Mechanism of visceral damage in fetofetal transfusion syndrome

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If twinning occurs when the blastocyst cells are still undifferentiated, two embryos and two chorions (placentas) develop. Although the two placentas may later fuse into one, their circulations will be separate. If twinning occurs after the blastocyst has already differentiated into an outer cell layer (destined to be tropheoblast) and an inner cell mass (the future embryo), two embryos and one chorion will develop. The result is one placenta with a shared circulation.

In a monochorionic placenta vascular anastomoses connecting the circulation of one twin to the circulation of the other twin are almost always demonstrable after delivery. These anastomoses can be direct artery to artery or vein to vein connections on the surface of the placenta, or indirect artery to vein connections within the parenchyma, where a cotyledon is perfused by the artery of one twin but is drained by a vein returning to the other twin. If it is as yet unresolved whether the demonstration of an anatomic connection between the circulations after birth can be taken as proof of intermingling of the circulations in utero. To determine whether some degree of shunting of blood is the rule in monochorionic multiple gestations, one would have to take a series of twin gestations suspected to be monochorionic on ultrasound examination (same sex, one placenta, thin membrane); inject a marker (such as adult red cells or pancytomin) into an umbilical vessel of the cord of one twin and then try to identify the marker (or its effects) in the other twin; and, finally, compare the results with the chorionicity of the placenta determined after birth. Such a study has not been done. In those cases, however, where there is already ultrasound evidence of fetofetal transfusion syndrome, such investigations have shown rapid intermingling.

Among monochorionic twin placentas the number, size, and direction of the vascular anastomoses varies greatly. Within the anastomosing vessels on the chorionic surface blood flow may repeatedly change direction. Within the parenchyma an indirect artery to vein shunt in one direction may be offset by a similar shunt in the opposite direction or its effect may be mitigated by a surface anastomosis. Vascular anastomoses are necessary, but not sufficient, to create the fetofetal transfusion syndrome; the diagnosis requires evidence of intertwin circulatory disequilibrium, a net transfusion from one twin to the other. If the shunting of blood between fetuses is haemodynamically balanced there may be no consequences such as growth discordance or haemoglobin differences. This is the case with most monochorionic multiple gestation, although acute fetofetal transfusion can still occur during the pressure changes of labour and is exemplified by the obstetric teaching always to clamp the cut cord of the first delivered twin lest the undelivered second twin bleed out through the cord of the co-twin. An acute fetofetal transfusion, with serious consequences to the survivor, can also occur if one fetus dies (see below).

If the shunting of blood between fetuses is haemodynamically imbalanced fetofetal transfusion syndrome develops, with a wide spectrum of severity. Some cases may be suspected only after birth by differences in birthweight and haemoglobin; but the neonatal diagnosis can sometimes be wrong and even if correct, the very fact that there are two surviving neonates in whom to compare birthweights and haemoglobin means that the disease was often mild or arose late in gestation. In other cases antenatal ultrasound screening may indicate discordant size, leading to suspicion of fetofetal transfusion as the explanation; but even with a monochorionic placenta, the discordance in size may be due to reasons, such as discordant placental volume, single umbilical arteries, velamentous cord insertion, that have nothing to do with vascular anastomoses, even if the passage of blood between twins can be demonstrated.

The most extreme and certain example of fetofetal transfusion syndrome is the 'stuck-twin' phenomenon which usually starts in the early second trimester. The donor twin is small, hypovolaemic with a small heart, has a small or non-visualisable bladder, makes very little urine and amniotic fluid, and has the amniotic membrane 'stuck' to its body. The recipient twin is larger, hypervolaemic with a large heart, has a persistently distended bladder, and every day produces volumes of urine, and hence amniotic fluid, that can exceed many times over its own blood volume. This extreme polyuria in the recipient twin has been ascribed to an increased colloid osmotic pressure, drawing fluid from the mother into the fetus's intravascular compartment, or to

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increased concentrations of atrial natriuretic factor in the recipient.\textsuperscript{13} Whatever the explanation, the gross hydramnios in the recipient’s sac leads to ruptured membranes and labour at pre-viable or very preterm gestations, with very high mortality.\textsuperscript{14-17} Repeated withdrawals of large volumes of amniotic fluid may permit prolongation of the pregnancy, or even halt or reverse interfetal blood flow by changing the intra-amniotic pressure and hence the external pressure on the surface anastomosing vessels. Even if amniocenteses can buy more time, and even sometimes seemingly halt the disease, the potential for fluctuating haemodynamics, with sometimes disastrous results, is ever present.\textsuperscript{18}

