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ORIGINAL ARTICLE

Multiple birth and cerebral palsy in Europe: a multicenter study

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Background. A European multicenter study (Surveillance of Cerebral Palsy in Europe, SCPE) was used to describe changes over time in multiple birth rates and cerebral palsy (CP) rates among multiple born infants, to compare CP rates and clinical types between multiples and singletons, and to analyse the influence of birth order in twins.
Methods. Data were collected from 12 European population-based CP registers on 6613 children born in 1975–90, as well as demographic data.
Results. The rate of multiple birth in the populations increased from 1.9% in 1980 to 2.4% in 1990, and the proportion of multiples among CP infants increased from 4.6% in 1976 to 10% in 1990. Multiples have a four times higher rate of CP than singletons [7.6 vs. 1.8 per 1000 live births, relative risk (RR) 4.36; 95% confidence interval (CI) 3.76–4.97] overall. The risk is marginally higher in multiples with birthweight >2500 g (RR 1.60; 95% CI 0.95–2.28) and born at term (RR 1.65; 95% CI 0.91–2.40), and there is no difference in the risk for the low-birthweight and preterm groups. Correcting for differences in gestational age and birthweight, the clinical type of CP was the same in multiples and singletons. Twin CP infants are more often second than first born (56% vs. 44%, $p < 0.05$).
Conclusions. Multiple born infants have a four times higher risk of developing cerebral palsy than singletons, mainly related to the higher risk of preterm birth in multiples. As the rate of multiples doubled through the 1980s, cerebral palsy cases in multiples increased in the same period.

Key words: cerebral palsy; multiple birth; twins; trend

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Introduction

Previous studies from the USA, Australia and Japan (1–4) have found that the rate of multiple births has increased through the most recent decades. This increase has been related to rapid development in fertility treatment (5) and higher maternal age at first pregnancy, two important factors in relation to multiple pregnancies. Twins and triplets have a higher risk for cerebral palsy (CP) and perinatal death compared to singletons (1–4, 6–9). Thus, the risk of having a CP-affected child has been estimated to be 47 times higher for a woman with a triplet pregnancy (4) and 8–12 times higher with a twin pregnancy compared to a singleton pregnancy (3,4). Furthermore, studies from California and Western Australia have found that intrauterine death of a co-twin is

Abbreviations:
SCPE: Surveillance of Cerebral Palsy in Europe; CP: cerebral palsy; RR: relative risk; OR: odds ratio; CI: confidence interval.

associated with a 13–15-fold higher risk for CP compared to twins where both are born alive (3,4). Additionally, it has been suggested that early loss of a co-twin increases the risk for CP in the surviving twin (5).

The higher risk of CP in multiple birth is closely related to low gestational age and birthweight, the two most important risk factors for CP (1–4,6,7). The previous studies on multiples and CP in Europe have been limited by small numbers, the largest including 64 twin cases (6). In 1998, a network of 14 CP registers and surveys from eight countries was formed across Europe, known as ''Surveillance of Cerebral Palsy in Europe'' or SCPE: France (two centers), the UK (five centers), Denmark, Sweden, Germany, Ireland (two centers), Italy and the Netherlands (10). The larger number of cases in this multicenter collaboration provides the possibility to study the trend over time, to estimate risk more precisely in different subgroups, and to describe the clinical picture of multiples with CP in a European context.

The aims of the present study are therefore:

1 to describe changes in rates of multiple birth and in CP rates in infants from multiple pregnancies through the 1980s in Western Europe;
2 to determine whether infants from multiple pregnancies have a higher risk for CP compared with singletons with the same birthweight and gestational age;
3 to compare CP type and severity of handicap between multiples and singletons with CP;
4 to determine whether the risk of CP in twins is related to birth order.

