**Fetal stroke and cerebrovascular disease**

*Advances in understanding from alloimmune thrombocytopaenia and monochorionic twins*

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**Abstract**

Fetal stroke is an important cause of cerebral palsy but is difficult to diagnose unless imaging is undertaken in pregnancies at risk because of known maternal or fetal disorders. Fetal ultrasound or magnetic resonance imaging may show haemorrhage or ischaemic lesions including multicystic encephalomalacia and focal porencephaly. Serial imaging has shown the development of malformations including schizencephaly and polymicrogyra after ischaemic and haemorrhagic stroke. Recognised causes of haemorrhagic fetal stroke include alloimmune and autoimmune thrombocytopaenia, maternal and fetal clotting disorders and trauma but these are relatively rare. It is likely that a significant proportion of periventricular and intraventricular haemorrhages are of venous origin. Recent evidence highlights the importance of arterial endothelial dysfunction, rather than thrombocytopaenia, in the intraparenchymal haemorrhage of alloimmune thrombocytopaenia. In the context of placental anastomoses, monochorionic diamniotic twins are at risk of twin twin transfusion syndrome (TTTS), or partial forms including Twin Oligohydramnios Polyhydramnios Sequence (TOPS), differences in estimated weight (selective Intrauterine growth Retardation; sIUGR), or in fetal haemoglobin (Twin Anaemia Polycythaemia Sequence; TAPS). There is a very wide range of ischaemic and haemorrhagic injury in a focal as well as a global distribution. Acute twin twin transfusion may account for intraventricular haemorrhage in recipients and periventricular leukomalacia in donors but there are additional risk factors for focal embolism and cerebrovascular disease. The recipient has circulatory overload, with effects on systemic and pulmonary circulations which probably lead to systemic and pulmonary hypertension and even right ventricular outflow tract obstruction as well as the polycythaemia which is a risk factor for thrombosis and vasculopathy. The donor is hypovolaemic and has a reticulocytosis in response to the anaemia while maternal hypertension and diabetes may influence stroke risk. Understanding of the mechanisms, including the role of vasculopathy, in well studied conditions such as alloimmune thrombocytopaenia and monochorionic diamniotic twinning may lead to reduction of the burden of antenatally sustained cerebral palsy.

Ischaemic or haemorrhagic stroke may occur in the fetus from 14 weeks gestation and may be defined as ‘fetal stroke’ or ‘prenatal stroke’ or ‘antenatally diagnosed stroke’ if diagnosed before the onset of labour. However, the fetus is typically asymptomatic and stroke is rarely recognised unless ultrasound or magnetic resonance imaging (MRI) is undertaken in the context of concerns about the health of the fetus or the mother. For the fetus, the context is typically monochorionic twin pregnancies at risk of twin-twin transfusion(1) or associated complications, which may need high-risk intervention and therefore follow-up. Much of our understanding about the range of pathology and underlying pathophysiological mechanisms has come from the study of monochorionic twin pregnancies. This will be discussed in detail in view of the insights provided into fetal stroke and cerebral palsy of antenatal origin in general. Other fetal conditions include hydrops fetalis(2) and fetal tachycardia(3). Concerns in the mother leading to neuroimaging include alloimmune(4) or autoimmune (3)(5)(6) thrombocytopaenia, von Willibrand disease(7), trauma(3), diabetes(3), sepsis(8), seizures(9) or pre-eclampsia. Interventions which carry a risk of fetal stroke include amniocentesis(3), amnioreduction(10)(11) or laser coagulation(11) for twin-twin transfusion and transfusions of whole blood for fetal anaemia(12) or platelets for thrombocytopaenia(6).

*Epidemiology*

In the Norwegian study using the Surveillance of Cerebral Palsy in Europe (SCPE), the prevalence of Cerebral Palsy in live births was 2.1/100,000, a third of which were unilateral(13). The prevalence of cerebral palsy is declining in Europe, but the proportion with unilateral cerebral palsy is now higher and this is statistically significant for those of normal or moderately low birthweight(14). Unilateral spastic cerebral palsy is the most common form in term-born infants, with a prevalence in developed countries, such as Canada, of 1.0 (95% CI, 0.64-1.36) per 1000 live births(15). Case series which have included neuroimaging suggest that in at least one third of children, the insult causing the hemiplegia is sustained antenatally,(16) including predominantly unilateral periventricular leukomalacia despite term delivery, and structural malformations such as porencephaly, schizencephaly and polymicrogyria.

Other patterns of cerebral palsy, including four limbed cerebral palsy (quadriplegia), and bilateral malformations may also have had a vascular aetiology(17): extensive focal ischaemia may lead to microcephaly(18) while antenatal cerebral ischaemic and haemorrhagic stroke may lead to ventriculomegaly or hydrancephaly after intraventricular haemorrhage, or behavioural difficulties after focal cerebellar damage (19). Any discussion of fetal stroke should also mention intraventricular haemorrhage and periventricular leukomalacia. Although considered to be global rather than focal mechanisms of injury typically seen in infants born prematurely they are also reported antenatally secondary to acute obstetric emergencies such as placenta abruption(20,21)(22) and in monochorionic twin fetuses(23).

