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Cerebral palsy and multiple births

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Abstract

***Aim*—To compare the birthweight specific prevalence of cerebral palsy in singleton and multiple births.**

***Methods*—Registered births of babies with cerebral palsy born to mothers resident in the counties of Merseyside and Cheshire during the period 1982 to 1989 were ascertained.**

***Results*—The crude prevalence of cerebral palsy was 2.3 per 1000 infant survivors in singletons, 12.6 in twins, and 44.8 in triplets. The prevalence of cerebral palsy rose with decreasing birthweight. The birthweight specific prevalence among those of low birthweight < 2500 g was not significantly different in singleton than in multiple births. Among infants weighing ≥ 2500 g, there was a significantly higher risk in multiple than in singleton births. The higher crude cerebral palsy prevalence in multiple births is partly due to the lower birthweight distribution and partly due to the higher risk among normal birthweight infants.**

***Conclusions*—Multiple birth babies are at increased risk of cerebral palsy. There is also an increased risk of cerebral palsy within a twin pregnancy if the co-twin has died in utero.**

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Keywords: cerebral palsy, multiple births, singletons, low birthweight.

Stillbirth and infant mortality rates are higher among twins and higher order births than singletons[1] as are rates of significant child morbidity such as cerebral palsy and learning disabilities.[2–4] Early studies that drew attention to the increased risk of cerebral palsy among higher order births noted that twins contributed disproportionately to the series, but were limited to a clinical series of cases.[2 3] The population denominator was not known, however, so prevalences in singletons, twins, and triplets could not be compared. More recently, population based studies from Western Australia[5] and the United States[6 7] have allowed comparisons of prevalence to be made. An important observation in these studies was that crude prevalence of cerebral palsy was higher in twins and triplets than in singletons, that birthweight specific rates among low birthweight groups (<2500 g) were not significantly different, but that cerebral palsy rates among infants of birthweight ≥ 2500 g were significantly higher in multiple than in singleton births.

Using a population based cerebral palsy register covering the counties of Merseyside and Cheshire, we compared the prevalence of birthweight specific cerebral palsy in singleton and multiple births.

Methods

The cerebral palsy register is on-going and comprises all cases of cerebral palsy born to mothers resident in the counties of Merseyside and Cheshire since 1966. Multiple sources of ascertainment of cases are used to ensure completeness of ascertainment; this has been described previously.[8] Birthweight specific numbers of singleton, twin, and higher order births and infant deaths were obtained from the birth and death tapes compiled from statutory birth and death registrations.

The main analysis is limited to those born in 1982-89 because denominator population data were only available from 1982 onwards and the ascertainment of cerebral palsy cases was considered to be complete up to 1989; compilation of the register is still in progress and, for those cases born in the 1990s, it is incomplete.

Once a case was ascertained and confirmed from paediatric and child health records, the obstetric records of the mother were abstracted. From these records the following were determined: the plurality of the pregnancy; the outcome of the co-twin or triplets—whether a fetal death or live birth; if the co-twin or triplet(s) was a live birth, whether (s)he also had cerebral palsy.

The prevalence of cerebral palsy was calculated per 1000 infant survivors—that is, after subtracting the number of infant deaths from the number of live births for a birthweight specific group.

Student's t test was used to test for the significance of the difference in proportions.

Results

There has been a sharp rise in the number of cases of cerebral palsy among multiple births in the 1980s (table 1). As the number of births from multiple pregnancies is not available

Table 1 Numbers of cerebral palsy cases among multiple births

Year	*Twins*	*Triplets*
1966-70	24	2
1971-5	18	0
1976-80	19	0
1981-5	38	1
1986-9*	36	5

* This row is for four years; all other rows cover five years.
This table shows numbers of cases not rates. The trend in rates cannot be determined because the denominator of total twins born before 1980 is not available.