Methods

The SCPE group initially harmonized the definitions and classification of CP (10), and these have been used here. CP is a syndrome defined as a disorder of movement or posture due to a nonprogressive defect, lesion or abnormality of the immature brain. The commonly described subtypes of CP are: spastic bilateral, spastic hemiplegic, dyskinetic and ataxic. Multiple birth includes all births with two or more infants registered at the time of birth. Birthweight is given in grams, gestational age in completed weeks and is largely confirmed by ultrasound dating. ''Severity of disability'' is classified as: Severe = severe mental retardation and unable to walk; Mild = normal intelligence and unaided walking; and Moderate = other. Because of missing values of either of the two variables intelligence and motor function, one group of cases was not classified.

The SCPE collaborating centers contributed data on CP cases to a central database, the number of cases from each center varying with the size of the geographic area covered and the number of years of data available. Two of the centers were not able to contribute data (centers 7 and 14). Data were without personal identifiers, and information on 45 variables including demographic, perinatal and neurological information in accordance with the criteria agreed by SCPE was provided. The age at inclusion as a CP case was at least 4 years, but if a child with clear signs of CP had died between the ages of 2 and 4, they were also included. In total, 6613 CP children born between 1975 and 1990 were included in the database.

In addition, each center provided population data based on the birth registries in the different countries. These data included, where available, numbers of live births, multiple births and neonatal deaths by gestational age and birthweight groups in the area covered by their center for the years 1976–90.

The present analysis is limited to CP children from 12 centers born in the relevant areas during 1976–90 and living there at the time of registration, excluding those of known postneonatal origin ($n = 357$). Thus, the study includes 5590 children with CP, of whom 4748 were singletons, 437 were multiples (432 twins), and 405 had an unknown status. The different centers and their number of cases are listed in Table I.

Table I. Collaborating centers in Surveillance of Cerebral Palsy in Europe (SCPE) and the distribution of cases in the present study

Center no.	Area covered by the center	Country	Years	Cerebral palsy cases		
				Multiples ($n = 437$)	Singletons ($n = 4748$)	Total ($n = 5590$)
1	Isere County	France	1980–89	17	179	196
2	Haute Garonne	France	1976–85	9	66	159
3	Scotland	UK	1984–90	70	626	731
4	Cork and Kerry	Ireland	1976–90	21	207	232
5	Northern Ireland	UK	1981–90	60	505	616
6	Göteborg region	Sweden	1976–90	51	573	624
7	Eastern Ireland	Ireland	–	–	–	–
8	Northern region	UK	1976–90	11	261	272
9	Oxford region	UK	1984–90	39	511	550
10	Tübingen	Germany	1976–86	17	197	220
11	Mersey region	UK	1976–89	76	619	919
12	East Denmark	Denmark	1976–90	61	948	1010
13	Viterbo province	Italy	1977–90	5	56	61
14	Gelderland	Netherlands	–	–	–	–

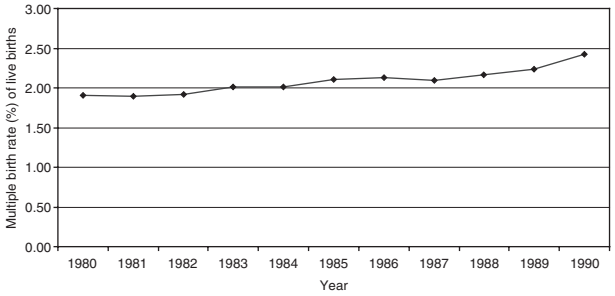

Fig. 1. Rate of multiple births (%) among live births, 1980–90. Population data are from catchment areas to centers 3, 6, 8, 9, 11, 12, 13.

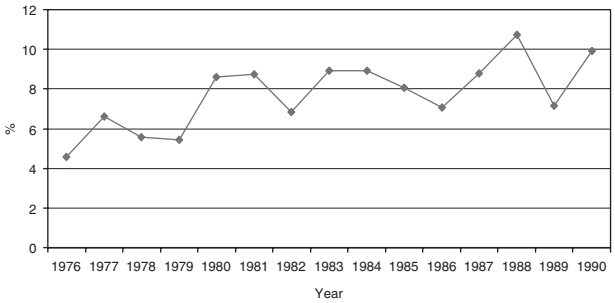

Fig. 3. Multiples in percentage of all cerebral palsy infants, 1976–90. Center 10 excluded.

