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Improved Outcome for Very Low Birth Weight Multiple Births

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This study describes time trends for very low birth weight multiple births in relation to very low birth weight singletons. Two cohorts of very low birth weight (less than 1250 gm) children recruited between 1983-85 (cohort 1, n = 115) and 1992-94 (cohort 2, n = 144) were compared. The Bayley Scales of Infant Development and a standardized neurologic examination were administered at 2 years corrected age. Neurodevelopmental outcome did not change between cohort 1 and 2 for singletons. For multiple births, mean Mental Developmental Index increased after adjustment for neonatal risk factors [adjusted mean (standard deviation) 81.8 (11.7) to 96.5 (18.6), analysis of covariance P = 0.007]. The prevalence of cerebral palsy decreased, however not significantly [adjusted odds ratio (95% confidence interval) 0.3 (0.1-1.5), P = 0.14]. The proportion of disease-free survival (no cerebral palsy and no developmental delay) increased for multiple births (7-37%, P = 0.002), but not for singletons. In cohort 2, neurodevelopmental outcome of multiple births was similar to that of singletons. The cognitive outcome of very low birth weight multiple births improved, possibly because of changes in perinatal practice. However, neurodevelopmental outcome was similar to that of very low birth weight singletons who were unaffected by changes in neonatal care with high proportions of motor delay and cerebral palsy.

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Introduction

Improved neonatal intensive care technologies and new treatments such as the introduction of antenatal corticosteroids [1] and surfactant therapy [2] have led to a decrease in mortality for very low birth weight infants, in particular in the late 1980s [3]. It remains controversial whether these advances were followed by an improved outcome. Time trends are described for cerebral palsy rates [4,5], but only few studies exist regarding cognitive and motor outcome. These studies, which mostly focussed on extremely low birth weight children, have observed no improvement in early childhood cognitive outcome [6,7].

Multiple births are an important population within very low birth weight children because the incidence of multiple pregnancies has increased over the past 10-15 years, mainly as a result of infertility treatments [8,9]. With improved survival, the number of multiple births has steadily increased [10]. Multiple births are reported to have a higher rate of cerebral palsy [11,12] and thus time trends in their neurodevelopmental outcome may differ from that of singletons. So far, no study has reported time trends for cognitive and motor outcome for multiple-birth very low birth weight children.

The aim of this study was to describe time trends in neurodevelopmental outcome for very low birth weight multiple births in relation to very low birth weight singletons by comparing outcome of children born in the early 1980s (1983-1985) to that of children born in the early 1990s (1992-1994).

Methods

Population

The study patients were prospectively recruited from the Maternity Hospital Zurich, a tertiary care center serving a population of approximately 1.7 million people. All eligible live born infants with birth weight below 1250 gm who were inborn at the Maternity Hospital could be

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enrolled. The recruitment periods for the two cohorts were January 1983 to December 1985 and July 1992 to June 1994. The study was approved by the local ethics committee. In cohort 1, 112 infants were life born, in cohort 2, 146 infants were life born. In cohort 1, 46 children died (41%) and in cohort 2, 45 children died (31%). No child died after discharge from the nursery. The proportion of life-born multiple birth infants increased from cohort 1 to 2 (30 [27%] to 52 [36%]), χ^2 $P = 0.10$). Within the group of multiple birth infants, the proportion of those who survived increased between cohort 1 and 2 (11 of 30 [36%] to 37 of 52 [71%], χ^2 $P = 0.005$) but remained stable for singletons (66-70%, χ^2 $P = 0.64$). In cohort 1, two multiple births were the product of assisted reproductive techniques (including hormonal induction) compared with 13 in cohort 2 (18% vs 35%, χ^2 $P = 0.20$). At age 2 years, 157 (94%) children could be examined, 37 twins and nine triplets. Ten children were lost to follow-up, one in cohort 1 (one singleton) and nine in cohort 2 (2 multiple births and 7 singletons).

