Intrauterine Growth and Cerebral Palsy in Twins: A European Multicenter Study

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Population-based studies in twins have been of insufficient size to explore the relationship between risk of cerebral palsy and intrauterine growth. Earlier studies in singletons have suggested an optimum size at birth for minimum cerebral palsy risk between the 75th and 90th percentiles of weight for gestational age. We aggregated data from nine European cerebral palsy registers for 1976 to 1990. Using sex-specific fetal growth standards for twins, a z score of weight-for-gestation was derived for each of the 373 twin cases. The rates of cerebral palsy in each z-score band were compared to the rate in the a priori reference band of 0.67 to less than 1.28 (equivalent to the 75th to less than 90th percentiles). In twins born at 32 weeks' gestation or more (92% of all twins), cerebral palsy rates were higher for both light and heavy-for-gestation babies compared to an optimum (i.e., minimum risk) in the reference band. However, the rate ratio for heavy babies (90th percentile or greater) did not reach conventional (95% confidence intervals [CI]) statistical significance (rate ratios = 1.76; 90% CI 1.02–3.03). For twins born at less than 32 weeks, the significantly higher risk for cerebral palsy was observed consistently in all z-score bands less than average compared to the reference band. This multi-center study demonstrates that for twins born at 32 weeks' gestation or more, an increased risk of cerebral palsy is associated with deviations from optimal intrauterine growth at about 1 standard deviation above mean weight, as was earlier reported for singletons. For twins born at less than 32 weeks' gestation, this pattern is only demonstrable for babies weighing below the optimum weight-for-gestation.

Cerebral palsy (CP) is the most common cause of severe physical disability among children in developed countries. Twins and higher order multiples are at greater risk of neurological morbidity than singletons. Thus, the prevalence of CP ranges from 7 to 12 per 1000 survivors in twins, compared with one to two in singletons (Grether et al., 1993; Petterson et al., 1993; Pharoah & Cooke, 1996; Williams et al., 1996; Yokoyama et al., 1995). The higher rate of CP in twins can not be entirely attributable to the higher proportion of low birthweight and preterm infants among twins, because the risk of CP in twins is also higher in normal birthweight twins compared to singletons of similar birthweight (Grether et al., 1993; Pharoah & Cooke, 1996; Williams et al., 1996). Other factors specific to multiple pregnancy, such as twin–twin transfusion and intrauterine death of a co-twin in a monochorionic pregnancy, may also contribute to the excess risk of CP in twins (Blickstein, 2002; Pharoah & Adi, 2000; Scher et al., 2002). A substantial increase in the proportion of multiples (from 5.3% in 1960–1969 to 10.3% in 1980–1989) among children with CP has been reported (Petterson et al., 1993). This is attributed to both the increasing survival of preterm babies and the increasing rates of multiple pregnancies in developed countries (Blondel & Kaminski, 2002; Topp et al., 2004) consequent to assisted conception and increasing maternal age.

Intrauterine growth retardation is a recognized risk factor for CP in singletons (Stanley et al., 2000a). However, there is insufficient evidence to confirm whether this association exists in twins, as previous research has been hampered by limited datasets. A study of CP in multiple births requires a large population base, as both CP and twinning are rare conditions. There are a few population-based studies, which have measured rates of CP amongst multiple

births (Grether et al., 1993; King & Johnson, 1995; Liu et al., 2000; Nelson & Ellenberg, 1995; Petterson et al., 1993; Pharoah & Cooke, 1996; Stanley et al., 2000b; Williams et al., 1996; Yokoyama et al., 1995). However, only some of these studies reported CP rates by gestational age (Liu et al., 2000; Pharoah & Adi, 2000; Scher et al., 2002; Williams et al., 1996; Yokoyama et al., 1995). Gestational age information is essential for studies of the relationship between intrauterine growth and CP in twins because analysis by birthweight alone is not able to distinguish the relative importance of poor intrauterine growth as opposed to preterm delivery (Stanley et al., 2000b). According to a comprehensive review of pathways to CP (Stanley et al., 2000b), gestational age at delivery appears to be a more important determinant of risk of CP in twins than in singletons.