*Fetal stroke and cerebral malformations*

Schizencephaly and porencephaly are important causes of spastic cerebral palsy(24) which may be diagnosed antenatally(25)(26). In the SCPE study, 8.6% of children with CP had congenital cerebral malformations and 0.9% were cysts likely to represent the endpoint of a focal ischaemic insult. In a large Californian population-based study, the prevalence of schizencephaly was 1.54 per 100,000(27). Population-based data from the United Kingdom gave a similar prevalence of 1.48/100,000(26). The prevalence of schizencephaly, porencephaly, encephalomalacia or hydranencephaly in a Japanese study was 8.3 (95% CI, 2.6-14.1) per 100,000 live births (28).

There is increasing evidence that schizencephaly,(29)(25)(30) focal dysgenesis(31) and polymicrogyria,(32)(33) hydrancephaly(34) and, more controversially, low grade focal cortical dysplasia(35) are, at least in some cases, the result of prenatal focal ischaemia. Vascular disruption secondary to focal ischaemia or haemorrhage appears to play a role in the development of schizencephaly and porencephaly, e.g. in monozygotic twinning(27), maternal alloimmune thrombocytopaenia(26) or warfarin use(36). There is evidence for involvement of the arteries of the circle of Willis in some cases of schizencephaly. Occlusion or absence of the middle cerebral artery (MCA) has been documented(37). Interestingly, schizencephaly in the middle cerebral artery (MCA) territory is commonly seen in association with septo-optic dysplasia, considered to be related to ischaemia in the anterior cerebral artery(26). Recent evidence suggests that the brain changes which lead to schizencephaly may be progressive, with ventriculomegaly, then a cleft (Figure 1), which is eventually lined with neurones after migration(26)(38).

**Fetal haemorrhagic stroke and venous infarction**

The imaging data for postnatally diagnosed stroke in term infants suggests that the majority have infarction in the territory of a major artery and haemorrhage is less common(39)(40). In contrast, although there are no population-based studies, in the published case series based on fetal ultrasound or magnetic resonance imaging (MRI) haemorrhagic stroke is more likely to be recognised(3). This is probably partly because of the imaging characteristics but also because haemorrhage is more likely to occur at lower gestational age. The common supratentorial types are periventricular (Figure 2), intraventricular (Figure 3), intraparenchymal (Figure 4), subdural, subarachnoid, and epidural, while infratentorial intracerebellar and subdural haemorrhages are also recognised(41). Although there is a long list of causes, even with an extensive workup, an underlying diagnosis is often not made. Intrauterine growth retardation is often associated with fetal hemorrhagic stroke (42).

For infants and children with clinical patterns of neuromotor impairment consistent with antenatal haemorrhagic stroke, e.g. apparently isolated hemiplegia presenting towards the end of the first year of life,(43)(44)(45)and otherwise unexplained general developmental delay(8) with a syndrome consistent with developmental cerebellar cognitive affective syndrome,(19) T2-weighted or susceptibility weighted imaging may show haemosiderin as evidence of previous haemorrhage.(43)(29)

*Peri- or intra-ventricular haemorrhage secondary to germinal matrix haemorrhage*

This may occur between 22 and 34 weeks gestation(2)(47–50) and is considered to be the fetal equivalent of the peri- or intra-ventricular haemorrhage seen in infants born prematurely, with some developing hydrocephalus (Figure 3). Fetal ultrasound typically shows an irregular intraparenchymal or intraventricular echogenic foci or periventricular echodensities with or without ventriculomegaly or frank hydrocephalus(51). Large haemorrhages may lead to obvious porencephaly(52) with or without progressive neuronal migration disorder.

*Unilateral parenchymal haemorrhages of presumed venous origin* *and presumed perinatal ischaemic stroke*

Small germinal matrix haemorrhages may be associated with venous congestion and infarction in the periventricular region(52) and may occur antenatally (Figure 2) as well as in prematurely delivered neonates. Recent susceptibility-weighted MRI suggests that an anatomical variant, with narrower curvature of the terminal subependymal veins, may play a role(53). One large study found that 14% of unilateral parenchymal haemorrhages of presumed venous origin were present at birth and imaging in a further 3% was consistent with antenatal onset(54). Recent evidence suggesting that this leads to reduced subcortical and cortical brain tissue volume(45) associated with hemiplegia presenting around 8-10 months of age (presumed perinatal ischaemic stroke) with relative preservation of cognitive function(43)(44)(45)

*Intraparenchymal*

The haemorrhages seen in alloimmune thrombocytopaenia are typically intraparenchymal (Figure 4), perhaps in relation to the associated endothelial dysfunction rather than the thrombocytopaenia (see below). Intracerebral and intracerebellar haemorrhage has also been reported in foetuses proven to have COL4A1 mutations(55). Vascular imaging with Doppler or MRA would be of interest in fetal intraparenchymal haemorrhage, which may also occur as a secondary phenomenon after infarction.

*Subdural, subarachnoid and epidural haemorrhage*

Supratentorial extra-axial (subdural, subarachnoid and epidural), as well as intracranial, haemorrhages(49)(56) are seen after maternal trauma(56)(57)(58)(59). Subdural haemorrhage is also seen in bleeding diatheses such as autoimmune thrombocytopaenia(5). Maternal warfarin intake may also play a role(56,60,61). There may be reverse flow on Doppler ultrasound, presumably secondary to raised intracranial pressure(62).