Perinatal and Demographic Variables

Gestation was assessed by last menstrual period and first trimester ultrasound. If both were unknown, the method of Dubowitz et al. [13] or Ballard et al. [14] was used to estimate gestation at birth. Small for gestation was defined as a weight below the 10th percentile for gestation. Maternal obstetric history, perinatal and neonatal data were extracted from hospital charts. Sepsis was diagnosed when there were clinical signs of systemic infection and if at least one blood culture was positive; bronchopulmonary dysplasia was defined as oxygen supplementation at day 28 of life, and patent ductus arteriosus was registered if therapeutic intervention (indomethacin) was required [15]. Intraventricular hemorrhage was classified according to Papile [16]. Ultrasound was performed on the first day of life and repeated weekly or every other week until discharge and if abnormal or suspect at 3 months corrected age. A neonatologist experienced in neonatal ultrasound read the ultrasound. Necrotizing enterocolitis was assumed in cases of progression to more than Bell's stage II A [17], and retinopathy of prematurity was graded using the criteria proposed by the International Committee [18]. Socioeconomic status was estimated by a 12-point scale that was based on paternal occupation and maternal education. Scores ranged from 2 to 12, with 2 being the highest and 12 the lowest socioeconomic level [19].

Neurodevelopmental Outcome at the Age of 2 Years

Neurodevelopmental testing was performed at 2 years of age. Age of testing was corrected for prematurity. The Bayley Scales of Infant Development was administered in both cohorts to assess mental (Mental Developmental Index) and motor development (Psychomotor Developmental Index)) [20]. Mental or motor developmental delay was defined as a Mental or Psychomotor Developmental Index of <84 (below -1 standard deviations). Mental retardation or severe motor developmental delay was defined as a Mental or Psychomotor Developmental Index of <68 (below -2 standard deviations). A standardized neurologic examination modified after Prechtl was performed [21,22]. Cerebral palsy was defined according to Bax [23] and impairment of motor function according to Palisano et al. [24]. Children were examined at the Growth and Development Center of the Children's University Hospital Zurich by pediatricians experienced in neurodevelopmental testing of normal and developmentally delayed children. Examiners were not involved in the neonatal care of the study patients but were different in cohort 1 and 2.

The quality of survival was expressed as the proportion of disease-free survival. A subject was defined as disease-free if neither cerebral palsy nor motor and cognitive delay (Mental and Psychomotor Developmental Index <84) were present at 2 years of age. Disease-free survival rate is the percent of children free of disease divided by all life born children. In cohort 1, 30 multiple births and 83 singletons were life born; in the second cohort there were 52 and 92 respectively.

Statistics

Data were analyzed by computer using Statistica software (Statsoft, Stata Corp, College Station, Texas). The continuous variables Mental Developmental Index and Psychomotor Developmental Index were not normally distributed, and thus Mann-Whitney test was used to calculate differences between the two cohorts for singletons and multiple births. Kruskal-Wallis test was used for ordinal data and χ^2 for categorical data. Multiple linear regression was performed to assess the independent effect of time (represented by the two cohorts) on continuous outcome variables (Mental and Psychomotor Developmental Index) and logistic regression for dichotomous outcome variables (Mental and Psychomotor Developmental Index <84, <68, and cerebral palsy). In the outcome category cerebral palsy, all severity forms of cerebral palsy were combined because the subgroup of severe cerebral palsy was too small. Variables in the model were the confounding variables socioeconomic status and intraventricular hemorrhage (both associated with predictor—time trend—and outcome). Gestation, small for gestation status, and bronchopulmonary dysplasia were also entered into the model although they were not associated with outcome in this study sample, but they have been associated with impaired neurodevelopmental outcome in the literature [25]. Variables solely correlating ($P < 0.1$) with outcome (patent ductus arteriosus) or only changing over time (maternal age, proportion of cesarean section) were not entered into the model. Data were expressed as odds ratio and 95% confidence intervals. No logistic regression analysis could be performed for Mental or Psychomotor Developmental Index below 68, owing to small numbers.

Results

Time Trends in Perinatal and Demographic Variables

Demographic and perinatal data for surviving infants of the two cohorts stratified for singletons and multiple births are summarized in Table 1. For multiple births, mean gestation and the proportion of children born small for gestation decreased from cohort 1 to 2. The proportion of cesarean section increased from cohort 1 to cohort 2 for singletons and multiple birth infants. Maternal age increased and socioeconomic status improved for multiple birth infants. The proportion of bronchopulmonary dysplasia increased from cohort 1 to 2. Intraventricular hemorrhage of any grade was diagnosed more often in cohort 2 as in cohort 1, however without a change in the proportion of severe intraventricular hemorrhage (grade 3 or 4).