The European network of CP registers (SCPE) has identified over 6500 cases of CP among babies born between 1976 and 1990 in eight European countries from 13 different CP surveys and registers (Anonymous, 2000), and offers the unique opportunity for a detailed study of the relationship between CP and fetal growth in twins. This study aims to determine whether there is an association between CP in twins and their intrauterine growth similar to that already reported for singleton cases in the same dataset (Jarvis et al., 2003).

Materials and Methods

SCPE Collaboration Methodology

Participating centers use a consensus definition of CP with the following key elements: CP is a group of disorders, that is, it is an umbrella term; it is permanent but not unchanging; it involves a disorder of movement and/or posture and of motor function; it is due to a nonprogressive interference/lesion/abnormality in the developing/immature brain. The main inclusion/exclusion criteria are: children should be at least 4 years old when meeting criteria for the definition of CP (with exception for deaths age 2–4 years), and if the definition criteria are met and the neurological signs of one of the subtypes of CP are present, children with recognized syndromes, brain abnormalities, or chromosome abnormalities are included. A range of sources was used for case ascertainment, and all centers used more than one source. The hierarchical classification system of CP subtypes adopted by the participants of SCPE is described in greater detail elsewhere, as are other methodological details of the SCPE collaboration (Anonymous, 2000).

Study Subjects

For the present study, cases of CP born outside the register catchments are excluded, together with those cases of known postneonatal origin. The characteristics of each case used in this analysis are, birthweight (grams), gestation in completed weeks (largely confirmed by ultrasound dating) and sex.

Not all of the contributing CP registers have complete data, so each analysis is confined within registers to those years for which the analyzed variables had less than 20% missing values. One register (Tübingen in Germany) records only cases of bilateral spastic CP and therefore is excluded from this analysis where all CP types are combined. Exclusions of cases with known postneonatal cause, those born outside the register catchments, the Netherlands register (no reliable denominators), the two French registers (> 20% of missing data for plurality, birthweight, or gestation in every year), 2 of the 15 years in the Southern Irish register (> 20% of data missing), all singleton and higher order (≥ 3) multiple cases led to a sample of 375 twins. Two further cases with gestational ages outside 24 to 40 weeks' gestation were excluded as appropriate weight standards were not available, which resulted in a final sample of 373 twins.

The association between CP and intrauterine growth in 4307 singleton cases, with a detailed description of the singleton dataset was reported earlier (Jarvis et al., 2003). Some of these data are recalculated here for comparison with those from twins.

Assessment of Intrauterine Growth

For assessment of fetal growth in twins we used 'fetal' growth curves based on ultrasound estimates of the mean weights by gestation for white male and female twins (N = 1026 twin pregnancies) from the United States (Min et al., 2000). All, except Swedish, CP cases were compared to the Min values adjusted to fit Scottish data (reference dataset of Scottish twin livebirths in 1975–1989; Anonymous, 1991). The Scottish standard was chosen as it aligns well with the only other published non-Scandinavian neonatal growth standard for European twins (Buckler & Green, 1994), covers the correct time period (1975–1989 vs. 1988–1992; Buckler & Green, 1994), and the majority of non-Swedish CP cases (245/323) were from United Kingdom and Irish registers. As Min's standard was too heavy for most European twin births (e.g., their mean weight for white male twins at 38 exact weeks of gestation = 2769 g vs. mean birthweight for Scottish male twins of 2665 g), we adjusted Min's values at each gestational age in proportion to 38 weeks' gestation (e.g., mean weight by gestation * 2665/2769 for Scotland), separating by sex. Twin cases from Sweden (n = 50) were compared to a separate Swedish birthweight standard (Rydhström, 1992), because Swedish babies are consistently heavier between 32 and 40 weeks of gestation. Min's standard was almost ideal for Swedish male twins (2771 g at 38 exact weeks of gestation) but slightly lighter for Swedish female twins, which required a similar adjustment. We then transformed mean weights for exact weeks of gestation (used in Min's standards) into those for completed weeks to maintain consistency with CP cases.