*Posterior fossa haemorrhage*

Infratentorial fetal haemorrhages (49)(12), including subdural(63) and intracerebellar(46)(64) bleeding, have been diagnosed in utero(8)(7). However, this possibility has often been considered only in the neonatal period or even in childhood when a destructive lesion of the cerebellum is recognised (Figure 5) and haemosiderin is seen on susceptibility weighted imaging(12). Causes include bleeding diastheses(7) and intrauterine transfusion, e.g. for presence of the anaemia of Rhesus disease(12), perhaps analogous to the haemorrhages associated with hypertension posterior reversible leukoencephalopathy after rapid transfusion in haemoglobinopathies. The acute hypertension of eclampsia might also play a role (Figure 5), but this has not been studied in detail. Subsequent poor growth and/or destructive lesions of the cerebellum are often associated with poor cognitive, behavioural and social outcomes(19).

**Focal ischaemia in an arterial distribution**

Antenatal focal ischaemia in an arterial distribution may be diagnosed acutely(65) if contemporaneous fetal ultrasound or MRI is undertaken, or if screening imaging is undertaken, e.g. in monochorionic twin pregnancies (Figure 7; see below) or where there is a known association with risk factors for cerebrovascular disease including maternal cocaine use(30)(34). In utero imaging which has been described includes increased echogenicity on fetal ultrasound consistent with recent haemorrhage into an acute infarct in the distribution of the middle cerebral artery (65). There is a much wider range of focal abnormalities of ischaemic origin in monochorionic twin pregnancies, including malformations such as schizencephaly, polymicrogyria and cortical migration disorders (see above) as well as porencephaly. The prevailing opinion is that the main mechanism in monochorionic twins is hypotension in the surviving twin following death of the co-twin with the survivor twin losing blood through the placental anastamoses into the other fetus and placenta, often resulting in severe anaemia. Alternatively, where there are large arterio-arterial anastamoses there may be acute inter-twin transfusions resulting in hypotensive damage, even when both twins survive(66). However, in utero vascular imaging e.g. with Doppler, has shown middle cerebral artery occlusion associated with unilateral schizencephaly after cocaine exposure(30). Alternative mechanisms in monochorionic twins and other cases of in utero ischaemic stroke include vasospasm(30), vasculopathy(67–73) and embolic infarction from a variety of sources including the placenta or the heart(74)(75)(76)(77) (see below). However, as for periventricular venous infarction, antenatal focal ischaemic infarction is more likely to be tentatively diagnosed when the child presents clinically, with seizures in the neonatal period or in infancy, or as presumed perinatal stroke presenting with asymmetry in tone and/or motor function around 8-10 months.(34)(78)

If not diagnosed acutely, the typical imaging findings in a child presenting with congenital hemiplegia/presumed perinatal ischaemic stroke are of porencephaly or encephalomalacia(43) in an arterial distribution e.g. middle or anterior cerebral artery territory.

**Antenatally diagnosed cerebrovascular disease**

*Venous abnormalities*

Dural venous sinus thrombosis and malformations may also be diagnosed on antenatal fetal ultrasound.(79) As the two pathologies may be difficult to separate, the term ‘dural venous ectasia with thrombosis’ (Figure 6) is often used(80). The Torcula Herophilae is typically involved(80)(79), but the appearance are similar in the sagittal(81) and transverse(79) sinuses. There may be bleeding(81), but recanalization is common and the outcome appears to be good in the majority born alive(80)(79)(81)*.*

Vein of Galen abnormalities may also be diagnosed antenatally on ultrasound and MRI. Although the feeding and draining vessels and any associated ventriculomegaly may be seen and this can assist with planning of treatment, it is difficult to distinguish high flow from venous thrombosis on fetal MRI, although on colour flow Doppler ultrasound the increased flow is easily distinguished(82).

*Arterial abnormalities*

Cerebrovascular disease associated with arterial ischaemic stroke in early life e.g. PHACES (posterior fossa abnormalities, haemangioma, arterial lesions, cardiac abnormalities or coarctation of the aorta and eye abnormalities syndrome)(83) has been diagnosed antenatally. It is also possible to recognise pial arteriovenous malformations(84).

**Risk factors**

The risk factors which have been described for each clinical presentation related or presumably related to fetal stroke are listed in Table 1. For fetal haemorrhage, bleeding diatheses have been most frequently reported, typically maternal with the most common being alloimmune thrombocytopaenia,(3)(5)(6) but also fetal(85), which may be missed if the fetus dies in utero or the pregnancy is terminated. Genetic disorders associated with cerebrovascular disorders in adults, such as autosomal dominant COL4A1 and COL4A2 mutations, have been reported in association with disorders likely to be of focal ischaemic or haemorrhagic origin, such as schizencephaly (Table 1), but whether they are causative in fetal intraventricular haemorrhage is controversial.(86) Prothrombotic disorders are relatively common in presumed perinatal arterial stroke, both with an arterial and a periventricular venous distribution(78). Infections, including cytomegalovirus, Zika and Parvovirus B19, may cause fetal stroke by a variety of mechanisms, including vasculopathy(87)(88)(72), acute anaemia(88) and venous thrombosis(89).