In cohort 1, mean gestation and the proportion of children who were born small for gestation was significantly higher for multiple births than for singletons (Table 1). In that cohort, mothers of multiple births were younger and of lower socioeconomic status compared with mothers of singletons. In cohort 2, multiple births were delivered more frequently by cesarean section and were more likely to have suffered from intraventricular hemorrhage of grade 1 or 2 than singletons in the same cohort. In cohort 2, mean gestation and birth weight were comparable between multiple births and singletons.

Time Trends in Neurodevelopmental Outcome at Age 2

For all children in both cohorts, mean Mental Developmental Index and Psychomotor Developmental Index

Table 1. Time trends in demographic and neonatal variables for surviving multiple births and singletons

	Cohort 1 1983-85		Cohort 2 1992-94	
	Multiple Births	Singletons	Multiple Births	Singletons
Number of children	11	55*	37	64
Birth weight (gm), mean (S.D.)	1045 (171)	1034 (134)	1021 (147)	1011 (135)
Gestation (weeks), mean (range)	30.7 (27-33)	29.1 (26-35)[#]	28.5 (26-33)[‖]	28.6 (25-33)
SGA, n (%)	9 (81.8)	25 (45.5)[¶]	13 (35.1)[§]	25 (39.1)
C-section, n (%)	9 (81.8)	35 (63.6)	35 (94.6)	50 (78.1)[¶]
Sex (male/female), %	45:55	47:53	51:49	41:59
Twins/Triplet, n	11/0		26/9	
Maternal age (yr), mean (S.D.)	27.2 (2.8)	30.5 (4.8)[¶]	31.2 (4.7)[§]	30.4 (5.4)
Socioeconomic status,[†] mean (range)	9.8 (8-12)	7.0 (2-12)[#]	6.0 (3-12)[‖]	6.2 (2-12)
5-minute Apgar, mean (S.D.)	8.5 (1.1)	7.5 (2.1)	7.5 (1.5)[‡]	7.6 (1.7)
Arterial cord blood pH, mean (S.D.)	7.29 (0.03)	7.28 (0.09)	7.24 (0.11)	7.28 (0.07)
Neonatal complications				
Sepsis, n (%)	2 (18.2)	13 (23.6)	8 (21.6)	17 (26.6)
Retinopathy of prematurity ≥ n (%)	0 (0)	1 (1.9)	0 (0)	4 (6.3)
Bronchopulmonary dysplasia, n (%)	1 (9.0)	6 (10.9)	22 (59.5)[§]	27 (42.2)[‖]
Mechanical ventilation (days), mean (range)	2.2 (0-8)	4.4 (0-38)	2.8 (0-25)	3.7 (0-25)
Patent ductus arteriosus, n (%)	1 (9.1)	3 (5.5)	3 (8.1)	4 (6.3)
Necrotizing enterocolitis, n (%)	0 (0)	4 (7.4)	2 (6.1)	5 (8.9)
IVH 1-2, n (%)	0 (0)	14 (25.5)[¶]	21 (56.8)[§]	24 (37.5)[#]
IVH 3-4, n (%)	0 (0)	0 (0)	1 (2.7)	1 (1.6)

* Percentages may differ due to incomplete neonatal data.
[†] Socioeconomic status: score 2 equals highest social status, 12 lowest social status.
Time trend stratified for singletons and multiple births: [‡] $P \leq 0.05$, [§] $P \leq 0.01$, [‖] $P \leq 0.001$.
Differences between singletons and multiple births within cohort: [¶] $P \leq 0.05$, [#] $P \leq 0.01$.
Analysis: Unpaired *t* test (continuous variables), Mann-Whitney (ordinal variables) and chi-square (dichotomous variables).

Abbreviations:
IVH = Intraventricular hemorrhage
SGA = Small for gestation

[mean (S.D.): 98.3 (17.1) and 96.1 (17.3)] were within normal range. The overall proportion of mild cognitive delay (11.1%), of mild motor delay (10.1%), and of mental retardation (3.9%) were comparable to those of a normal population. Severe motor developmental delay was diagnosed in 7% of all children, more than expected in the normal population. The prevalence of severe cerebral palsy was 2.5%, of moderate cerebral palsy 10.6%, and of mild cerebral palsy 8.9%.

