Twins and locomotor disorder in children

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Several locomotor disorders in children that come to the attention of orthopaedic surgeons have their origin in fetal life and present as congenital anomalies. These include cerebral palsy (which may be considered as a congenital anomaly as, in the majority of cases, the impairment is prepartum in timing), club foot and arthrogryposis. Alternatively, conditions that present as locomotor disorders may arise from impairments that have occurred intra-partum or in early childhood. Cerebral palsy also features strongly in this group. This annotation will consider the role of twinning in the pathogenesis of locomotor disorders and will focus on cerebral palsy, but will also consider the possible role of twinning in other congenital anomalies.

Pathogenic mechanisms of impairment in twins

Crucial to the pathogenesis of many abnormalities in twins is the zygosity and chorionicity of the conception. The fertilisation of two ova produces dizygous twins which are dichorionic and have separate placental circulations. Division of a single fertilised ovum leads to monozygotic (identical) twins and the timing of the division determines chorionicity. Early division leads to dichorionic twins, later division to monochorionic twins and very late division to incomplete separation or conjoined twins. Concerns arise with monochorionic twinning owing to placental vascular anastomoses that are present. Chronic haemodynamic instability between fetuses results in the fetofetal transfusion syndromes. These anastomoses are also a channel for other mechanisms which may damage the fetus.

A proposed hypothesis is that thromboemboli or thromboplastin, released from the dead fetus, produce ischaemic damage in the co-twin. However, emboli or disseminated intravascular coagulation from thromboplastin release have rarely been demonstrated. An alternate hypothesis is that the dead fetus acts as a low resistance vascular sump with shunting of blood from the live to it leading to ischaemic damage in the survivor. Both hypotheses demand the death of one fetus as crucial to the pathogenesis of abnormalities in the co-twin. However, occasionally both twins survive with a congenital anomaly or cerebral palsy. When both twins are affected they are usually discordant for the anomaly. More frequently, one twin has a congenital anomaly and the co-twin is normal. To account for this, a third hypothesis suggests that haemodynamic instability between monochorionic twins causes episodes of acute fetofetal transfusion which result in ischaemic damage to either or both twins. Occasionally the damage to one twin is lethal and the surviving co-twin suffers from a congenital anomaly or cerebral palsy. Trueta recognised the role of prenatal ischaemic damage when he stated “In the human embryo, from the time circulation is established, development goes on according to both the amount and the quality of blood distributed through its tissues and organs. Any substantial alteration of either one or both of these factors may cause damage to the embryo, which will be directly proportional to the intensity of vascular abnormality”.

The poor prognosis for fetal and infant death and severe morbidity in monochorionic twins has long been a recognised hazard of obstetric practice. Numerically, however, most congenital anomalies or cerebral palsy are found among singletons and this requires explanation. Two important sources of error occur in the recording of twin births. One arises from the failure to register a dead fetus erroneously leads to the assumption that the surviving twin...
is a singleton. This is extremely important when the pathogenesis of cerebral palsy in singletons is considered. In six of 18 cases of cerebral palsy where fetal death of the cotwin was noted in the hospital obstetric records, only a singleton had been registered at birth.7 Another misapprehension of a singleton birth may arise when there is very early loss of one twin in the first trimester of pregnancy. Twin conceptions are much more frequent than twin births because one conceptus in a multiple pregnancy may be lost very early in gestation. The development of ultrasound examination and its routine use in early pregnancy has led to the recognition of the ‘vanishing’ twin phenomenon.31 The question of registration of a ‘vanishing’ twin does not arise because of lack of its physical evidence at birth. Nevertheless, the survivor is the product of a twin conception. This has led to the proposal that a significant proportion of cases of spastic cerebral palsy in apparent singletons is attributable to ischaemic cerebral impairment in a twin conception in which the co-twin suffered very early loss as a ‘vanishing’ twin.12

The double jeopardy of cerebral palsy in twins compared with singletons is largely limited to the subgroup of monochorionic within monozygotic twins. To the consequences of placental haemodynamic instability in monochorionic twins, should be added the additional risk in monozygotic compared to dizygotic twins of being born preterm. Estimates from national birth registrations in England and Wales show that 25% of twins of birthweight ≥ 3000 g, but almost 50% of birthweight < 1000 g, are monzygous. This difference is probably attributable to monochorionicity, as 7.5% of monochorionic compared to 1.7% of dichorionic twins are below the fifth percentile.13 This highlights the importance of always recording zygosity and chorionicity in multiple births.

