Cerebral palsy in multifoetal pregnancies

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Cerebral palsy (CP) consists of a wide range of lifetime physical disabilities caused by damage to the brain during intrauterine and early neonatal life. The risk of CP is increased among survivors of prematurity and in low-birthweight (LBW) infants. Increased prematurity and LBW rates are more common in multifoetal pregnancies, therefore, these pregnancies have also been associated with increased rates of CP. Given the world wide epidemic dimensions of multiple births, this paper discusses current concepts regarding CP in multifoetal gestations.

CP in multiple compared with singleton pregnancies

The increased risk of CP in multiple births has no geographical restrictions. Javier Laplaza and coworkers compiled data from 11 CP studies in the United States and showed a 7.4% prevalence of twins among those with CP. Other studies, from England and the United States, have shown similar increased prevalence of CP in twins compared with singletons: 7.4 versus 1 in 1000 survivors to 1 year and 6.7 versus 1.1 in 1000 survivors to 5 years. Similar results were obtained in China and Japan.

The prevalence of CP in triplets exceeds that of twins and of singletons: 28 versus 7.3 versus 1.6 per 1000 survivors to 1 year and 44.8 versus 12.6 versus 2.3 per 1000 survivors to 3 years. Japanese data confirm this trend in quadruplets as well: 0.9% versus 3.1% versus 11.1% for twins, triplets, and quadruplets, respectively. The reported CP prevalence in singleton and multiple pregnancies shows a significant exponential relationship. Data clearly indicate that the higher the number of foetuses, the greater is the prevalence of CP. Moreover, the increase in CP with the number of foetuses is exponential.

Relation between CP and twins’ birthweight and gestational age

The most relevant question is whether increased prevalence of CP among multiple births is a true association or is an overrepresentation of multiple births among LBW and preterm infants. Although there are no data related to higher-order multiples, several series stratified the prevalence of CP in twins and singletons according to birthweight. Williams and colleagues showed that the relative risk of CP was greatest (4.5-fold) among twins weighing ≥2499 g. Grether and colleagues and Pharoah and Cooke showed a comparable risk for CP among very LBW twins and singletons, whereas twins weighing ≥2500 g had a higher risk of CP than singletons of similar weight.

Liu and coworkers found that the lower prevalence of CP in LBW multiple births results from the higher mortality of LBW twins compared with singletons. In normal birthweight categories, where multiple births have similar mortality rates, there are more survivors to demonstrate a higher prevalence of CP than in singletons.

It is expected that similar findings will be observed regarding gestational age due to the fact that birthweight and gestational age are related. Yokoyama and coworkers found that the risk of CP in multiple births was 20 times higher in births before 32 weeks’ gestation than at ≥36 weeks’ gestation. A strong correlation between the risk of CP in twins and gestational age at birth was also found by Williams and colleagues. When comparing twin with singleton births, the relative risk of CP was greatest and significant, only for twins delivered at ≥37 weeks’ gestation.

Data, therefore, imply that multiple and singleton pregnancies have similar risks for CP until term, and although LBW and preterm birth are apparently the most significant risk factor for CP, the disadvantage of twin pregnancies becomes evident near term. Excess risk for CP beyond 37 weeks’ gestation may suggest that ‘term’ occurs earlier in twins, in accord with observations that twins experience increased morbidity compared with singletons, and are at increased risk of death and severe disability after reaching 38 weeks’ gestation. This constitutes a strong argument for delivering twins by 38 weeks’ gestation.

Relation between assisted reproductive technology and CP in multiple pregnancy

A significant proportion of multiple births result from ovulation induction or assisted reproductive technology (ART) and are termed iatrogenic multiple pregnancies. By integrating the excess risk of CP in multifoetal pregnancies with that of neonatal CP, it was possible to estimate the risk of this complication after ART. Estimated rates of CP were significantly
lower after spontaneous conception (2.7 per 1000 neonates) than after the transfer of three embryos (16.86 per 1000), or two embryos (8.77 per 1000), or after the transfer of three embryos with a reduction of triplets to twins (10.31 per 1000). In addition, the estimated rate of CP was significantly higher after the transfer of three embryos than after the transfer of two or after a reduction of triplets to twins. By contrast, the estimated rates of CP are expected to be similar after the reduction of triplets to twins and after the transfer of two embryos. Similar methodology was used by Kiely and colleagues who estimated that in the USA there might be an 8% increase in the prevalence of CP due solely to the rise in multiple births, which was largely due to infertility treatment.