**Common clinical settings**

*Thrombocytopaenia*

*Fetal and neonatal alloimmune thrombocytopaenia (FNAIT)*

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is an important cause of intracranial bleeding in the fetus (Figure 4)(90)(91), although it accounts for a relatively small proportion of perinatal intracranial haemorrhages overall(92). Analagous to Rhesus disease, in FNAIT there are maternal alloantibodies against human platelet antigens (HPAs). The condition is relatively rare, affecting between one in 1000 and 5000 pregnancies(93), including primigravidae, unlike Rhesus disease, although potentially immunogenic prior miscarriages are relatively common. Intracranial haemorrhage has been reported to be more likely in multigravidae(94) but in Norway, where the low risk of intracranial haemorrhage means that prophylaxis is not offered, HPA antibodies were lower and platelet count was higher in subsequent pregnancies(95). Intraparenchymal bleeding into the temporal, parietal and occipital lobes with the development of porencephaly is typical(96), but cerebellar destruction(97)(98), isolated ventriculomegaly, and intraventricular, subdural and subarachnoid haemorrhage have also been reported(90)(96). Although there are few fetal imaging data from consecutive cohorts, the available antenatal ultrasound(99)(100)(101)(102) and fetal MRI(96)(100)(103), as well as the neonatally acquired imaging(96)(104), suggest that the majority of intracranial haemorrhages occur in the second and third trimesters of pregnancy. Intrauterine fetal death is also relatively common. Retinal haemorrhage may be noted after birth, with optic atrophy diagnosed at follow-up; visual disability appears to be a specific feature(105).

There are at least 33 different HPAs(91)(91), and perinatal intracranial haemorrhage occurs in some, including HPA1, HPA5b and HPA15b(106). HPA1 is the most common in Caucasians, and around half, including HPA1, are in the GPIIIa (β3 integrin subunit). Allo-immunisation occurs if mother is HPA negative (2% of the population are HPA1 negative with the less common alleles, b, i.e. HPA1bb) while father is HPA positive (HPA1ab or HPA1aa) so that the fetus inherits at least one ‘a’ allele. The antibodies against platelets in the fetus cause thrombocytopaenia and until recently treatment strategies focussed on improving platelet counts. Human leukocyte antigen status may also influence whether there is bleeding(94). However, it has become clear, using murine models, that there is also evidence of disruption of angiogenesis and endothelial function. Intracranial haemorrhage occurs, brain and retinal vessel density is reduced, angiogenic signalling is impaired and endothelial apoptosis is increased only in anti-β3 integrin-mediated FNAIT(107).

In a UK series, 26 of 200 infants had intracranial haemorrhage, of whom 19 were born alive; one died and 13 had permanent neurological sequelae, mainly cerebral palsy including hemiplegia(106). In view of the poor neurological outcome intervention in pregnancy has been justified. Fetal blood sampling for diagnosis of thrombocytopenia and fetal platelet transfusion were initially proposed(90), but there was a high incidence of fetal loss, premature delivery and perinatal death after these invasive procedures(106)(108). Recent evidence suggests that intravenous immunoglobulin with or without steroids(105)(108) is more effective in preventing in utero or neonatal intracranial haemorrhage(90). If intracranial haemorrhage is prevented, long term neurodevelopmental outcome is excellent whether the treatment is platelet transfusion or intravenous immunoglobulin(109). In a study from Australia the only intracranial haemorrhages were in unanticipated cases with invasive procedures(4).

*Twins and other multiple pregnancies*

Cerebral palsy is more common in twins than in singletons, particularly if they are the same sex, born later in gestation and with a co-twin death ante- or post-natally(110)(111). Dizygotic twins almost always have separate placentas (dichorionic diamniotic), although occasionally there may be fusion. However, placentation in monozygous twins depends on how soon after fertilization the ovum splits: dichorionic diamniotic if <3 days, monochorionic diamniotic if 4-8 days or monochorionic monoamniotic if >8 days(111).

It is well recognised that monochorionic diamniotic twin pregnancies may be complicated by twin-twin transfusion syndrome (TTTS), related to placental vascular anastomoses (venous-venous, arterial-arterial or arterial-venous)(112). In chronic TTTS, the recipient is usually the larger, but may sometimes be the smaller (113). Typically, the recipient has circulatory overloaded, with increased urine output and polyhydramnios as well as effects on the heart and systemic and pulmonary(114) circulations which probably lead to systemic and pulmonary hypertension(115)(116)(117) and even right ventricular outflow tract obstruction(118). The donor is hypovolaemic, with decreased urine output and oligohydramnios. The chronic development of oligohydramnios in the donor and polyhydramnios in the recipient (Twin Oligohydramnios Polyhydramnios Sequence, TOPS) is thought to be occur when there are prominent arterial-venous anastomoses so that blood tends to flow in one direction(119).

Placental histopathology suggests that there is a vascular anastomosis in 100% of monochorionic twin pregnancies but twin-twin transfusion affects <10%(120), probably because the majority do not have major arterial-venous anastomoses(119). Originally, after birth, the diagnosis was made when there was a 5.0 g/dL difference in haemoglobin(120). However, there is rarely such a large difference at birth(119) or at fetal blood sampling(121), despite other evidence of a significant anastomosis between twins in utero, such as hydrops or differences in the amount of amniotic fluid on fetal ultrasound (TOPS), in estimated weight (selective Intrauterine growth Retardation; sIUGR), or in fetal haemoglobin (Twin Anaemia Polycythaemia Sequence; TAPS). However, large arterial-arterial and venous-venous anastomoses may allow flow in both directions with the risk of acute TTTS after the death of a co-twin(122), after amnioreduction(10), or at birth(119). In the latter situation, one twin may be acutely anaemic without reticulocytosis, sometimes requiring transfusion, while the other is polycythaemic, sometimes requiring exchange(119).