As data collection in the different centers has not been uniform, it has been necessary to restrict some of the analyses; thus some of the centers did not have information on gestational age in the background population. In addition, CP rates are calculated by 1000 births and not by neonatal survivors because of restricted information. Centers were excluded from individual analyses if they had more than 20% missing data for one or more of variables used or they were not able to provide population data. Center 10 included only spastic bilateral CP children and was excluded when relevant. Centers included in each analysis are shown in the tables and figures.

Statistics

In Figs 1 and 2, logistic regression analysis on grouped data was used to see if there were year or country effects on the multiple birth rate in the population. A threshold alpha of 0.005 was chosen for these multiple comparisons. In Fig. 3, the proportion of multiples among all CP infants includes those with unknown status. Trends with time were investigated using logistic regression with linear and quadratic effects. Sensitivity to the proportion of unknown births was investigated by adding the unknown cases first to singletons and then to multiples. In all tables, data were analyzed by χ^2-tests, and in Tables IV–VI logistic regression analysis was applied.

Results

The multiple birth rate over time in four different countries (the UK, Denmark, Sweden and Italy) based on the catchment areas of seven centers significantly increased from 1.9% in 1980 to 2.4% in 1990 ($p < 0.0001$; Fig. 1). No interaction between center and year was found. There was no significant trend in the CP rate in multiples in any birthweight group for the same centers (Fig. 2) and no interaction between year and center. The curve on children below 1500 g has a decreasing trend but is not significant ($p = 0.03$), and by excluding centers 3 and 9 starting in 1984 the trend disappears. The proportion of multiples among all CP infants increased from 4.6% in 1976 to 10% in 1990 ($p < 0.01$, Fig. 3).

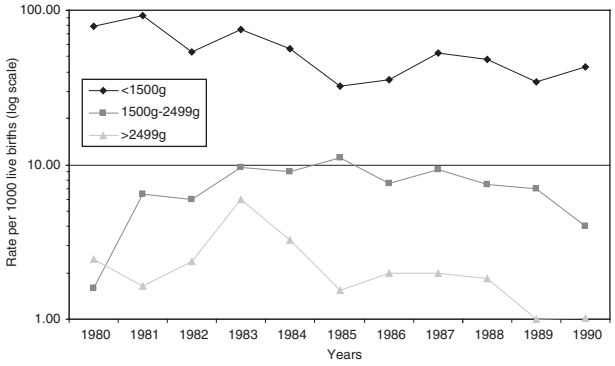

Fig. 2. Cerebral palsy rates in multiple born infants by birthweight (per 1000 live births), 1980–90. Data are from centers 3, 6, 8, 9, 11, 12, 13.

The CP rate for multiples born in 1984–90 was 7.6 and for singletons 1.8 per 1000 live births [relative risk (RR) 4.36; 95% confidence interval (CI) 3.76–4.97]. Although the total CP rates in multiples is about four times higher than in singletons, this difference largely reflects the higher proportions of singletons born at term (56% vs. 14% in multiples; Table II). Looking at birthweight-specific CP rates, there is no difference in the groups below 2500 g, and in normal birthweight the 1.6 times higher rate in multiples is marginally significant (RR 1.61; 95% CI 0.95–2.28; Table III). A similar pattern is seen with gestational age.

In comparison to singleton cases, the percentage of multiples with spastic CP was significantly higher than for other CP types [91% vs. 87%, odds ratio (OR) 1.59, $p = 0.006$; Table IV]. Multiples with spastic CP were significantly more likely to have bilateral CP than singletons (73% vs. 65%, OR 1.57, $p < 0.001$; Table V). Both differences

Table II. CP rates in multiples ($n = 139$) vs. singletons ($n = 1574$) by gestational age. Birth years 1984–90, five centers (3, 6, 8, 12, 13), per 1000 live births