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Table 2 Birthweight specific cerebral palsy prevalence rates in singletons, twins and triplets: Mersey 1982-89

Birthweight group (g)	Number of livebirths	Number of infant survivors	Number of cerebral palsy cases	Cerebral palsy rate per 1000 infant survivors (95% CI)
Singletons:				
< 1000	656	315	27	85.7 (57.2 to 122.3)
1000-1499	1156	949	88	92.7 (75.0 to 113.0)
1500-1999	2447	2286	72	31.5 (24.7 to 39.5)
2000-2499	9511	9322	69	7.4 (5.8 to 9.4)
≥ 2500	237790	236733	326	1.4 (1.2 to 1.5)
Not stated	2800	2720	0	0.0
All weights	254360	253232	582	2.3 (2.1 to 2.5)
Twins:				
< 1000	114	38	6	157.9 (60.2 to 312.5)
1000-1499	259	222	23	103.6 (66.8 to 151.4)
1500-1999	643	626	16	25.6 914.7 to 41.2)
2000-2499	1490	1470	8	5.4 (2.4 to 10.7)
≥ 2500	2618	2602	11	4.2 (2.1 to 7.6)
Not stated	83	69	0	0.0
All weights	5207	5073	64	12.6 (9.7 to 16.1)
Triplets:				
< 1000	15	9	2	222.2 (28.1 to 600.1)
1000-1499	35	33	2	60.6 (7.4 to 202.3)
1500-1999	43	43	2	46.5 (5.7 to 158.1)
2000-2499	36	36	0	0.0
≥ 2500	12	12	0	0.0
Not stated	1	1	0	0.0
All weights	142	136	6	44.8 (16.6 to 94.9)

before 1982, rates among multiple births before 1982 cannot be determined. Nevertheless, the increased number is probably related to the increase in the number of multiple pregnancies that have occurred during the 1980s following developments in infertility treatment[9] and the improved survival of twins of lower birthweight.

As there were only six cases of cerebral palsy among triplet births, the birthweight specific prevalence had very wide confidence intervals. The prevalence of cerebral palsy among singleton and multiple births increases sharply with decreasing birthweight (table 2). The difference in prevalence between singletons and twins was highly significant for those in the ≥2500 g birthweight group only: twin-singleton difference was 2.9 (95% CI 1.0 to 6.2; P=0.0001) per 1000 infant survivors. None of the low birthweight groups, compared individually, showed a significant difference in prevalence of cerebral palsy between twins and singletons. A comparison of all infants of <2500 g as a single birthweight entity also showed no significant difference between twins and singletons: twin-singleton difference was 2.6 (95% CI 9.8 to -3.3) per 1000 infant survivors.

The crude prevalence of cerebral palsy among singletons—of all birthweight groups—was 2.3 per 1000 infant survivors, and among twins was 12.6 per 1000 infant survivors. This difference in crude prevalence is partly attributable to twins being of lower birthweight and partly to the higher prevalence of cerebral palsy in twins of birthweight ≥ 2500 g.

Comparison with the Western Australian series is shown in table 3. Mersey and Western Australia had similar numbers in the denominator populations in all the birthweight groups for singletons, twins, and triplets. Cerebral palsy prevalence among all birthweight groups for singletons, twins, and triplets was consistently higher in the Mersey population than in Western Australia.

Analysis was also carried out to determine what effect there might be on the risk of cerebral palsy if the co-twin were a live or stillbirth. Figure 1 shows that in 46 out of 2572 twin pregnancies in which both infants were live births, one of the twins had cerebral palsy—that is, if both twins are live births, there is a 1.8% (95% CI: 1.3% to 2.4%) probability that one twin has cerebral palsy. In six pregnancies, both twins had cerebral palsy—a probability of 0.2% (95% CI 0.1% to 0.5%). In contrast, among the 63 pregnancies in which one of the twins was a stillbirth, six of the co-twin survivors had cerebral palsy—9.5% (95% CI 3.6% to 19.6%). This is a fourfold increase compared with twin pregnancies in which both infants were live births. It is evident that, if one of a twin pregnancy is a stillbirth, there is a high probability that the co-twin will have cerebral palsy. Triplet pregnancies are also at increased risk but numbers are insufficient for a confident estimation of risk.