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Birthweight for gestation for each twin case was compared to these standards separately by sex to derive a *z* score. Cases were then allocated to *z*-score bands chosen to equate to conventional growth percentiles.

Denominators

The rate of CP in twins is estimated using as denominator the actual number of live-births and an average twinning rate specific to each register source population. This approach was used as not every register in the SCPE collaboration provided the number of twin births for every year. This total number of twin births was then allocated to two gestational age groups (< 32 or ≥ 32 completed weeks). A cut-off of 32 weeks of gestation was selected for separating preterm twins and more mature twins as the percentage of twins born at less than 32 weeks of gestation in a Scottish reference dataset (Anonymous, 1991) was similar to the percentage of singletons born at less than 37 weeks of gestation (about 8% in the Scottish population). The estimated number of births within each gestational age group (e.g., 24–31 weeks) was then divided between *z*-score bands assuming a normal distribution (e.g., 10% of twins are assigned to the *z*-score band less than –1.28 — approximately equivalent to less than the 10th percentile). In order to take into account the relatively high neonatal mortality of twins especially at low gestational ages, the number of neonatal survivors in each *z*-score band by gestation was derived using the neonatal survival rate in each equivalent *z*-score band in Norway in 1976 to 1990 (Glinianaia et al., 2000). Rate comparisons are between *z*-score bands and are not reliant on exact denominator allocation to gestational age categories.

For the purpose of consistency, singleton CP rates and rate ratios (RR) were also presented for gestational bands less than 32 and 32 or more weeks' gestation (Table 1 and Figure 1), and CP rates were calculated per 1000 neonatal survivors using contemporary neonatal survival rates by *z* score (Dr Edmund Hey, personal communication).

Statistical Analysis

The rates of cerebral palsy in each *z*-score band were compared to the rate in the reference band of 0.67 to less than 1.28 found previously to be associated with the lowest rate of cerebral palsy in singleton births (Jarvis et al., 2003). Rate ratio confidence intervals (95%, if not specified otherwise) are calculated as described by Morris and Gardner (1989).

Results

A total of 373 twins were included in the analysis. The overall CP rate in twins born at 24 to 40 weeks' gestation during 1976 to 1990 was 7.6 per 1000 neonatal survivors.

Figure 1 shows prevalence of CP in twins and singletons per 1000 neonatal survivors by *z* score of weight for gestation based on fetal standards. For births between 32 and 40 weeks of gestation (92% of all twins), the patterns of CP rates in twins are similar to those in singletons though twins are at higher risk in each *z*-score band. The optimum weight for gestational age, expressed in lowest CP rates, is located in the 0.67 to 1.28 *z*-score band with CP rates tending to increase away from this optimum for both light and heavy-for-gestation babies. For twins born at less than 32 weeks' gestation, the pattern of CP rates did not mirror that in singletons. Thus, in contrast to singletons, the risk of CP in twins was not elevated at high weight for gestation compared to the reference band.

Table 1 shows the distribution of twins and singletons with CP by *z*-score band of weight for gestation and the corresponding RR for risk of CP compared to the reference band. For births at 32 to 40 weeks' gestation, the RR for twins, as amongst singletons, were significantly higher in all *z*-score bands below 0 compared to the reference band. The RR for heavy twins was also higher than for twins in the reference band, but in contrast to singletons did not reach conventional levels (95% CI) of statistical significance (RR = 1.76, 90% CI 1.02–3.03). It is notable that this RR value in heavy twins is actually higher than the significant equivalent value in singletons. For twins born at less than 32 weeks an increasing risk for cerebral palsy was observed across all categories of twins in *z*-score bands less than 0 compared to the reference band. However, unlike singletons, heavy twins at less than 32 weeks' gestation do not show elevated rates over those in the reference band.