Unique risks of CP in multiple pregnancy

ZYGOSITY AND CHORIONICITY

Monozygotic twins comprise roughly one-third of spontaneous twins and 1:10 to 1:15 of iatrogenic twins.14 Brain damage in the survivor following single foetal demise is almost exclusively seen in monochorionic twins (about two-thirds of monozygotic twins) in which intertwin-transplacental vascular connections are always found. In 10 to 15% of such chorionic settings, an unbalanced flow develops via the vascular connection, producing a vascular shunt, and resulting in various degrees of the twin–twin transfusion syndrome.15 It was assumed that following the death of one twin, emboli of tromboplastin-like material is shunted through the vascular connection into the survivor’s circulation causing end-organ damage (the ‘embolic’ theory). Alternatively, it has been proposed that blood is shunted via an open anastomosis into the low-resistance vascular system of the dead foetus resulting in acute hypovolemia, ischemia, and end-organ injury (the ‘ischemic’ theory).

Pharoah and Adi18 collected data of all registered twin births in England and Wales between 1993 and 1995 in which one twin was registered as having died in utero. Gestational age-specific prevalence of CP after foetal death of the twin was much higher than that reported for the general twin population. This study clearly showed that the surviving twin was at an overall 20% risk of cerebral impairment. In a more recent study, Pharoah19 compared birthweight specific neonatal death rates and CP prevalence rates in same-sex and different-sex twins whose co-twin had died in infancy. The author found that the prevalence of CP in the extremely LBW group (<1000 g) was marginally higher in same-sex than different-sex twin survivors as opposed to significant figures in the birthweight group 1000 to 1999 g. The author concluded that immaturity of itself predisposes the foetuses to cerebral damage but same-sex twins may sustain cerebral damage that is in excess of that due to immaturity.

In the absence of accurate zygosity testing, the expected excess risk for monozygotic twins may be estimated by comparing same-sex to different-sex pairs. Peterson and colleagues20 and Nelson and Ellenberg20 found a similar prevalence of CP in like- and unlike-sex pairs, whereas Javier Laplaza and coworkers did not.2 Using zygosity estimations, similar risks of CP were found in monzygotic and dizygotic pairs.21 Monochorionic placentation constituted the highest risk for CP and severe disability (OR 6, 95% CI 1.7 to 21.3) in a group of prospectively examined preterm infants.22

Owing to the fact that one-third of monozygotic twins have dichorionic placentas indistinguishable from same-sex dichorionic–dizygotic twins, zygosity assessment based on placentation only is not reliable. The inconsistent results of the few comparative studies must, therefore, be interpreted with caution.

TWIN–TWIN TRANSFUSION SYNDROME

Vascular communications in monochorionic placentas seem to explain the mechanism of neurological disability in cases of single foetal death. However, in cases of the twin–twin transfusion syndrome, the risk of CP may also be unrelated to foetal death. For example, it was claimed that amnioreduction to alleviate the syndrome-associated polyhydramnios might be implicated in the aetiology of CP.23 By contrast, Mari and coworkers24 evaluated long-term outcomes of pregnancies complicated by twin–twin transfusion syndrome treated with one or more amnioreductions. The authors concluded that in the group of foetuses in which both twins were delivered alive after 27 weeks’ gestation without congenital malformations and survived the neonatal period, no major neurological disabilities developed in any of the infants. The observation of Mari and coworkers24 was not supported by a case–control study by Cincotta and colleagues.25 Periventricular leukomalacia and cerebral atrophy were seen in 17% of the twin–twin transfusion syndrome group, but in none of the control group. Among survivors of the syndrome, 22% had CP and global developmental delay. The authors concluded that long-term neurodevelopmental morbidity in survivors of the twin–twin transfusion syndrome is high. A third paper determined the outcome in infants with twin–twin transfusion syndrome over a period of 5 years. In the 18 pairs studied, two recipients died in utero as the result of chronic twin–twin transfusion syndrome and their surviving donors developed spastic CP.26 It appears that neurological damage in the twin–twin transfusion syndrome is gestational-age dependent and associated with syndrome-related structural anomalies or with death of one of the twins.

GROWTH RESTRICTION

In addition to absolute intrauterine growth restriction, relative growth discordance may implicate an adaptive measure to promote an advanced gestational age by reducing the uterine volume.27 Williams and O’Brien28 found that twinning significantly correlated with both CP and neonatal mortality, but the low-weight:length ratio (a marker of asymmetric growth restriction) was a better correlate of both outcomes, suggesting that asymmetric growth restriction is an important correlate of neonatal morbidity in twins. An opposing view came from the Swedish population-based study by Rydhstroem.29 He found no significant difference between the distribution of birthweight discordance when twins with disability were compared with a population of all live-born twins having a birthweight <2500 g. Twins with a disability had a significantly lower birthweight for gestational age, but only 8.7% of the twins had a birthweight below 2SDs of the mean. Also, no difference in the incidence of disability was found for either twin or for same-sex versus different-sex twins, however, the larger twin in the pair had a significantly higher incidence of CP than the smaller. Rydhstroem concluded that birthweight discordance seems not to be related to disability later in life. These conflicting opinions suggest that more remains to be discovered about the contribution of growth restriction, a common phenomenon in multiple pregnancy, to the increased frequencies of CP.
EMBRYONIC AND FOETAL DEMISE