For multiple births, mean Mental Developmental Index significantly increased between cohort 1 and cohort 2 (Table 2), and the proportion of children with a Mental Developmental Index below 84 decreased. After adjustment for covariables (socioeconomic status, gestation, small for gestation status, bronchopulmonary dysplasia, and grade of intraventricular hemorrhage), mean Mental Developmental Index was still significantly higher in cohort 2 than in cohort 1 (adjusted mean Mental Developmental Index cohort 2: 99.5 vs cohort 1: 81.8, analysis of covariance $P = 0.007$). However, the proportion of cognitive delay (Mental Developmental Index <84) was not significantly lower in cohort 2 than in cohort 1 (Table 3) after adjustment for covariables. Mean Psychomotor Developmental Index did not change but the proportion of motor delay increased somewhat, however not significantly (Psychomotor Developmental Index <84, χ^2 $P = 0.28$; Psychomotor Developmental Index <68, χ^2 $P = 0.46$) (Table 2). The prevalence of cerebral palsy, predominantly of mild and moderate, decreased somewhat from cohort 1 to 2. The proportion of disease-free survival increased significantly from cohort 1 to cohort 2 (Table 2).

In cohort 2, neurodevelopment outcome of multiple births was compared with that of singletons and was not significantly different (Table 2, analysis not presented). Disease-free survival was also not significantly different between multiple births and singletons (χ^2 $P = 0.23$) in cohort 2. Males were at increased risk for severe cognitive delay compared with females, however only within the group of multiple births (χ^2 $P = 0.04$).

For singletons, mean Mental Developmental Index did not change and the proportion of cognitive delay (Mental Developmental Index <84, <68) remained similar (Table 2). Mean Psychomotor Developmental Index remained unchanged; the proportion of severe motor delay increased (4.3 to 10.7%, χ^2 $P = 0.22$), but not significantly. The prevalence of cerebral palsy, regardless of severity, was similar in both cohorts. The proportion of disease-free survival remained constant between cohort 1 and cohort 2.

Adjustment for covariables did not alter the lack of change over time (Table 3). The variable socioeconomic status was

Table 2. Time trends in neurodevelopmental outcome at age 2 for multiple births and singletons

	Cohort 1 1983-85		Cohort 2 1992-94	
	Multiple Births	Singletons	Multiple Births	Singletons
n total	11	54	35	57
MDI, mean (S.D.)	79.4 (11.7)	99.7 (14.9)	96.9 (18.6)†	100.8 (17.1)
<84, n (%)	6 (66.7)	4 (7.4)	7 (20.0)†	6 (10.9)
<68, n (%)	1 (11.1)	0 (0)	3 (8.6)	2 (3.6)
PDI, mean (S.D.)	93.6 (7.6)	95.2 (14.9)	93.5 (18.6)	98.7 (19.5)
<84, n (%)	1 (11.1)	6 (12.5)	10 (28.6)	8 (14.3)
<68, n (%)	0 (0)	2 (4.3)	2 (5.7)	6 (10.7)
CP				
mild/moderate n (%)	5 (45.5)	8 (14.8)	7 (20.0)	8 (14.6)
severe n (%)	0 (0)	2 (3.7)	1 (2.9)	1 (1.8)
Disease-free survival,* n (%)	2/30 (6.7)	36/83 (43.4)	19/52 (36.5)†	43/92 (46.7)

* Disease-free survival: Number of children without developmental delay (MDI or PDI < 84) and without CP; denominator: life born multiple births or singletons respectively.
Time trend stratified for singletons and multiple births: † $P \leq 0.01$.
Analysis: Unpaired *t* test (continuous variables) and chi-square (dichotomous variables).

Abbreviations:
CP = Cerebral palsy
MDI = Mental Developmental Index
PDI = Psychomotor Developmental Index

independently associated with cognitive outcome and intraventricular hemorrhage with cognitive and motor outcome, as well as with cerebral palsy (data not shown).

Discussion

With the introduction of new neonatal intensive care technologies and treatments in the late 1980s and falling mortality rates, time trends in neurodevelopmental outcome for very low birth weight children could be expected. Time trends may differ for singletons and multiple births, and thus time trends for each group were reported in the present study. Time trends have been described for very low birth weight multiple births in regard to the prevalence of cerebral palsy [4], but not for developmental impairments. This study is the first investigation to report time trends in developmental outcome for very low birth weight multiple births.