Discussion

To our knowledge, there is only one published study on CP in multiples which has reported CP rates by birthweight standardized for gestational age, but it was limited to 28 cases of CP (Liu et al., 2000). Our study used data on over 370 twins with CP from the SCPE database with available information on both birthweight and gestational age. We report that for babies born at 32 to 40 weeks' gestation, an increased risk of CP in twins is associated with deviations from optimal intrauterine growth. This optimum birthweight-for-gestation is located at about 1 standard deviation heavier than mean expected weight. This excess risk is most noticeable in very light-for-gestation twins (*z*-score band less than –1.28) but significant at all weights less than average and with an indication of an increase in risk at heavier-than-optimum weights. However, for 'preterm' twins (< 32 weeks), the significantly higher risk for cerebral palsy was consistently observed in all categories of lighter-than-average weight twins only.

There are a number of limitations of this study that need to be acknowledged. Any inaccuracy of denominators from the use of average twinning rates or during allocation to gestational age categories has very little effect on the RR. Rather the first concern about validity of the analysis is the accuracy of the estimated denominators within each weight-for-gestation category (i.e.,

Table 1

Rate Ratios of Cerebral Palsy by z-score Band of Weight for Gestation in Twins and Singletons[a]

	z-score band				Reference	
	< −1.28	−1.28 to < −0.67	−0.67 to < 0	0 to < 0.67	0.67 to < 1.28	≥ 1.28
Twins[b]						
Gestation (weeks)						
24–31 (n)	24	34	58	37	16	9
RR (95% CI)	3.93 (2.13–7.25)	3.03 (1.69–5.41)	2.73 (1.59–4.70)	1.57 (0.88–2.79)	1	0.90 (0.40–2.01)
32–40 (n)	41	32	54	31	17	20
RR (95% CI)	3.67 (2.09–6.45)	1.89 (1.05–3.39)	1.91 (1.11–3.29)	1.09 (0.61–1.97)	1	1.76 (0.92–3.36)
% of neonatal survivors[c]						
at 24–31 weeks	53.7	65.8	74.7	83.0	93.8	87.9
32–40 weeks	98.3	99.4	99.3	99.8	99.6	99.9
Singletons						
Gestation (weeks)						
24–31	215	162	212	150	88	130
RR (95% CI)	3.62 (2.84–4.61)	1.83 (1.44–2.33)	1.47 (1.17–1.85)	1.01 (0.80–1.27)	1	2.30 (1.77–2.99)
32–40	1071	595	609	528	264	283
RR (95% CI)	6.11 (5.34–6.99)	2.26 (1.97–2.58)	1.38 (1.21–1.58)	1.20 (1.05–1.37)	1	1.61 (1.38–1.88)
% of neonatal survivors[c]						
at 24–31 weeks	88.0	87.3	85.2	88.0	86.9	83.8
32–40 weeks	99.5	99.8	99.8	99.9	99.9	99.8
Equivalent percentiles[d]	< 10	10 to < 25	25 to < 50	50 to < 75	75 to < 90	≥ 90
% of births	10%	15%	25%	25%	15%	10%

Note: [a] z scores of weight for gestation were calculated using plurality- and sex-specific fetal growth standards, RR were compared to the reference band.

[b] Twin fetal standards (Min et al., 2000) adjusted for completed weeks of gestation for Scottish (Anonymous, 1991) and Swedish (Rydhström, 1992) standards.

[c] Data for twins based on the Norwegian twin dataset 1976–1990 (Glinianaia et al., 2000) and for singletons on the North of England Standard Maternity Information System 1976–1985 (Dr Edmund Hey, personal communication).

[d] NB: equivalence of z-score bands to percentile ranges assumes a Gaussian distribution of fetal weight in each gestational age band.

RR and CI are given to two significant figures throughout the table.

