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Neurodevelopmental Outcomes of Twins

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In population-based studies, the prevalence of neurodevelopmental disability is consistently higher in twins than singletons. This is largely because birth weight and gestational age (GA) distributions of twin births are shifted to the left when compared with singleton births, and lower birth weight and lower GA are associated with increased risk of neurodevelopmental disability. From a pathophysiologic perspective, a question of interest is whether neurodevelopmental outcomes of twins differ from singletons after controlling for covariates. If significant differences in outcomes persist, this would suggest that the twining process itself or something intrinsic to shared life in the womb may be responsible for observed differences. From a clinical perspective, when counseling parents at risk for preterm delivery of twins, it is useful to understand how twin outcomes compare relative to singleton outcomes at the same birth weight or GA. The purpose of this review is to examine the long-term neurodevelopmental outcomes of twins compared with singletons with control for important covariates.
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In comparisons of prevalence rates in population-based studies from the United States, United Kingdom, Australia, Sweden, and China—in which normal birth weight and term infants predominate—the prevalence of cerebral palsy (CP) is consistently higher in twins with relative risks (RRs) ranging from 4 to 7.4 compared with singletons.[1-7] Three large population-based studies comparing intelligence quotients (IQs) of twins and singletons in the United States, United Kingdom, and Scotland—in which normal birth weight and term infant predominate—reported deficits of 1.4-5.1 points in twins.[8-10] These findings are not surprising because the birth weight and gestational age (GA) distribution of twin births is shifted to the left when compared with the singleton births,[1,2,5,6] and lower birth weight and lower GA are each associated with increased risk of neurodevelopmental disability in singleton newborns. From a pathophysiologic perspective, a question of interest is whether neurodevelopmental outcomes of twins differ from singletons after controlling for variables that are associated with both being a twin and with long-term neurodevelopmental outcomes. This may be accomplished by matching based on 1 or more covariates, adjustment for covariate effects using multiple regression analysis, or to some degree by delimiting the sample by GA or birth weight. If significant differences in outcomes persist after controlling for potentially important covariates, then that would suggest that the twining process itself or something intrinsic to a shared intrauterine environment may be responsible for these differences. From a clinical perspective, when counseling parents at risk for preterm delivery of twins, it is useful to understand how twin outcomes compare relative to singleton outcomes (for which there are much more data) at the same birth weight or GA. The purpose of this review is to examine the long-term neurodevelopmental outcomes of twins compared with singletons with control for important covariates.

Potential Covariates

To examine this issue, potential covariates that might confound or modify the prevalence of neurodevelopmental disabilities in twins and singletons must be identified. Birth weight and GA are the most important covariates to be considered. Gender also has an important effect on neurodevelopmental outcome, with females in general having better outcomes than males for both twins and singletons.[1,5,7,10] Intrauterine growth restriction (IUGR) is more common in

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twins than singletons and has been reported to be associated with increased risk of neurodevelopmental disability in singletons and twins.[4,7,10,11] Being the second of twins born has been reported to be associated with increased risk of neurodevelopmental disability in extremely preterm infants in 1 small study.[12] However, the difference was likely not significant, although the data supporting this conclusion were not provided. In another small study, Hay and O'Brien[13] reported first-born twins of like gender performed better on 4 of 13 tests of cognitive function. By contrast, Leonard et al[14] found no differences in neurodevelopmental outcome at early school age, and Posthuma et al[15] found no difference in Wechsler Adult Intelligence Scale-III scores in adolescence or middle age between first- and second-born twins. Two large population-based studies[6,16] found no effect of birth order on the prevalence of cognitive disability or CP. If an effect of birth order does exist, it may well be influenced by obstetrical management. Congenital anomalies are more common in twins,[17] and some (eg, congenital heart disease) are associated with increased risk of neurodevelopmental disability. Artificial reproductive technology is more common among twins and singletons, especially in more contemporary cohorts. In a large population-based study, the risk of CP was not associated with artificial reproductive technology[18] (Table 1). This was confirmed in a systematic review of controlled studies in which artificial reproductive technology per se was not significantly associated with increased risk of neurodevelopmental problems in twins.[19] However, the authors cautioned that limited data did not allow the possibility of an effect to be excluded. Large prospective studies of outcome at school age are required.