Differences in haemoglobin have been reported in monochorionic diamniotic twin pregnancies in TTTS, TAPS and sIUGR. TAPS occurs where there are only a few (one or two) narrow inter-twin anastamoses resulting in progressive polycythaemia in one twin and anaemia in the other(119). In the absence of TOPS, TAPS with fetal anaemia in the donor can now be inferred if the MCA peak systolic velocity (PSV) on Doppler scanning is high(123)(124), while low MCA PSV is seen in the polycythaemic recipient twin(124). The diagnosis is confirmed if at delivery, the donor twin has a haemoglobin 8.0 g/L less than the recipient but with a higher reticulocyte count, excluding acute TTTS(119). Interestingly, there are similar discrepancies in MCA PSV in sIUGR, suggesting that part of the pathology involves TTTS. However, intrauterine growth restriction of any cause can result in polycythaemia, so there may be differential haemoglobin levels at delivery in monochorionic twins with sIUGR unrelated to TTTS. In these fetuses there is an unequal share of placental territory with the smaller twin usually having a marginal or velamentous cord insertion and only a third or less of the placenta.

*Death of one twin with vascular disruption in the other: autopsy data*

Reviewing the literature, Carlson and Towers (125) suggested that the risk of death or disability after death of the cotwin was 17% (5/29 reported in 4 manuscripts) and was as common in dichorionic as in monochorionic twinning (1.4%). However, in Carlson and Towers’ series(125), the infant with twin-twin transfusion and the one with multicystic encephalomalacia were both monochorionic. Twin-twin transfusion may be associated with in-utero death of one twin, more commonly the donor(116)(126). Intrauterine growth restriction plays a part in a significant proportion, and in the majority of cases, it is the smaller twin that dies; there may be overlap between these aetiologies as it is not easy to exclude TTTS. Although the surviving twin may be normal at follow-up, he or she is at risk of neonatal death or long term disability. There is a risk of cord knot in monochorionic monoamniotic twin pregnancies which may lead to death of one twin and brain damage in the other(123). However, this is rare and TTTS and sIUGR are less common monochorionic monoamniotic than in monochorionic diamniotic twins (116)(127), while the described neurological complications are usually those of premature delivery e.g. intraventricular haemorrhage(127). The dead twin may be acardiac with Twin Reverse Arterial Perfusion (TRAP)(128). Hydrancephaly, global (125)(129)(130,131)(132) or parieto-occipital(132)(133) multicystic encephalomalacia, and focal infarction or porencephaly(134), typically involving the parietal region(135)(136) but also the cerebellum(125)(136), spinal cord(134), thalamus(23), caudate, occipital(136), temporal and frontal(137) lobes, has been described at autopsy. There may also be limb(138), skin, renal(123)(136), hepatic(113), gut (atresia and gastroschisis) and splenic(136) infarction, sometimes with thrombus in the supplying arteries as well as pulmonary artery thrombus(129).

*Fetal imaging after death of a twin*

Laser photocoagulation to reduce shunting across the placental vascular anastomosis appears to be associated with a lower risk of fetal loss and neurological impairment than conservative management of TTTS or serial amnioreduction(23)(139)(140). Pregnancies at risk are therefore now imaged regularly in order to plan intervention. Antenatal ultrasound and latterly magnetic resonance imaging (MRI) after death of the donor or the recipient twin has shown a wide range of imaging abnormalities in the survivor(23). Focal ischaemic abnormalities include infarction within the territory of the middle (MCA)(141)(142) or posterior (PCA)(66) cerebral artery, germinolytic cysts(142), capsular cyst with ipsilateral periventricular dilatation(143) considered to be of venous origin(43), hemispheric asymmetry(144), porencephaly(49), polymicrogyria(142)(144)(49), and subdural (49) and intracranial(142) haemorrhage which may be associated with transverse sinus thrombosis(142). Global abnormalities include ventriculomegaly(143), hydrancephaly(143), global or posterior encephalomalacia(38) and bilateral parasagittal and periSylvian ischaemia(38). In a European multicentre study of 434 pregnancies complicated by intrauterine death of one fetus, either spontaneous or after intervention, Conte et al documented isolated ventriculomegaly in 15, while 42 (9.7%; 34 monochorionic diamniotic twins, 4 monochorionic monoamniotic twins and 4 triplets) had parenchymal abnormality, 21 global and 21 focal(38). Risk factors for cerebral injury in the surviving twin include diagnosis of TTTS, later gestational age at which the co-twin dies (141) and earlier gestation at which the survivor is born (116).

*Fetal stroke in twin pregnancies where both survive*

Unilateral cerebral palsy may also occur perinatally in one twin even if both survive(145)(144)(23) and is occasionally associated with brain damage in the other survivor(23)(146). Although some of the data is antenatal(23)(145)(144), some comes from children diagnosed after birth so it could not be certain that the stroke occurred in utero. Golomb et al reported 4/35 (11%) infants with presumed perinatal arterial stroke were one of a surviving twin pain(147); at least 2 were dizygous. Interestingly one of 35 (3%) presenting in later childhood was also a twin and it is possible that in utero factors determine differences in manifestations of cerebrovascular disease in twins in childhood(148) and possibly in later life(149)(150). Benders et al showed that stroke in premature infants is also more common in one of a pair of twins, typically monochorionic with TTTS(151); in more than half the pairs both survived. In another series from the Indianapolis group, of 23 infants born prematurely who had focal infarction, 5 were one of surviving twin pair; one had had twin-twin transfusion(152).