We observed an increasing number of multiple pregnancies. In addition, the proportion of multiple births who survived increased between the early 1980s and the 1990s. Other population-based studies have reported similar

Table 3. Independent time trends for multiple births and singletons: Unadjusted and adjusted odds ratios

Cohort Effect (Cohort 2 vs 1)	Multiple Births OR (95% CI)			Singletons OR (95% CI)		
	Unadjusted	Adjusted*	*P* adj.	Unadjusted	Adjusted*	*P* adj.
	n = 46			n = 111		
MDI						
<84	0.4 (0.2-0.8)†	0.4 (0.1-1.9)	0.27	1.2 (0.6-2.4)	1.5 (0.6-3.6)	0.40
<68	0.9 (0.3-2.8)			‡		
PDI						
<84	1.8 (0.6-5.4)	1.6 (0.3-8.1)	0.67	1.1 (0.6-1.9)	0.8 (0.4-1.7)	0.57
<68	‡			1.6 (0.7-3.7)	1.8 (0.5-6.1)	0.34
CP						
any	0.6 (0.3-1.1.2)	0.3 (0.1-1.5)	0.14	0.9 (0.6-1.5)	0.8 (0.5-1.5)	0.57

* Analysis: logistic regression for time trends (cohort 2 vs 1): adjustment for socioeconomic status, gestation, small for gestation status, bronchopulmonary dysplasia, and grade of intraventricular hemorrhage; due to small number adjustment not possible for MDI < 68 and for PDI < 68 for multiple births.
Time trend unadjusted: † $P \leq 0.01$.
‡ Cannot be calculated due to zero in cell.

Abbreviations:
CI = Confidence interval
CP = Cerebral palsy
MDI = Mental Developmental Index
OR = Odds ratio
PDI = Psychomotor Developmental Index

trends [4,9]. For the group of multiple births in the present study, parental socioeconomic status and maternal age increased between these two time periods. The rise in mean maternal age is likely due to the fact that more mothers are delaying child bearing but it also leads to a higher proportion of multiple pregnancies [26]. The change of socioeconomic status for multiple births most likely reflects the increased rate of assisted reproductive technologies in a population of mothers with a higher mean maternal age. The changes in outcome for multiple birth children may appear to be solely attributable to the socioeconomic improvement observed between the two cohorts. However, the trend in cognitive outcome remained significant also after adjusting for changes in socioeconomic status. Despite this trend, a residual confounding by socioeconomic status cannot be excluded. We observed a reduction in mean gestation and in the proportion, as well as the severity of small for gestation status for multiple births. This shift is most likely a result of altered obstetric and perinatal care. Because the inclusion criteria for both cohorts were a birth weight below 1250 gm without specification of gestation, a higher than expected proportion of small for gestation children were enrolled in both cohorts. This selection bias is a known phenomenon of studies on prematurely born infants when definition is given by birth weight rather than by gestation. The proportion of children who were small for gestation differed only in cohort 1 between singletons and multiple birth children. The prevalence of neonatal complications remained constant, except for a rise in the proportion of bronchopulmonary dysplasia and intraventricular hemorrhage grade 1 and 2. The increase in grade 1 and 2 intraventricular hemorrhage most likely represents different ultrasound ascertainment with improved ultrasound techniques and machine sensitivity in the second cohort. The increased prevalence of neonatal risk factors in cohort 2 could be expected to be associated with a poorer outcome for multiple births in cohort 2 compared with cohort 1. Despite the increase in neonatal risk factors, the cognitive outcome improved for multiple births, also after adjustment for demographic and neonatal variables. This finding supports the idea that progress in obstetric and perinatal care may have led to such amelioration in outcome.

The prevalence of cerebral palsy also decreased somewhat between cohort 1 and 2, however not significantly. This change may have occurred by chance in these relatively small cohorts. Another explanation for the changes in the prevalence of cerebral palsy may be assessment bias in the neurologic examination of the children or the use of different examiners for each cohort. However, moderate and in particular severe cerebral palsy can easily be identified by different examiners [27]. In addition, a recent study by Surman et al. reported a decline in the overall cerebral palsy rate for children born weighing $<$1500 gm from 6.3 per 1000 in 1984-1986 to 4.5 per 1000 in 1993-1995 [4]. Their reported trends were not related to changes in neonatal risk factors. Time trends were also reported separately for singletons and multiples births, but owing to small numbers no clear trend over time could be delineated for multiple births alone. In contrast, a steady rise in the cerebral palsy rate between the mid-1970s and the 1990s could be observed for multiples in the population-based Western Australian Cerebral Palsy Register with consistent methodology [26].