Parental education and socioeconomic status have major effects on cognitive outcome and are always important to consider as potential covariates in any study of cognitive outcomes. In some studies, parental education and socioeconomic status are higher in twins than singletons.[9,20] Maternal age at delivery is often greater for twins than singletons,[8-9] but the number of older siblings may be fewer in twins that in singletons.[9] Both have been reported to be associated with better cognitive function in singletons and in twins.[8,9] Cognitive ability of twins has been reported to improve from 18 months to 6 years of age.[21] Effects of covariates on cognitive ability may be gender specific.[13] Zazzo et al[22] showed the cognitive deficit in twins compared with singletons to be similar to that in closely spaced singletons, suggesting that family disruptions caused by twins may contribute to cognitive discrepancies between twins and singletons.

The effect of twin-to-twin transfusion syndrome (TTTS) and intrauterine death of a co-twin on neurodevelopmental outcome is specific to monochorionic (MC) twins. Dickinson[23] performed a case-control study of a regional cohort of 52 twins with TTTS born in 1992-99 in Western Australia. Of 31 pregnancies, 22 were treated with serial amnioreductions. Forty-four of the 52 were matched for gender, GA, and birth weight ratio with 44 singleton controls; 27 of the 52 were matched with 27 twin controls without TTTS. Both subsets of twins with TTTS had statistically and clinically significant reductions in intelligence scores at 3-6 years of age when compared with their respective control groups: 95 ± 15 for twins with TTTS vs 104 ± 10 for singleton controls ($P = 0.002$), and 91 ± 14 for twins with TTNS vs 104 ± 11 for twin controls ($P < 0.001$). Most of these differences were accounted for by twins with TTTS <33 weeks, whose mean IQ was 89 ± 16. In the same study, the prevalence of CP in this cohort twins with TTTS was not significantly different from that in a regional cohort of unmatched singletons <33 weeks or that in unmatched twins without TTNS <33 weeks: 3/32 of twins with TTNS (6.2%, 95% confidence interval [CI[0.8-20.8) vs 17/510 of singletons (3.3%, 95% CI: 2.0-5.3) vs 9/194 of twins without TTTS (4.9%, 95% CI: 2.3-9.1). There was fetal demise of the co-twin in 6 of twins with TTTS. One of these was lost to follow-up. Of these 5, all 5 had normal IQ scores; 1 had CP. This suggests that the lower IQ associated with TTTS was independent of the death of a co-twin, although this may not be the case for CP.

Another question of interest is whether neurodevelopmental outcomes differ between twins with TTTS managed with serial amnioreduction compared with those managed with endoscopic laser ablation. The prevalence of CP with TTTS managed with amnioreduction has been reported to be 13%-26%,[20,24-26] but as low as 5%,[27] and the prevalence of neurodevelopmental disability to be 22%[20] and 28%.[26] The prevalence of CP with TTTS managed with laser ablation has been reported to be 3%-11%[28-34] and the prevalence of neurodevelopmental disability to be 12%-33%.[32,34,35] These data are very difficult to compare because many of the studies are small, GA at delivery varied among studies, no studies included GA-matched controls, not all cases of TTTS received intervention, there was variation in the distribution of Quintero stages among studies, inclusion of information about the proportion of survivors whose co-twin died in utero was often not provided, and there was variation in age at follow-up and criteria for defining CP and neurodevelopmental disability. In the only randomized controlled trial of amnioreduction vs laser ablation for TTTS with long-term follow-up,[36] there were no significant differences in neurodevelopmental outcomes at age 6 years. The prevalence of CP was 15% (6/41) with amnioreduction vs 13% (9/69) with laser ablation. The prevalence of CP, blindness, or deafness was 20% (8/41) with amnioreduction vs 17% (12/69) with laser ablation. The Wechsler Intelligence Scale for Children full scale IQ was 90.6 ± 19.9 with amnioreduction and 91.0 ± 33.1 with laser ablation.

With fetal demise of a co-twin, the risk of long-term neurologic neurodevelopmental disability in the surviving twin is clearly greater for MC than for dichorionic (DC) twins. In a systematic review of 17 studies of long-term neurologic outcome after fetal demise of a co-twin in 267 twin pregnancies, the prevalence of neurologic abnormality in the surviving twin was 17% (95% CI: 11-26%) for MC twins vs 1% (95% CI: 0-7%) for DC twins, with an odds ratio (OR) of 4.07 (95% CI: 1.32-12.51).[37]

In a small study of 53 MC-MZ, 33 DC-MZ, and 173 dizygotic (DZ) twin pairs, there was no effect of chorionicity or zygosity on IQ.[38] Posthuma et al found no difference in Wechsler adult intelligence scale-III (WAIS-III) scores be-