*Development of cortical malformations in twins*

Schizencephaly is twice as common in monozygotic twins (27). In a study from Seattle of hydrancephaly and porencephaly, 6 of 56 (11%) were twins, 5 same sex (all both male)(153). Polymicrogyria type II has also been reported in both the smaller and the larger of monochorionic twins with suspected TTTS, in some in association with focal infarction(154). The timing of the insult is consistent with an effect before or during neuronal migration at the time of the formation of the cortical plate(154). Bilateral parietal-occipital polymicrogyria has been reported in the recipient twin, suggesting that polycythaemia may play a role and that the vascular compromise might be venous(155). Polymicrogyria was seen on ultrasound and MRI in a donor twin(156) but postnatal data were not available as the mother chose feticide; the surviving recipient twin was normal in this case. Bilateral perisylvian polymicrogyria with periventricular heterotopia was documented in a recipient survivor where the donor died at 18 weeks gestation; the survivor had clinical features consistent with the syndrome. Griffiths also reported schizencephaly and ‘reparative’ polymicrogyria in cystic lesions, consistent with ongoing neuronal migration and cortical reorganisation typical of the second trimester, on antenatal MRI of the survivor after co-twin death in the third as well as the second trimester(157). Conte et al undertook serial imaging in two cases with focal lesions. In one with focal cortical thinning at 21 weeks gestation there was a cortical plate abnormality at 25 weeks gestation confirmed as polymicrogyria postnatally. In the other with bilateral posterior encephalomalacia at 21 weeks, repeat MRI at 27 weeks showed extensive loss of brain volume and communication between the cysts and the lateral ventricle with the communication lined with cortical plate, consistent with a diagnosis of open lip schizencephaly(38).

*‘Stroke syndrome’ patterns on fetal and neonatal imaging in donor and recipient twins in TTTS*

Some authors have included details which may allow separation by donor/recipient status. Glenn described the development of unilateral encephalomalacia with polymicrogyria on fetal MRI in the recipient at 23 weeks after death of the donor at 18 weeks(158). Van Klink et al documented focal infarction in the territory of the MCA, as well as multicystic encephalomalacia and widespread cortical and white matter destruction in the surviving recipient twin(116). Neonatal imaging in the same series showed cystic periventricular leukomalacia in a surviving recipient and intraventricular haemorrhage in surviving donors and a twin with sIUGR without TTTS(116). Robinson reported donor/recipient status for fetuses with co-twin death after laser photocoagulation, and documented torcular dural venous thrombosis in a donor and a cyst in the frontal lobe, associated with later speech delay, and asymmetrical ventricles in a recipient(144). The donor had unilateral ventriculomegaly and the recipient had a small cerebellum in a pair from the same series where both survived(144).

Robinson et al also reported on 15 twin pairs both alive at the time of ultrasound and fetal MRI: 11 with TTTS, 2 with TAPS and 2 with sIUGR(144). They documented unilateral ventriculomegaly in one donor and left-sided diffusion-weighted imaging (DWI) changes consistent with acute parieto-occipital infarction in another donor as well as more widespread encephalomalacia, also in donors(144). One TTTS and one TAPS recipient in this series had increased subarachnoid spaces; this could be evidence of subarachnoid haemorrhage although none was mentioned.

In Denbow’s series reporting neonatal cranial ultrasound in 11 twins with TTTS born prematurely, including 4 pairs where both survived, periventricular leukomalacia, white matter cysts and unilateral ventricular dilatation were mainly documented in donors, although both of one pair had this pattern(145). The temporo-parietal infarct occurred in a recipient and lenticulostriate vasculopathy was only recorded in recipients(145). Lenticulostriate vasculopathy, a mineralising angiopathy involving the perforating arteries supplying the basal ganglia, is well recognised in neonatal twins and is more commonly seen in the recipient(70)(71), although it has been reported in the donor(69). Spruijt et al noted left MCA territory stroke in 4 neonates who had been recipients, although overall they found no difference in the prevalence of severe lesions between donors and recipients(159).

Vein of Galen malformation, considered to occur at 6-11 weeks gestation, has been documented in a donor twin of a pair where the pregnancy was complicated by TTTS, while the recipient had transposition of the great arteries and died at 18 weeks (160). The smaller twin had a choroidal Vein of Galen malformation while the larger was normal in another twin pair without TTTS; in this case whole exome sequencing excluded previously reported genetic associations and abnormal copy number variation(161).

Pregnancies complicated by TAPS or sIUGR are also at risk for central nervous system problems, typically the recipient twin in TAPS(162) and the larger twin in sIUGR, consistent with the possibility that TTTS plays a role(163). However, cognition is more likely to be compromised in the smaller twin(164). In a meta-analysis of 11 studies of sIUGR monozygotic twins, cerebral injury was reported in 0-33% of cases, with an average of 8%. Intra-uterine death of the co-twin, umbilical artery Doppler abnormalities and earlier gestation at delivery were also risk factors(163).

*Fetal stroke mechanisms in twins*

The initial reports reported thrombus and suggested embolism from the dying twin to the surviving twin in the context of disseminated intravascular coagulation(129), which has been reported in mothers carrying a dead twin for several weeks and in some cases has been treated with maternal heparin(165)(166)(134). However, in Fusi’s case, fetal blood sampling in the larger survivor within 24 hours of the smaller co-twin death did not find evidence of fetal disseminated intravascular coagulation but did demonstrate acute anaemia confirmed after delivery 2 days later(167). It was therefore hypothesised that the acute fall in blood pressure in the dying twin allows shunting of blood from the survivor, causing acute hypovolaemia, hypotension, hypoxia, acidosis and anaemia in that twin. Anaemia has been reported in the surviving twin at birth (129)(113)(138) and the acute blood loss has been considered to be the main cause of perinatal death(129) and/or brain damage (168)(169)(113). There is some evidence for acute anaemia in the surviving twin on fetal blood sampling, when the haematocrit may halve acutely from 35-40% to less than 20 in the surviving twin (168).