When outcome of multiple births in the present study was expressed as the proportion of disease-free survival, the extent of improvement became more evident. Even when disease was defined not only as severe impairment but also included mild motor and cognitive delay, multiple births experienced a significant increase in the proportion of disease-free survival from 6% to 37%.

In cohort 2, cognitive and motor outcome, as well as the prevalence of cerebral palsy were comparable between multiple births and singletons. This finding indicates that, despite improved outcome, multiple births remained at a similar risk for neurodevelopmental impairment as singletons. Our results also confirm previous studies reporting an increased risk for developmental disturbances for very low birth weight children compared with term children, independent of plurality status [6,28,29].

In the present study, the introduction of new techniques in the care of the very premature did not affect neonatal or developmental outcome for singletons. Except for a rise in the proportion of bronchopulmonary dysplasia, all neonatal complications remained at a similar level. Other studies have also reported a rise in the rate of bronchopulmonary dysplasia [30] and have associated bronchopulmonary dysplasia with lower intelligence quotient scores and more difficulties with fine and gross motor skills, independent of neurologic problems and birth weight [25]. When specifically comparing developmental outcome of very low birth weight children born before and after 1990, similar results of constant or even increased prevalence of neurodevelopmental disabilities have been reported for extremely low birth weight [6] and very low birth weight children [31].

A major limitation of the present study was the relatively small number of children in both cohorts, in particular of multiple births in cohort 1. The numbers of children with adverse outcome were even smaller, in particular those with severe neurodevelopmental impairments. This may in part explain the lack of significance for changes of adverse outcomes between cohort 1 and 2 or for differences between multiple births and singletons within cohort 2. In addition, because of the small sample size, only a selected number of variables could be entered into a multivariate regression model. Thus additional potential confounding variables such as maternal age, Apgar scores, or prenatal and neonatal infections could not be included in the regression model. Cerebral white matter injury was routinely assessed by ultrasound only in cohort 2, and no magnetic imaging studies were performed. Thus we could not relate adverse neurodevelopmental outcomes

with cerebral injury other than intraventricular hemorrhage. Moreover, intraventricular hemorrhage, in particular low-grade intraventricular hemorrhage, is known to poorly correlate with neurodevelopmental outcome [32].

Although our patient group was recruited from a tertiary care center, the description of time trends for multiple births deserves attention because all eligible children were enrolled during the given time period. Most children born at early gestation and especially those who are of multiple gestation are being transferred intrauterinely to and delivered at a tertiary care center [33].

Multiple births represent an important subgroup of very low birth weight infants, who are already at risk. They are of public health interest because the proportion of surviving multiple births has dramatically grown owing to an increase in infertility treatments [8] paralleled by a decrease in mortality [9]. The rise in artificial reproductive technologies has also been observed in Switzerland in the decade between the early 1980s and the early 1990s [33]. It remains unanswered whether multiple birth children warrant special attention in addition to their very low birth weight status. In the present study, despite an improvement in outcome between the early 1980s and the early 1990s, they remained at similar risk for developmental impairment. We could not demonstrate that they were at a greater risk than singletons. Little data are available on the cognitive outcome of multiple births. In a recent study on children born prematurely (before 35 weeks gestation), matched for type and extent of brain lesions, gestation, and birth weight, multiple births performed similar to singletons at 6 years of age in perceptuo-motor competence and verbal ability [34]. However, in that study, the inclusion of children with a lower risk for developmental difficulties than very low birth weight children may have influenced the negative findings. Because of a greater availability of cerebral palsy registers, more results have been published regarding the association between multiple births and cerebral palsy. Studies report a consistently raised risk for cerebral palsy for twins (on average 4.7-fold) in a normal birth weight category (more than 2500 gm) [4,26] but less consistent for the very low birth weight category [35,36]. The question has been raised whether artificial reproductive technologies per se may pose a risk for developmental impairment. Recent studies reported comparable outcome for children with different forms of artificial reproductive technologies compared with children without artificial reproductive technologies at 3 [37] and 5 years of age [38]. In these studies, socioeconomic status played a more important role in determining outcome than the mode of conception.

In conclusion, multiple births have experienced amelioration in cognitive outcome between the 1980s and 1990s. However, multiple births born prematurely are at similar risk for neurodevelopmental impairment as very low birth weight singletons. To delineate whether this is also true for all very low birth weight multiple births, population-based studies are needed to assess outcome for very low birth weight multiple births and singletons.

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