The escalation of the proportion of multiple births arising from techniques of assisted reproduction inevitably raises questions as to whether there are adverse implications for the prevalence of congenital anomalies and cerebral palsy. A degree of complacency is acceptable, as these techniques result in dizygotic and, therefore, dichorionic conceptions. There is a caveat, however, since monzygous splitting may occur in 10% to 15% of assisted reproduction techniques conceptions.14,15

### Cerebral palsy and twins

Cerebral palsy is not a single nosological entity and more than one pathogenic mechanism may result in cerebral impairment which presents as cerebral palsy. The impairment may occur peripartum during fetal development, peripartum or post-peripartum. The prevalence of cerebral palsy is between 2 and 2.5 per 100016 of which about 10% occur post-peripartum due to head injury, cerebral infection and severe hypoxia.17,18 Twins are at no greater risk than singletons in this group. Peripartum impairment, generally attributable to hypoxic-ischaemic episodes, accounts for between 10% and 15% of cerebral palsy.19,20 Infants of low birthweight have an increased risk of peripartum impairment and twins a greater risk than singletons because of the greater probability of preterm birth. There remains between 70% and 80% of cerebral palsy where the cerebral impairment occurs prenatally and the risk for twins in this group is of particular interest.

The increased risk of cerebral palsy in twins compared with singletons was recognised over a century ago by Freud.21 Twins comprise 5% to 10% of children with cerebral palsy but only 1.6% of all births.22 The risk of cerebral palsy increases inversely with birthweight and it is pertinent to compare the birthweight specific prevalence of cerebral palsy in twins and singletons (Table I). There is no significant difference in the prevalence of cerebral palsy in twins compared with singletons for those of low birthweight (< 1500 g and 1500 to 2499 g). However, twins of normal birthweight (≥ 2500 g) have a threefold increased risk of cerebral palsy. Thus, the overall fivefold increased risk of cerebral palsy in twins compared with singletons is attributable to twins suffering a double jeopardy, a higher proportion are of low birthweight and those of normal birthweight are at increased risk.

Here it is relevant to consider why twins of normal birthweight are at an increased risk of cerebral palsy. A greater variety of abnormalities of the central nervous system such as polymicrogyria, multicystic encephalopathy, porencephaly and cortical atrophy which present as cerebral palsy and other neurological syndromes, occurs in a twin whose cotwin has died in utero.23-27 These observations are confirmed in population-based cerebral palsy registers and in a national survey of surviving twins. In such cases, the risk of cerebral palsy in the surviving twin is extraordinarily high at one in ten28,29 indicating the circulatory risks to the fetus in twin pregnancy. Case reports invariably note that the risk is specific to monochorionic twins.

### Other locomotor disorders associated with twinning

While cerebral palsy predominates among the locomotor disorders attributable to twinning, it is entirely plausible that other congenital anomalies with locomotor manifestations may result from fetal ischaemic damage. Although monzygous compared with dizygous twins show greater concordance for congenital anomalies, nevertheless, both monzygous and dizygous twins are more likely to be discordant.31 The lack of concordance for many congenital

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**Table I. Birthweight specific prevalence of cerebral palsy in twins and singletons**

<table>
<thead>
<tr>
<th>Birthweight</th>
<th>Twins</th>
<th>Singletons</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1500 g</td>
<td>60.0</td>
<td>60.4</td>
</tr>
<tr>
<td>1500 to 2499 g</td>
<td>10.6</td>
<td>10.6</td>
</tr>
<tr>
<td>≥ 2500 g</td>
<td>4.9</td>
<td>1.5</td>
</tr>
<tr>
<td>All</td>
<td>11.1</td>
<td>2.3</td>
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anomalies indicates that a genetic aetiology is unlikely and other pathogenic mechanisms must be considered.

The aetiology of talipes equinovarus is largely unknown and is probably multifactorial with genetic and environmental factors. Undoubtedly there is a genetic component as a higher risk is associated with first, second and third-degree relatives of the proband. There is also a higher risk of both twins being affected if they are monozygotic than if dizygotic. However, among monozygotic twins, the concordance for talipes is not high and environmental factors must enter the equation. Current opinion is that although there is a genetic component in congenital club foot, non-genetic factors play a dominant role. The question that arises is whether the pathogenesis of congenital club foot is consistent with prenatal ischaemic impairment. If it is, club foot, even in singletons, could be attributable to monochorionic twinning in which one twin was lost early in gestation. It is pertinent that the anterior tibial vascular tree is poorly developed in children with club foot.

Arthrogryposis multiplex congenita presents with many congenital joint contractures with clubfoot being particularly refractory to correction. The condition may present in association with other congenital anomalies, in particular with neuronal migration disorders characterised by polymicrogyria on MRI scanning and presenting with pseudo-bulbar palsy, epilepsy and cognitive disability. Neuronal migrational disorders have often been reported in monochorionic twins and are considered to have an ischaemic pathogenesis during early fetal development. Of particular interest is the case report of arthrogryposis and polymicrogyria in which one twin was lost before the 12th week of gestation. This suggests that the damage to the surviving twin occurred in the first trimester, a period when the loss of one twin is most likely.

Loss of one conceptus in a multiple pregnancy, either as a vanishing twin in the first trimester or as a fetus papyraceous with neuronal migration disorders characterised by polymicrogyria on MRI scanning and presenting with pseudo-bulbar palsy, epilepsy and cognitive disability.

References
6. Heys RF. Selective abortion: dead fetuses might have to be registered as stillbirths. BMJ 1996;313:1004.