However, acute anaemia has not been established as the unique cause of brain damage in the survivor. Haemoglobin at birth is almost always higher in the second twin delivered and the same discrepancy also occurs in dichorionic twins, suggesting that delay in cord clamping may be the main factor(170). Many surviving twins have normal haemoglobin at birth(122), even if there is multicystic encephalomalacia(130), probably because of resolution of polycythaemia in recipients or compensatory erythropoiesis in donors during pregnancy. In fact, in D’Alton’s case, although the placenta suggested that the twins were monochorionic diamniotic, there appeared to be breakdown of the membrane and both twins had knots in their cords, perhaps associated with hypotension without anaemia accounting for multicystic enchalomalacia in the survivor(130). In fact, the only surviving twin with porencephaly and neurological disability in Nicolini’s series had the highest haematocrit (29%) recorded after the co-twin’ death and a cord knot, suggesting that this was a monochorionic monoamniotic pregnancy. Another in this series with a haematocrit of 20% and porencephaly died in the neonatal period; neither had fetal blood sampling before the co-twin’s death. Anaemia after the co-twin’s death was also reported in 7 pregnancies by Okamura(171) but haemoglobin was lower in 3 of the surviving twins without brain damage than in the 3 with CNS abnormalities (ventriculomegaly, periventricular leukomalacia and diffuse low density). Acute anaemia at birth in the recipient has also been described and plethora in the dead donor suggests that this is related to acute reversal of the shunt(126). One of Okamura’s survivors with acute anaemia had hydrops and cardiomegaly consistent with originally having been the polycythaemic recipient(171).

The fact that there was no abnormality of platelets, D-dimer or fibrin degradation products(167)(171) has been considered to be evidence against an embolic cause for brain damage. However, brain damage in the survivor in *spontaneous* fetal death is more common than in feticide by bipolar diathermy cord occlusion, where the vascular anastomoses remain, potentially allowing acute transfer of blood from the survivor during death of the twin (141), so other mechanisms should be considered. In addition, it is difficult to explain the associated loss of a gangrenous limb in the surviving twin (172) without considering the possibility of an embolic mechanism(173)(174). Data showing a wide range of imaging abnormalities on antenatal ultrasound(23) or MRI after co-twin fetal death, including focal stroke in the MCA territory, suggest that embolic infarction may be part of the mechanism, even if acute TTTS with severe anaemia extends the extent of the damage, e.g. in multifocal encephalomalcia and periventricular leukomalacia(141). In fact, multicystic encephalomalacia involving the parietal, occipital and frontal cortex(125) has typically been reported in those with evidence that they were recipients e.g. polyhydramnios, oedema, jaundice, even if acute anaemia was found at birth. There are few angiographic data but Yoshioka demonstrated occlusion or poor filling of the MCA on conventional angiography in 2 of his 3 patients(175), consistent with a vasculopathy or an embolic aetiology. The polycythaemia might lead to venous thrombosis in the peripheral veins as well as the cerebral venous sinuses(144). Pulmonary hypertension in the recipient(117) in the context of a patent foramen ovale, with or without right ventricular outflow tract obstruction(118), might also facilitate embolisation from recipient or from the donor via anastomoses which may also allow the passage of prothrombotic erythropoietin from the donor rather than or in addition to thromboplastin after agonal disseminated intravascular coagulation. This type of mechanism is more likely than acute TTTS to explain focal infarction, typically in the middle cerebral artery (MCA) territory, seen in surviving twins (157,176). The fetuses may also exposed to maternal risk factors, including hypertension and diabetes(177).

Other mechanisms, including venous sinus thrombosis(144)(133) and posterior reversible leukoencephalopathy syndrome secondary to hypertension in a recipient followed by hypotension after acute TTTS may explain the parieto-occipital distribution. Bilateral parietal polymicrogyria with arthrogryposis and seizures was documented after loss of a co-twin in the context of maternal gastroenteritis(178); the location of the lesions and the likelihood of dehydration raising the possibility of venous sinus thrombosis. Pre-eclampsia was present in 4/16 (25%) of the pregnancies complicated by death on one twin (8 monochorionic) (122) and may play a role in the distribution of lesions in the parieto-occipital region consistent with acute hypotension in the context of previous reversible posterior leukencephalopathy syndrome.

In addition, as for childhood stroke, it is possible that there are additional risk factors, including infection and prothrombotic disorders. For example, multicystic encephalomalacia has also been reported in the twin with the higher haemoglobin (17.6 vs 14 g/dL) in a pregnancy where both twins survived also complicated by maternal asymptomatic cytomegalovirus excretion (179). Of Kocoman’s series of infants presenting with hemiplegia and presumed perinatal stroke(180), 4 of 35 (11%) were one of a twin pair and all had either the methylene tetrahydrofolate reductase (MTHR) C677T polymorphism and/or the Factor V Leiden mutation. High Factor VIII, antiphospholipid antibodies, lipoprotein(a) and MTHFR polymorphisms were detected in Golomb’s series(147).

Ideally the diagnosis of TTTS would be made in the first trimester so that appropriate treatment could start as soon as possible. However, although there are associations with nuchal translucency in one or both twins and with crown-rump length discrepancy of >10%, these ultrasound markers are not good predictors(181).