Table 3 Comparison of singleton, twin, and triplet birthweight specific cerebral palsy prevalence rates in infant survivors: Mersey and Western Australia

Birthweight (g)	Mersey 1982-9			Western Australia 1980-9			Difference (95% CI)
	Number of infant survivors	Number of cerebral palsy cases	Cerebral palsy prevalence	Number of infant survivors	Number of cerebral palsy cases	Cerebral palsy prevalence	
Singleton:							
< 1500	1264	115	91.0	1147	59	51.4	39.5 (19.2 to 60.2) P < 0.0001
1500-2499	11608	141	12.1	8688	66	7.6	4.6 (1.8 to 7.3) P=0.001
≥ 2500	236733	326	1.4	214918	233	1.1	(0.3 90.1 to 0.5) P=0.003
Twin:							
< 1500	263	29	110.3	248	9	36.3	74.0 (30.1 to 121.6) P=0.001
1500-2499	2096	24	11.4	2031	16	7.9	3.6 (−2.5 to +9.9) NS
≥ 2500	2601	11	4.1	2636	11	4.2	0.0 NS
Triplet:							
< 1500	42	4	95.2	55	4	72.7	22.5 (−93.9 to +157.4) NS
1500-2499	79	2	25.3	139	2	14.4	10.9 (−29.7 to +74.5) NS
≥ 2500	13	0	0	21	0	0	NS

NS = not significant.

Discussion

The observation that twins of normal birthweight (≥2500 g) are at higher risk of cerebral palsy than singletons, but that in the low birthweight groups there is no significant difference in risk, confirms the findings from Western Australia[5] and the United States.[6 7] The consistency of this observation indicates that twins are at higher risk of cerebral palsy; this is partly due to their lower birthweight distribution than singletons and partly to the higher risk among twins of normal birthweight. Ideally, a comparison of cerebral palsy prevalence between multiple and singleton births should examine gestational age rather than birthweight specific rates, because, for a given gestational age, multiple births are smaller than singletons. Unfortunately, although the gestational age data for all the cases of cerebral palsy in this study are