Denominator for twins (3968 for < 32 and 46,455 for 32–40 weeks' gestation) was estimated from 2,444,008 known total live-births using an average twinning rate in the source populations and allocated according to gestational age distribution of Scottish twin live-births 1975–1989 (Anonymous, 1991). Rates (as illustrated in Figure 1) can be calculated for each z-score band for gestation by allocating the denominator to the percentage of births in the final row and the percentage distribution of neonatal survivors in a given gestational category (e.g., no. of neonatal survivors among twin live-births with weight < 10th percentile at 24–31 weeks' gestation = 3968*0.1*0.537).
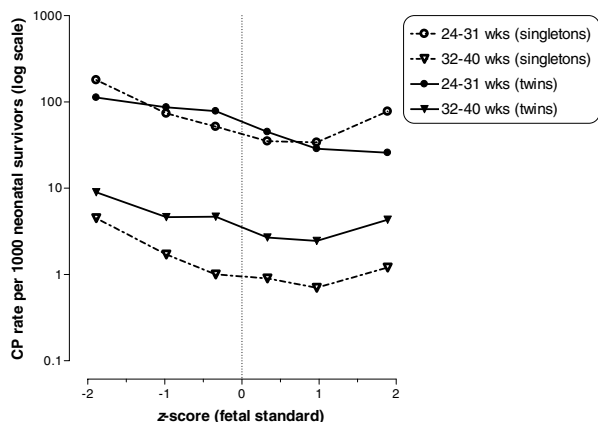
Denominator for singletons (20,060 for < 32 and 2,375,068 for ≥ 32 weeks' gestation) was estimated from 2,395,128 known total singleton live-births allocated according to the gestational age distribution of Scotland 1980–1992 (Bonellie & Raab, 1996).

as between z-score bands). Two potential errors can affect the z-score band denominators: first, the assumption of normality might be incorrect so that 10% of twin births are not less than −1.28 weight z score, and second, the neonatal mortality rates used to estimate the number of survivors within each band may be inappropriate. The Norwegian data used for these latter estimates are for the same study period, and the pattern of their twin neonatal mortality rates across z-score bands is probably representative of other European countries. The distribution of Norwegian twin weights at 32 weeks' gestation or more is normal, and this appears also to be the case for estimated fetal (i.e., *in utero*) weights at all gestations (Min et al., 2000).

We sought to avoid a further potential source of error by the assignment of growth z scores to cases using fetal growth standards rather than standards based on weight at delivery. As was shown in our earlier report on singletons (Jarvis et al., 2003), such 'neonatal' standards are biased by an excess of light-for-gestation babies among preterm births, the negative skewness of birthweight distribution attributed by Gardosi (2004) to the association between spontaneous preterm birth and fetal growth restriction. The same disparity between neonatal and fetal growth curves also appears to occur amongst twins (Figure 2). For the current study we therefore used 'fetal' growth curves based on ultrasound estimates of the mean weights by gestation for 1026 healthy twin pregnancies from the United States (Min et al., 2000). These were the only published data providing estimated weight for gestation and based on a large cohort of twins. These standards were not ideal for our purpose because they required adjustment to fit the observed mean weights at 38 weeks' gestation

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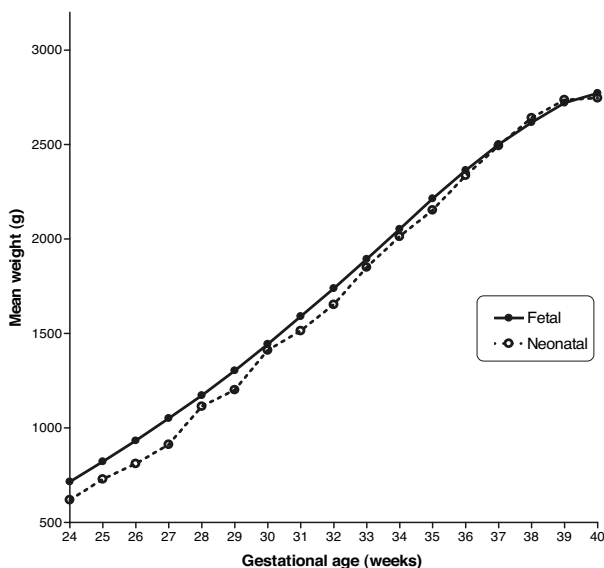
Figure 1

Prevalence of cerebral palsy in twins and singletons (per 1000 neonatal survivors) by z score of weight for gestation using fetal standards.