Gestational age (weeks)	CP rate, % (n)		
	Multiples	Singletons	Relative risk (95% CI)
< 28	42.9 (22)	40.4 (97)	1.06 (0.68–1.69)
28–31	41.1 (48)	49.7 (300)	0.83 (0.59–1.09)
32–36	7.6 (50)	6.3 (289)	1.21 (0.86–1.59)
≥ 37	1.8 (19)	1.1 (888)	1.65 (0.91–2.40)

Table III. CP rates in multiples ($n=217$) vs. singletons ($n=2318$) by birthweight. Birth years 1984–90, seven centers (3, 6, 8, 9, 11, 12, 13), per 1000 live births

Birthweight (g)	CP rate (*n*)		
	Multiples	Singletons	Relative risk (95% CI)
< 1000	35.1 (25)	29.5 (107)	1.19 (0.71–1.76)
1000–1499	47.1 (74)	45.3 (343)	1.04 (0.79–1.31)
1500–2499	7.9 (95)	8.7 (608)	0.91 (0.72–1.11)
≥ 2500	1.6 (23)	1.0 (1260)	1.61 (0.95–2.28)

disappeared after adjusting for differences in gestational age and birthweight (OR 1.03, $p=0.880$ and OR 1.01, $p=0.925$). There were no significant differences between multiples and singletons with CP in motor function (Table V) (univariate: OR 1.09, $p=0.425$ and multivariate: OR 1.11, $p=0.358$), visual impairment, when severe visual impairment was compared to other levels (Table IV) (univariate: OR 1.26, $p=0.134$ and multivariate: OR 1.22, $p=0.224$), intellectual function comparing normal intelligence with others (Table VI) (univariate: OR 0.97, $p=0.750$ and multivariate: OR 0.88, $p=0.219$), or severity of disability (Table VI) (univariate: OR 1.00, $p=0.985$ and multivariate: OR 1.20, $p=0.236$).

In Table VII, twin cases were distributed according to birth order and gestational age. Assuming that twin CP cases are distributed equally in first and second born, significantly more twin CP children were second than first born (56% vs. 44%, $p<0.05$). The mean birthweight in the two birth orders was the same in all the groups of gestational age and sex, except in girls below 32 weeks of gestation where the second born infants were smaller (1190 g vs. 1160 g, $p=0.04$).

Table IV. CP type, motor function and visual impairment in multiples vs. singletons. Birth years 1976–90, 11 centers (center 10 excluded); multivariate adjustments for birthweight and gestational age. Values are *n* (%)

	Multiples ($n=420$)	Singletons ($n=4551$)	*p*-value univariate	*p*-value adjusted
CP type				
Spastic	384 (91)	3961 (87)	0.006	0.880
Dyskinetic	18 (4.3)	310 (6.8)		
Ataxia	10 (2.4)	179 (3.9)		
Unclassified	8 (1.9)	101 (2.2)		
Motor function				
Unable to walk	130 (31)	1324 (29)	0.425	0.358
Walking limited, with aids	70 (17)	737 (16)		
Walking restricted but unaided	116 (28)	1338 (29)		
Unaided walking	29 (6.9)	374 (8.2)		
No functional consequence	60 (14)	621 (14)		
Unclassified	15 (3.6)	157 (3.4)		
Visual impairment				
Severe	55 (13)	485 (11)	0.134	0.224
Mild/moderate	130 (31)	1145 (25)		
Normal vision	188 (45)	2481 (55)		
Unclassified	47 (11)	440 (10)		

Table V. Type of spasticity in multiples vs. singletons. Birth years 1976-90, 11 centers (center 10 excluded); multivariate adjustments for birthweight and gestational age. Values are n (%)

	Multiples ($n=380$)	Singletons ($n=3886$)	*p*-value univariate	*p*-value adjusted
Bilateral	279 (73)	2539 (65)	< 0.001	0.925
Hemiplegic	101 (27)	1347 (35)		

Discussion

The present study is based on more than 400 multiple-born CP cases, giving very precise estimates of rates. The validity of data is ensured by the preceding work in the SCPE group harmonizing definitions and inclusion criteria, and, before pooling data in trend analyses, checking for interactions between year and center effect.