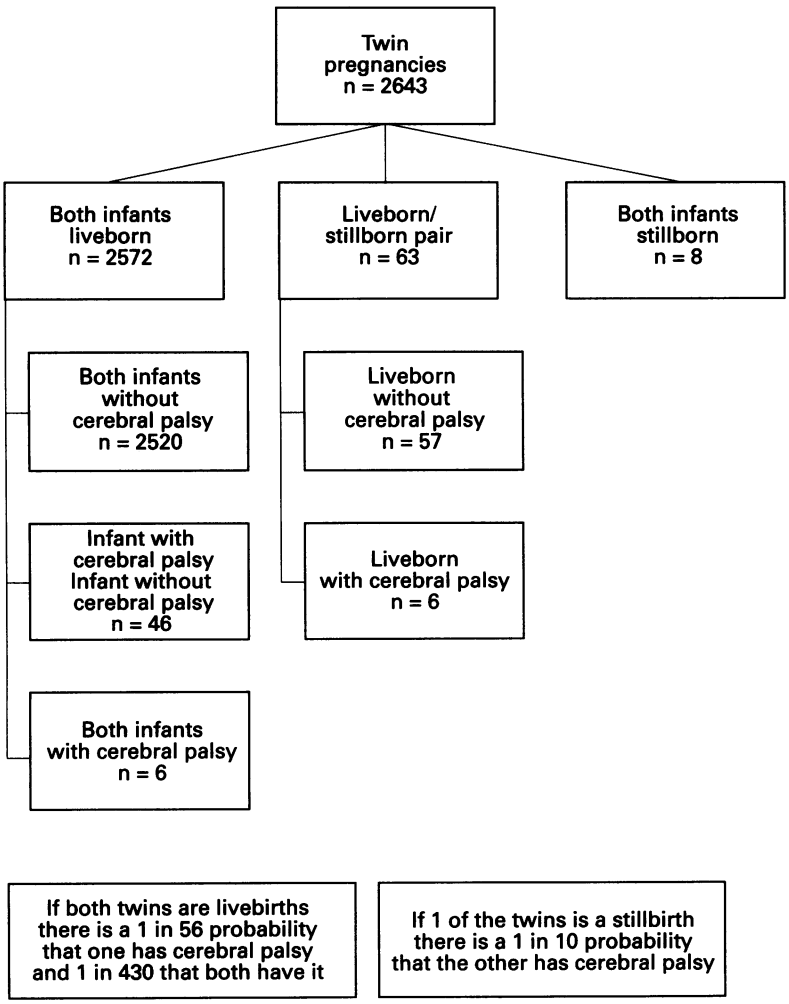

Figure 1 Prevalence of cerebral palsy among twin pregnancies in Mersey Region 1982-89

known from the obstetric records, the denominators for gestational age were not known. The routine data systems regionally and nationally did not include gestational age.

The difference in the cerebral palsy prevalence between the Mersey and the Western Australian series is intriguing. Differences in the completeness of ascertainment of cases is unlikely as both case registers use similar definitions of a case and use multiple sources of ascertainment. One partial, but incomplete, explanation is that for the Mersey register, recording a cerebral palsy case as being one of twins was made when the maternal obstetric records were abstracted. In six instances the co-twin was recorded as a stillbirth; in two of these the co-twin was a fetus papyraceous and the remaining four fetal deaths were recorded as macerated stillbirths. It is a legal requirement that these fetal deaths be registered, but fetus papyraceous in particular, and perhaps even macerated stillbirths might not be registered, with the result that the cerebral palsy case is registered as a singleton. These six cases were checked with the Office of Population Censuses and Surveys birth registrations. In three cases twin births had been registered and in the remaining three cases only one of each twin was registered as a birth. These three cases should be analysed among the singletons. However, it would make only a marginal difference to the birthweight specific prevalence. In the Western Australian series four children were reported in the parental interview or the medical records as being one of twins but were notified as singletons. This highlights the bias that will be introduced if birth registration or notification data are used. If a twin cerebral palsy birth is misclassified as a singleton, the prevalence of cerebral palsy in twins will be underestimated and that among singletons will be overestimated.

A further explanation for the difference in the birthweight specific prevalence of cerebral palsy could arise as a result of differences in neonatal survival. Table 4 compares Mersey-Western Australian neonatal mortalities for singletons, twins, and triplets. The difference for singletons was marginal and not significant, and therefore cannot account for the difference in singleton cerebral palsy prevalence. Among twins there is a difference in neonatal mortality between the two series which could account for the difference between the two series in the cerebral palsy prevalence in twins. If, among the low birthweight twins who die in the neonatal period, there is a disproportionate number of cases of cerebral palsy, they will not be counted because the cerebral palsy will not have been recognised before death and the prevalence would be artificially lower.

The increased risk of cerebral palsy in a twin pregnancy where the co-twin died in utero has been observed before[5 7] The magnitude of this risk reported here must be interpreted with caution if some fetal deaths were not registered. Although a twin pregnancy was recognised from the obstetric notes, failure of such recognition when birth was registered will have led to an overestimation of the risk of cerebral palsy when the co-twin died in utero.

The common use of ultrasonography early in pregnancy has shown that a multiple pregnancy may frequently result in fetal loss, with a reduced number of viable fetuses.[10 11] The fetal death may occur very early in gestation and not be recognised, but it may influence the development of cerebral palsy in the co-twin.

