2000–2499 g, and ⩾ 2500 g), and outcome of fetal death, infant death, or survivor, were obtained from national published statistics[8 9] and from data specifically provided by the Office for National Statistics (ONS). These data comprised the denominators.

For those twins that had died, copies of the non-confidential section of the fetal and infant/child death certificates were provided by the ONS.

Information on all surviving twins was obtained from two national surveys. The first survey covered all surviving twins born in England and Wales in 1993–1995 whose co-twin suffered a fetal or infant death. The general practitioner was sent a questionnaire enquiring whether or not the child had cerebral palsy. This survey has been described previously.[5 6] The children reported here are a subset from this survey who were born in 1994 and 1995.

The second survey, the Twins Early Development Study (TEDS), covered twin pairs in which both twins survived until their first birthday. Parents of twins born in England and Wales in 1994 and 1995 were initially contacted by ONS inviting them to take part in the study. Parents who agreed to participate were sent a booklet in which they reported on the twins' sex, birth weight, and health. Parents responded to open ended questions asking whether their twins had any medical, physical, visual, genetic, or chromosomal problems. They were asked also for general comment on their children's health. In subsequent phases of the study, the parents continued to report on the twins' health in a similar, open ended way.

Table 1 Twin maternities in England and Wales 1994/1995

	Both fetal deaths	1 fetal death + 1 infant death	1 fetal death + 1 infant survivor	Both live births: Both infant deaths	Both live births: 1 infant death + 1 infant survivor	Two infant survivors	Total
Like sex	99	43	258	192	298	10728	11618
Unlike sex	8	7	101	51	142	5261	5570
Total	107	50	359*	243	440	15989	17188*

*Excludes 12 maternities in which the fetal death was registered as "indeterminate" sex.

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Table 2 Birthweight specific cerebral palsy (CP) prevalence in infant survivors of twin maternities

Birthweight group	No of survivors	No of responders (response rate)	No with CP	CP prevalence per 1000
Not stated	499	316 (63%)	1	3.2
<1000 g	452	297 (66%)	26	87.5
1000–1499 g	1743	973 (56%)	29	29.8
1500–1999 g	4362	2398 (55%)	23	9.6
2000–2499 g	9743	6029 (62%)	19	3.2
≥2500 g	15978	9313 (58%)	18	1.9
All birth weights	32777	19326 (59%)	116	6.0

Table 3 Birthweight specific cerebral palsy (CP) prevalence in twin infant survivors of a co-twin fetal or infant death

Birthweight group	No of infant survivors	No of responders (response rate)	No with CP	CP prevalence/1000
Like sex				
Not stated	17	8 (47)	0	–
<1000 g	89	71 (80)	15	211.2
1000–1499 g	134	100 (75)	21	210.0
1500–1999 g	86	51 (51)	7	137.3
2000–2499 g	100	81 (65)	4	49.4
≥2500 g	130	84 (65)	1	11.9
All birth weights	556	395 (71)	48	121.5
Unlike sex				
Not stated	10	5 (50)	0	–
<1000 g	46	35 (76)	6	171.4
1000–1499 g	41	36 (88)	1	27.8
1500–1999 g	28	21 (75)	1	47.6
2000–2499 g	47	26 (55)	0	–
≥2500 g	71	54 (76)	0	–
All birth weights	243	177 (73)	8	45.2

Values in parentheses are percentages. Like-sex compared with unlike-sex Mantel-Haenszel weighted relative risk 2.55 (95% CI 1.23 to 5.27); p=0.01.

Any mention of cerebral palsy, hemiplegia, diplegia, or quadriplegia allowed the child to be included as a case of cerebral palsy.

Birthweight specific prevalence rates of cerebral palsy were determined for like-sex and unlike-sex twins in birthweight groups < 1000 g, 1000–1499 g, 1500–1999 g, 2000–2499 g, and ≥ 2500 g.

Statistical method

Crude and Mantel-Haenszel weighted relative risks with their 95% confidence intervals (CI) were determined using the Epi-Info 6 statistical package.

RESULTS

In England and Wales in 1994/1995, there were 17 200 twin maternities (34 400 registered births). Table 1 shows the number of twin births where at least one survived according to whether they were of like or unlike sex and whether the outcome of the co-twin was a fetal or infant death. Like-sex twins are at much greater risk of fetal or infant death than unlike-sex twins. Comparing like and unlike-sex twins, the relative risk for both twins to die in utero is 5.93 (95% CI 2.89 to 12.19; $p < 0.0001$). For one twin to die in utero and the co-twin to die in infancy, the relative risk is 2.95 (95% CI 1.33 to 6.54; $p < 0.01$). For both twins to be live births and both die in infancy, the relative risk is 1.80 (95% CI 1.33 to 2.45; $p < 0.01$).

In the first survey, there were 799 twin survivors of a co-twin fetal or infant death. (In an additional 12 cases the fetal death was registered as being of "indeterminate" sex. These were excluded from the analyses because they could not be ascribed to the like or unlike-sex twin categories). Of the 799 twin infant survivors, five from like-sex twin pairs died in childhood. For two of these, the registered cause of death was cerebral palsy. A completed questionnaire was obtained for 572 surviving children, a response rate of 71.6%.