Note: Values for singletons are based on the previously reported analysis (Jarvis et al., 2003).

from Scottish and Swedish neonatal standards. This gestational age is suggested to be 'term' for twins (i.e., where fetal and neonatal standards should coincide) as optimal perinatal survival occurs 2 weeks earlier in twins compared with singletons (Allen & Donohue, 2002; Hartley et al., 2001; Kiely, 1998; Minakami & Sato, 1996), possibly associated with accelerated organ maturation (Allen & Donohue, 2002; Leveno et al., 1984). This approach is similar to that used by Gardosi et al. (1995) for creating sin-

Figure 2

Weight standards for Scottish female twins, 1975–1989.

Note: The Min et al. (2000) values were adjusted at each gestational age in proportion to 38 weeks' gestation (e.g., Min's mean weight by gestation * mean weight for Scottish female twins at exact 38 weeks / Min's mean weight at 38 weeks) and then transformed to mean weights for completed weeks to maintain consistency with the CP cases.

gleton fetal growth charts and in effect assumes that the twin growth trajectory from the Min's standard (USA; Min et al., 2000) can be applied to other populations of twins which differ in their mean expected term weight. Comparison of Min's proposed trajectory to that from another study by Yarkoni et al. (1987) using a smaller number of twins suggests that this approach may have flaws particularly at low gestational ages. If the expected mean fetal weight at less than 32 weeks should actually be slightly lower than those used in our study (as per Yarkoni et al., 1987) then a greater number of preterm cases would be assigned to higher z scores.

In this study we reported the CP rates and RR in twins for two gestational age categories: 24 to 31, and 32 to 40 weeks. We were not able to present the findings by more detailed gestational age or z-score categories due to the lack of CP cases. We selected less than 32 weeks of gestation as a cut-off for separating preterm twins and more mature twins because the percentage of twins born at less than 32 weeks of gestation is similar to the percentage of singletons born at less than 37 weeks of gestation (about 8% in the Scottish population; Anonymous, 1991).

Another potential source for bias might be secular variations in the methods of determining gestational age. This was discussed in an earlier paper on singletons (Jarvis et al., 2003), where no difference was reported in the results when using data for a second half of the study period, a time when ultrasound estimation of gestational age was more widely used.

Information on chorionicity or zygosity, as well as on the outcome and sex of the co-twin, was not available in the database. The antenatal mechanisms of CP in twins might involve additional pathways to those suggested for singletons (e.g., endocrine pathways, Nelson & Ellenberg, 1986; infection, Grether & Nelson, 1997; and coagulation defects, Thorarensen et al., 1997). Thus monochorionic twin pregnancies which have an increased probability of vascular anastomoses and twin-to-twin transfusion syndrome, are at a higher risk of perinatal mortality (Loos et al., 1998) and neurological morbidity (Adegbite et al., 2004; Lopriore et al., 2003) compared to dichorionic twins. Furthermore, where one of a monochorionic twin pair dies there is the potential for neurological impairment in the survivor due to hemodynamic events following death of the co-twin (Bajoria et al., 1999; Glinianaia et al., 2002; Nicolini & Poblete, 1999; Pharoah & Adi, 2000).

In summary, this study shows that the increased risk of CP in twins is associated with deviations from optimal intrauterine growth (about 1 SD above average) for babies born at 32 weeks' gestation or more. At these gestational ages, the patterns of CP rates by weight for gestation are virtually identical in two different populations (twins and singletons). This consistency suggests that there may be a generic mechanism for the association between brain damage and

abnormal intrauterine growth. In twins, like in singletons, obstetricians should view deviations away from optimum growth-for-gestation at 32 weeks' gestational age or more as signals for fetal abnormality originating antenatally, or for the onset of factors increasing fetal vulnerability to delivery-related stress. The pattern of risk amongst twins of less than 32 weeks' gestational age is less clear. This may be an issue of small number or of identifying appropriate fetal weight standards for preterm twins, and remains to be determined.

Acknowledgments

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