If fetal death of a co-twin increases the risk of cerebral palsy, what is the possible pathological mechanism? One possibility is that an insult causes the death of one fetus and, simul-

Table 4 Comparison of neonatality martality in singleton and multiple births: Mersey (1982-9) and Western Australia (1980-9)

	Singletons			*Twins*			*Triplets*		
	Live births	*Neonatal deaths*	*Neonatal mortality (per 1000)*	*Live births*	*Neonatal deaths*	*Neonatal mortality (per 1000)*	*Live births*	*Neonatal deaths*	*Neonatal mortality (per 1000)*
Mersey	254360	1146	4.5	5207	134	25.7	142	6	42.3
Western Australia	226517	1086	4.8	5132	188	36.6	225	9	40.0

taneously, produces cerebral impairment in the other. Alternatively, an insult may lead to fetal death in one twin which in turn affects the development of the second twin. If this latter mechanism is responsible, monozygous twins, in which one dies, are likely to be at greater risk than dizygous twins. This is of relevance to the treatment of fertility where multiple birth is common and both mono- and dizygous rates are increased, and if selective fetocide is used. Whether the difference observed between the Mersey and Western Australian series is real or is an artefact of survival, or of differences in twin classification and registration, requires further investigation. Unfortunately, few data are available worldwide to examine the comparative risks of singleton and multiple births. The lack of routine data sources for determining the prevalence of cerebral palsy means a continuing dependency on registers which are population based. Such registers are of relevance to health service provision, to outcomes of the treatment for infertility, and may provide clues to aetiology.

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Commentary

There has been much media coverage recently about multiple births and their risk to mother and children. It is therefore timely to be able to review two separate papers (cerebral palsy and multiple births; cerebral palsy: effects of twinning; birthweight and gestational age) which both discuss the association of cerebral palsy with multiple births.

There is a great public awareness about the implications for the provision of services to families where a child has cerebral palsy. A study from North East Thames Regional Health Authority confirms the importance of twinning as a risk factor for cerebral palsy. Other factors include gestational age and fetal growth. These three factors act independently of each other. It must be remembered, however, that these risk factors only account for a minority of cases of cerebral palsy. A study from Liverpool shows an increased risk of cerebral palsy within a twin pair if the co-twin was a fetal death. Multiple births run a greater risk of cerebral palsy than a singleton birth. This is partly due to their lower birthweight distribution and partly to a higher risk among normal birthweight infants. Currently, the number of multiple births is increasing, largely as a result of infertility treatment. Thus an increased risk of disability and mortality for twins and higher order births is important for both the potential parents and professionals who would have to provide care for the surviving children. We therefore need to be able to identify and quantify the risk factors.

The number of cases covered in both these studies is small so it is welcome that a multicentre study is in progress which combines data from cerebral palsy registers in Britain, the USA, and Australia. It is unfortunate, however, that we have no United Kingdom based data of child morbidity to answer questions on cerebral palsy. A report in July 1995 to the NHS Central Research and Development Committee stated that routine information systems, including morbidity data, for child health are at present inadequate. [1] The Advisory Group recommended that integrated and accessible information systems should be developed to identify accurately the health and healthcare needs of mothers and children. The Office for National Statistics (ONS) is starting a trial which brings together data from different local child health systems. We recognise that cerebral palsy is one of the issues that we will be able to examine with such a database. In addition to the new child health system, we have recently begun to set up a register of twins at ONS. It is in its very early stages, dependent on funding through research proposals. Nevertheless, the long term potential of such a register is that these morbidity issues could be investigated using a much larger register of multiple births than has been possible with the studies published here. The Liverpool study also suggests that long term follow up of children born as a result of infertility treatment is needed. We have only limited data from which we can measure any increased risk for the children born as a result of these treatments. The data available are for techniques of gamete manipulation rather than drugs taken to stimulate ovulation.

It is only by long term follow up of babies born as a result of a complete range of all these procedures that we can begin to have a complete understanding of the long term outcome for these births. I therefore welcome these papers which take forward our knowledge and understanding of the epidemiology of cerebral palsy. I hope that the issues they raise can be developed further using data from a longer time period and larger sample sizes.

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