The increasing trend in multiple birth rate from 1980 to 1990 confirms findings from other studies. Recently, results from fertility databases have focused on the high morbidity and mortality, especially in triplets and higher order multiples. We hope that this knowledge will result in a change in clinical guidelines for fertility treatment and a subsequent decrease in higher order pregnancies in the future (5).

Surprisingly, there was no significant trend in the CP rate in multiples, indicating that the CP risk among multiples did not change over time. However, the total CP rate in 1976–90 in the SCPE material, published elsewhere (11), showed a small increasing trend. This trend can partly be explained by the increasing proportion of multiples among those with CP more than doubled from 4.6% in 1976 to 10% in 1990. Thus, despite the size of our material, the number of multiples

Table VI. Intellectual function and severity of disability in multiples vs. singletons. Birth years 1976–90, 10 centers (centers 3 and 10 excluded); multivariate adjustments for birthweight and gestational age. Values are *n* (%)

	Multiples ($n=350$)	Singletons ($n=3925$)	*p*-value univariate	*p*-value adjusted
Intellectual function			0.750	0.219
IQ < 50	90 (26)	1124 (29)		
IQ 50-84	59 (17)	676 (17)		
IQ ≥ 85 or normal schooling	166 (47)	1856 (47)		
Unclassified	35 (10)	269 (6.9)		
Severity of disability			0.985	0.236
Severe	67 (19)	753 (19)		
Moderate	107 (31)	1184 (30)		
Mild	152 (43)	1788 (46)		
Unclassified	24 (6.9)	200 (5.1)		

Table VII. Birth order in twin CP children, related to gestational age. Birth years 1976–90, 12 centers. Values are *n* (%)

	< 32 weeks ($n=157$)	32-36 weeks ($n=131$)	≥ 37 weeks ($n=58$)	Total ($n=346$)
First born	64 (41)	66 (50)	23 (40)	153 (44)
Second born	93* (59)	65 (50)	35 (60)	193*(56)

*$p<0.05$

with CP per year is still small, but the changes over time have social implications.

The fourfold higher CP rate in multiples compared to singletons is consistent with previous findings (1–4,6–9). As the rates are the same for multiples and singletons in gestational age and birthweight groups below 37 weeks and 2500 g, respectively, the increased CP risk in multiple born infants is mainly associated with the risk of being born preterm. The borderline higher CP rate in multiples born at term and with a birthweight above 2500 g might be related to the higher risk of growth retardation in multiples.

The difference in CP type between multiples and singletons is well explained by multiples being more preterm. Preterm born children with CP often (12,13) have brain lesions in the form of periventricular leukomalacia, changes related to the fragility of the brain vessels in the immature brain and highly associated with bilateral spastic CP (14,15). The severity of disability does not seem to be affected by either multiple status or gestational age.

There was a higher proportion of second- than first-born twins, which might be explained by a higher risk of intrapartal asphyxia in the second-born twin in vaginal delivery. A more precise picture of the influence of birth order will include information on the outcome of the co-twin (such as intrauterine death) and the delivery mode. Another hypothesis to be investigated is that in twin–twin–transfusion syndrome in monochorionic pregnancies, the recipient twin with polyhydramnios for mechanical reasons will more often present as twin A, whereas the donor twin, presumably at higher risk of asphyxia and CP, is born as twin B.

In this register-based study, it has not been possible to investigate risk factors for CP in multiples in more detail or to separate twins from higher order multiples. However, as most of the cases are twins, our conclusions are limited to this group. To determine the influence of *in vitro* fertilization, chorionisity, death of a co-twin and other complications in pregnancy, case-control studies with subsequent retrieval of case-based information from medical records are needed.

Conclusions

The main conclusion of this paper is that cerebral palsy due to multiple birth has increased through the 1980s. This finding has implications for fertility treatment: twin pregnancies should be avoided because of a four times higher risk of cerebral palsy in each child.

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