If one fetus in a monochorionic twin (or triplet) set dies, either as an end result of chronic fetofetal transfusion syndrome or from some other cause, the surviving fetus/es) is(are) also in danger of dying or they may sustain severe neurological damage.\textsuperscript{19,20} The mechanism underlying the high rate of brain damage in the surviving infant has traditionally been attributed either to disseminated intravascular coagulation in the survivor’s circulation, initiated by the transfer of tissue thromboplastin from the dead fetus, or to the actual passage of necrotic thromboembolic tissue across the vascular anastomosis from the dead fetus to the survivor’s brain. However, there has never been convincing evidence that these events occur. In vivo there is no evidence of coagulopathy in the surviving fetus or neonate, and perhaps, most tellingly, it is hard to explain how material could be propagated from the circulation of the dead or dying fetus (where the blood pressure is zero or almost zero) to the circulation of the live fetus.\textsuperscript{21} A more logical explanation is that shunting of blood from the survivor to the dying or dead fetus – whose blood pressure must be failing to, or is already, zero – leads to acute hypovolaemic ‘shock’ and ‘hypoxic ischaemic’ damage to the survivor.\textsuperscript{21-23} The situation is analogous to the phenomenon of a healthy twin exsanguinating into a deteriorating twin,\textsuperscript{24} and accounts for the otherwise surprising finding that sometimes with stillborn twins, the smaller twin is plerotic and the larger one is pale. Support for this hypothesis is the finding that when selective termination of one of a pair of monochorionic twins is carried out in the second trimester, the other twin almost invariably dies within hours,\textsuperscript{25} presumably by exsanguination into the low pressure system formed by the dead twin.\textsuperscript{26}

More direct support for this ‘pressure sink’ theory comes from information obtained by fetal blood sampling. In one report four pairs of twins were followed up for suspected fetofetal transfusion syndrome; the smaller donor fetus died (Nicolin U, ‘the dying twin’. Proceedings of the advanced course in fetal medicine, May 1993, Queen Charlotte’s Hospital, London). A fetal blood sample was obtained within 24 hours from the surviving, chronically recipient, fetus. In each instance the surviving fetus, who would have been expected to be polycythaemic, was, in fact, anaemic; there was also no evidence of coagulopathy. Three of the four survivors were neurologically damaged at follow up. Another report,\textsuperscript{27} of five monochorionic twin gestations where one fetus died, also showed anaemia (and no coagulation abnormalities) in the surviving fetuses; three of the five surviving twins had neurological morbidity postnatally, presumably from hypotensive ischaemia of the brain as a result of haemorrhage into the dead twin.

Based on this information it is evident that intervention to prevent morbidity and mortality of a living fetus must actually be attempted before the death of the donor fetus, rather than after death, when acute haemodynamic alterations and damage have probably already occurred.\textsuperscript{28} Once one fetus of a monochorionic twin pair dies, the damage to the survivor probably occurs within minutes or hours. By the time the death is diagnosed, the damage to the survivor has been done. Early delivery is of no use to the survivor and may simply add the problems attendant on prematurity to whatever damage might already have occurred. The currently used methods of assessing fetal wellbeing may show nothing amiss in the survivor,\textsuperscript{26} because the fact of survival means that the acute haemodynamic compensation has been corrected, and because the current tests of fetal wellbeing do not evaluate cerebral hemispheric function. Ultrasonographic evidence of brain injury (porencephaly, leucomalacia) takes weeks to develop. If delivery of the survivor does not take place until some weeks have elapsed, however, even then the survivor, the neonate may have no overt signs of neurological deficit at birth, and only follow up months or years later would indicate that something bad had occurred in utero.

As our case report\textsuperscript{29} illustrates, however, fetal death is not necessary to cause haemodynamic disequilibrium and in utero brain injury. Several reports have described antenatal intraventricular haemorrhage or brain infarction in several twin gestations where both fetuses were born alive.\textsuperscript{11,17,31,32} Blood flow can be bi-directional in the surface and deeper vessels in pairs of monochorionic twins, between hypovolaemia (hypotension) and hypervolaemia (hypertension), and this cardiovascular instability could injure the brain.

Acute, transient, reversible imbalances of blood flow, largely undetected by our methods of surveillance, are a possibility in monochorionic multiple gestations due to the presence of vascular anastomoses. Chronic imbalances of blood flow – the fetofetal transfusion syndrome – can be strongly suspected on antenatal ultrasound examination and confirmed by injection studies. Many approaches have been proposed to deal with the problem of fetofetal transfusion syndrome, including: selective feticide with intracardiac injections or mechanical obstruction to one twin’s umbilical cord vessels; removal of a fetus by hysterotomy; laser ablation of anastomotic vessels; serial amniocenteses; and indomethacin administration to the mother. The multitude of approaches attests to the fact that none is very successful.\textsuperscript{14}

It may be that in some cases early delivery is a
better alternative than other antenatal interventions. However, 'prophylactic' premature delivery as early as 28 or 30 weeks will not solve the problems of death or damage occurring before this time, and may merely substitute the dangers of extreme prematurity for the dangers of fetofetal transfusion syndrome.