**Outcome**

It is likely that there is a very broad spectrum of outcomes for fetal stroke. Those which are diagnosed antenatally are often reported as lethal and pregnancies where there is a severe abnormality, e.g. hydrocephalus or widespread encephalomalacia, may be terminated. On the other hand, the outcome for Grade I intraventricular haemorrhage in the premature neonate is good and this is probably true if that occurs in the fetus, which is rarely diagnosed. Fetal intraventricular haemorrhages of Grades II-IV may have outcome similar to those described in premature infants, including congenital hemiplegia. The extent and location of abnormality on neuroimaging is useful in predicting outcome.

**Conclusion**

Fetal stroke is an important cause of CP, in particular unilateral CP. Diagnosis is rarely made antenatally; in a large proportion of affected infants imaging is performed and diagnosis is made only when infants present later with neurological symptoms. Causes of ischaemic or haemorrhagic stroke are numerous, and often multifactorial, in particular in ischaemic stroke. Recognised, but rare causes of haemorrhagic stroke are alloimmune and autoimmune thrombocytopaenia, maternal and fetal clotting disorders and trauma. Twin pregnancies appear to pose a particular risk for ischaemic fetal stroke. Neurological outcome varies, depending on gestational age at time of insult as well as extent and location of the injury. In addition to genetic investigation of e.g. COL4A mutations, new imaging techniques, including diffusion tensor, perfusion and susceptibility MRI as well as further use of Doppler and MR angiography are likely to shed light in aetiology of prenatal stroke presenting in utero, in the perinatal period and later in childhood as cerebral palsy.

**Table 1 Causes of fetal stroke associated with patterns of injury on neuroimaging**

**Schizencephaly**

COL4A1(29)(182)(183)

Maternal cocaine use(30)

Monochorionic twinning

**Porencephaly**

*Genetic*

COL4A1(184,185)(55)(29)(31), COL4A2(186)(187)

*Acquired*

Carbon monoxide (188)

**Arterial ischaemic stroke +/- haemorrhage**

***Occlusion artery by embolus***

 Placental (65)

 Monochorionic twinning

 Cardiac(75)

**Germinal matrix/intraventricular haemorrhage with venous infarction**(43)(44)(45)

***Bleeding diastheses***

*Maternal*

Maternal autoimmune thrombocytopaenic purpura(49) (189)

Maternal idiopathic thrombocytopaenia

Maternal Warfarin use(3)(46)(190)(191)

 *Fetal*

Von Willibrand disease

 ***Genetic disorders***

COL4A1(55)

***Hypertension/acute seizures***

Maternal seizure(s)/epilepsy

(and risk of bleeding diasthesis with anticonvulsants) (3)(9)

Pre-eclampsia(192) and Eclampsia

***Placental dysfunction***

Haemorrhage

 Abruption

***Trauma***

Maternal accident (vehicle, domestic)(49)

Maternal abuse

***Fetal prothrombotic disorders***

 Homozygous protein C deficiency

***Fetal metabolic disorders***

Pyruvate carboxylase deficiency

**Infratentorial haemorrhage**

Severe anaemia

 Rhesus alloimmunization(49)

 COL4A1(55)

**Subdural haemorrhage**

***Bleeding diasthesis***

*Maternal*

Warfarin use by mother (60)

*Fetal*

Factor X deficiency(85)

***Trauma***

Maternal car accident(49)

Maternal abuse

**Presumed perinatal ischaemic stroke/congenital hemiplegia**

***Prothrombotic disorders***

Anticardiolipin antibodies,(193)

Methylene tetrahydrofolate reductase deficiency(194)(178)

Factor V Leiden(195)(196)

 ***Monochorionic twinning*** (197)

**Figures**

Figure 1: Transabdominal fetal ultrasound at 21 weeks showing the cleft of schizencephaly

Figure 2: Transvaginal fetal ultrasound at 28 weeks showing intraventricular haemorrhage, haemorrhagic parenchymal infarction and obstructive hydrocephalus with echogenic lining of the ventricle in a 28 week fetus.  A. Coronal section  B. Para-sagittal section showing right ventricle

Figure 3: Intraventricular haemorrhage, haemorrhagic parenchymal infarction and obstructive hydrocephalus with severely enlarged 3rd and 4th ventricle and lack of extracerebral space in a 28 week fetus.

Figure 4: Intraparenchymal haemorrhage in alloimmune thrombocytopaenia. In Vitro Fertilization pregnancy, history of miscarriages, abnormal movements in utero week before delivery; born 39+2 weeks gestation by forceps and Ventouse; Apgars 9 at 1, 5 and 10 minutes. Neonate presented at the age of 12 hours with myoclonic jerks of the left leg, spreading to the left arm A. MRI showing antenatal intraparenchymal haemorrhage on day 2 B. Further postnatal intraparenchymal haemorrhage on Day 7 MRI. At2 years the child had impairment of gross and fine motor co-ordination and cognitive and behavioural problems but no seizures

Figure 5: A Axial and B Sagittal views showing a destructive lesion of the cerebellum in a 21 year old who had been exposed to maternal eclamptic seizures at 29 weeks gestation and had severe cognitive and behavioural problems requiring special school

Figure 6: Transvaginal fetal ultrasound at 20 weeks showing venous sinus ectasia posteriorly (left of the figure with the face at the right)

Figure 7: MRI aged 9 years showing cerebellar infarction on the left side, due to presumed infarction, in the smaller monochorionic twin with lower haemoglobin at birth (6 g/dL discrepancy but both >15 g/dL). This child had some cognitive and behavioural problems compared with the twin but attended mainstream school.

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