Spontaneous reduction in foetal number is frequently seen and the embryo(s) may disappear creating the so-called 'vanishing twin' syndrome. Recently, Pharoh and Cooke hypothesized that the vanishing twin syndrome may be implicated in the aetiology of spastic CP, by a mechanism similar to that causing brain damage in the survivor following single foetal demise in advanced pregnancies, which requires the opening of an existing anastomosis. Because the sonographic image of the vanishing twin syndrome is highly suggestive of dichorionic placentas that are devoid of anastomoses, the 'classical' sonographic image may cast doubts on that hypothesis. This discrepancy may be settled if some form of first-trimester inter-twin circulation exists in dichorionic twins. Such vascular communications are suspected because various forms of chimerism were recognized in dizygotic pairs, and because we do not know if the first trimester dichorionic placenta lacks such anastomoses. If such anastomoses exist, they may have disappeared together with the vanished twin and be missed by examining second and third trimester placentas. In fact, anastomoses are found, although rarely, in term dichorionic placentas.

A strong argument against the relation between vanishing twin syndrome and CP is derived from the lack of reported cases of the syndrome following multifetal pregnancy reduction which, in essence, is not different from the vanishing twin syndrome. Opponents of this view suggest that this is because CP was attributed to factors such as preterm birth or low birthweight. Indeed, Geva and coworkers found that in a cohort of preterm infants who developed periventricular leukomalacia, 28.6% were exposed to multifetal pregnancy reduction, compared with 1.9% of the control individuals (OR 20.9, 95% CI 5.5 to 79.4). Results suggest that multifetal pregnancy reduction may be an additional risk factor for brain lesions among preterm infants, regardless of twinning. Taken together, the association of first-trimester vanishing twin syndrome and CP cannot be disproved unless further research on this subject is carried out.

MODE OF DELIVERY

Multiple births might be associated with increased intrapartum risks. Rydströem studied the effect of Cesarean section on CP and learning disability in twins weighing less than 1500 g. The analysis failed to reveal any significant impact of abdominal birth on the CP rates for LBW twins, even when foetal presentation was taken into consideration. Rydströem also evaluated the effect of Cesarean section on delivery of twins whose birthweight was discordant by 1 kg or more. In this cohort, no correlation was found between mode of delivery and CP and/or learning disability at the age of 8 years or more. Cesarean birth seemed to have little impact on either short or long-term outcome.

Comment

The importance of the hypothetical and clinical aspects of CP in multifetal pregnancy is increasing at the same pace that the world wide epidemic numbers of multiple births are increasing. It is clear that a multifetal pregnancy constitutes a genuine risk for lifelong disability. As the duration of the epidemic of multiple births is about a decade, there were few opportunities to fully appreciate the magnitude of the problem. This is especially true for CP that may not be fully diagnosed in the first years of life. In addition, the wide range of pathophysiological characteristics of maternal–foetal and foetal–foetal interaction, during pregnancy and birth, are serious confounders to many assessments of multiple pregnancy. Table I summarizes the accepted and uncertain views about the association between CP and multiple pregnancy.

Because the predominant risk factor associated with multifetal births in most developed countries is assisted conception, it has been suggested that measures should be implemented to reduce the number of the potentially preventable iatrogenic pregnancies. A 3- to 6-fold increased risk for CP associated with a multiple birth cannot be considered successful; therefore, couples and their caregivers should have a realistic perspective of the potential obstetrical, neonatal, and associated lifelong complications.

Table I: Accepted and uncertain views on association between CP and multiple pregnancy

<table>
<thead>
<tr>
<th>Accepted views</th>
<th>Uncertain views</th>
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<tbody>
<tr>
<td>CP rates increase with plurality</td>
<td>Monzygotic twinning (without anomalies or twin–twin transfusion syndrome) not at increased risk of CP</td>
</tr>
<tr>
<td>CP rates are invariably increased among low-birthweight infants</td>
<td>Monochorionic gestations (without anomalies or twin–twin transfusion syndrome) are not at increased risk of CP</td>
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<tr>
<td>Infants of multiple births weighing &gt;2500 g have an excess risk over that of singletons</td>
<td>Twin–twin transfusion syndrome, without single foetal death, may increase the risk of CP</td>
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<tr>
<td>CP rates are invariably increased among preterm infants</td>
<td>Birthweight discordance probably does not increase risk of CP</td>
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<tr>
<td>Infants of multiple births delivered after 37 weeks' gestation have an excess risk over that of singletons</td>
<td>Growth restriction of multiple foetuses increases risk of CP</td>
</tr>
<tr>
<td>Single foetal demise invariably increases risk of CP in survivor(s), especially in monochorionic twins</td>
<td>Cesarean section for LBW or birthweight discordance does not reduce risk of CP</td>
</tr>
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Accepted for publication 24th October 2001.

References


North American: mental retardation.