In the second survey, there were 15 989 twin pairs where both twins survived infancy, of which 10 958 (68.5%) families returned reply cards indicating their interest in participating in the survey. These families were sent a questionnaire booklet, and 9380 completed booklets were returned, giving an overall response rate of 58.7%.

Table 2 gives the birthweight specific cerebral palsy prevalence rates of all infant survivors from twin maternities. The increasing prevalence with decreasing birth weight is clear. This confirms other reports that both low birth weight and multiple pregnancy are important risk factors in cerebral palsy.[10]

A breakdown of the birthweight specific cerebral palsy rates according to whether the twins were of like or unlike sex and whether or not the co-twin survived infancy shows significant differences in prevalence rates (tables 3 and 4). When the co-twin suffered a fetal or infant death, the like-sex survivor was at significantly greater risk of cerebral palsy than an unlike-sex twin (table 3; Mantel-Haenszel weighted relative risk 2.55 (95% CI 1.23 to 5.27; $p = 0.01$)). Among the extremely low birthweight infants, < 1000 g, cerebral palsy prevalence was marginally greater in like-sex than unlike-sex twins. In all the other birthweight groups, cerebral palsy prevalence was considerably greater in like-sex twins.

When both twins survived infancy, the birthweight specific cerebral palsy prevalence rates were significantly less than if

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Table 4 Birthweight specific cerebral palsy (CP) prevalence in twins both of whom survive infancy (Twins Early Development Study data)

Birthweight group	No of survivors	No of responders (response rate)	No with CP	CP prevalence/1000
Like sex				
Not stated	327	212 (65)	1	4.7
<1000 g	199	128 (64)	3	23.4
1000–1499 g	1118	610 (55)	4	6.6
1500–1999 g	2997	1632 (54)	12	7.4
2000–2499 g	6565	4093 (62)	11	2.7
⩾2500 g	10250	6001 (59)	13	2.2
All birth weights	21456	12676 (59)	44	3.5
Unlike sex				
Not stated	145	91 (63)	0	–
<1000 g	118	63 (53)	2	31.7
1000–1499 g	450	227 (50)	3	13.2
1500–1999 g	1251	694 (55)	3	4.3
2000–2499 g	3031	1829 (60)	4	2.2
⩾2500 g	5527	3174 (57)	4	1.3
All birth weights	10522	6078 (58)	16	2.6

Values in parentheses are percentages. Like-sex compared with unlike-sex Mantel-Haenszel weighted relative risk 1.26 (95% CI 0.71 to 2.22); not significant.

the co-twin had died. Although like-sex twins were still at greater risk than unlike-sex twins, the difference was not significant (table 4; Mantel-Haenszel weighted relative risk 1.26 (95% CI 0.71 to 2.22).

DISCUSSION

There were important differences in the two surveys. The first survey had the aim of determining the prevalence rates of cerebral palsy in the surviving twins where the co-twin suffered a fetal or infant death. The questionnaire, which was completed by the general practitioner for more than 70% of the children, specifically inquired if the child had cerebral palsy. It is probable therefore that, in this group, there was no underascertainment of cerebral palsy among the responders.

The second survey questionnaire did not specifically inquire about cerebral palsy, was completed by the child's parents, and the response rate was marginally under 60%. Therefore the possibility of underascertainment of cerebral palsy in this group must be entertained. The crude twin cerebral palsy prevalence among all infant survivors of 6.0 per 1000 is less than the 10.4 and 12.6 per 1000 reported from the Western Australian[11] and Mersey[3] cerebral palsy registers respectively. This suggests that the prevalence of cerebral palsy when both twins survive infancy may have been underestimated.

A striking feature of the data reported here is the highly significant difference in birthweight specific cerebral palsy prevalence rates among surviving twins whose co-twin suffered fetal or infant death compared with twins both of whom survive (compare table 3 with table 4). This difference largely accounts for the excess prevalence of cerebral palsy in twins compared with singletons. When both twins survive, the birthweight specific cerebral palsy prevalence is slightly lower than that among singletons reported from the Mersey and Western cerebral palsy registers.[3 11] Allowing for the fact that there may have been underascertainment of cerebral palsy in the second survey, it is probable that singleton and twin cerebral palsy rates, where both twins survive, are similar.

Table 4 shows that the crude cerebral palsy prevalence is greater in like-sex twins than unlike-sex twins. However, the difference is not statistically significant. Two caveats need to be noted in interpreting this finding. The number of infants with cerebral palsy in both groups is small, and the sample size may have been insufficiently large to show a statistically significant difference, a statistical type 2 error. Also, if monozygosity is important in the development of cerebral palsy, errors in birth registration mean that twins of unlike sex are not necessarily both from a dizygotic conception. In a national study of death certificates from multiple pregnancies, there were several instances where only twins were registered although triplets or even quadruplets were recorded in early pregnancy.[12] It is still tenable that most cases of cerebral impairment manifest as cerebral palsy, even among unlike-sex twins, may be attributable to monozygosity and, specifically, to monochorionicity.

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Authors' affiliations

P O D Pharoah, Department of Public Health, University of Liverpool, Liverpool L69 3GB, UK
T S Price, R Plomin, Social, Genetic and Developmental Psychiatric Research Centre, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, UK

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