Twin–twin transfusion syndrome

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Twin–twin transfusion syndrome is a complication of monochorionic twin pregnancies associated with extremely high perinatal morbidity and mortality. This article describes the ultrasound features associated with this condition and possible pathophysiological mechanisms. Management options are outlined, including recent developments such as laser ablation of placental vascular communications.

Perinatal morbidity and mortality are increased sixfold in multiple compared with singleton pregnancies, due to complications such as preterm labour, intrauterine growth restriction and congenital anomalies (Spellacy et al, 1990). Monochorionic (MC) twin pregnancies are particularly at risk of complications because of the presence of vascular connections between the fetoplacental circulations of each twin. Two-thirds of monozygotic twin pregnancies (i.e. derived from one egg) are MC, and if splitting of the preimplantation blastocyst occurs during the latter part of the first week, each twin will have an individual amniotic sac (i.e. MC diamniotic (MC/DA) twin pregnancy) (*Figure 1*). If the splitting occurs in the second week the twins share the same placenta and sac (i.e. MC monoamniotic twin pregnancy).

Twin–twin transfusion syndrome (TTTS) is a specific complication of MC/DA twin pregnancies, and it may also occur in higher order multiple pregnancies in which two or more fetuses are MC. The condition usually presents early in the second trimester and if left untreated results in a perinatal loss rate approaching 100% (Urig et al, 1990). TTTS affects 4–35% of MC/DA twin pregnancies (i.e. 0.1–0.9 per 1000 pregnancies), but is responsible for up to 17% of overall perinatal deaths in twins (Steinberg et al, 1990). A haemodynamic mismatch is thought to occur between the twins because of placental vascular communications between their circulations (Bajoria et al, 1995).

ULTRASOUND APPEARANCES

Table 1 lists the ultrasound findings in TTTS. The syndrome is characterized by markedly discordant amniotic fluid volume and birthweight between the twins. The larger twin (classically called the recipient) is polyuric with a large bladder on ultrasound scan, and subsequently may develop severe polyhydramnios. The smaller 'donor' twin is often severely growth restricted, becomes oliguric and there is marked oligohydramnios. Because of this the amniotic membrane often appears to enshroud the smaller twin, which moves little and gives rise to the appearance of being 'stuck' against the uterine wall (*Figure 2*).

Doppler studies of the fetal circulation in TTTS have been consistent with decreased venous return caused by hypovolaemia and increased cardiac afterload caused by increased placental resistance in the donor twin (Hecher et

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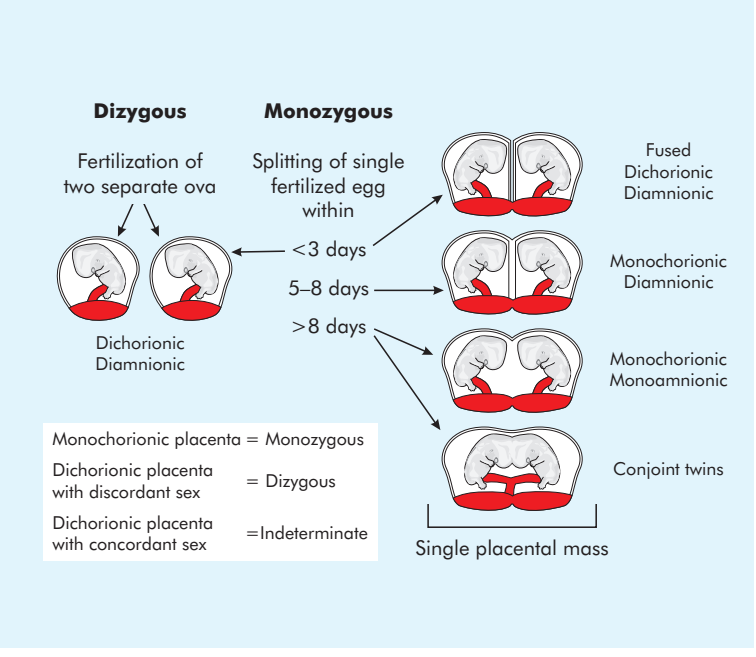

Figure 1. Relationship between chorionicity and zygosity.

TABLE 1.
Ultrasound findings in twin–twin transfusion syndrome

Single placental mass
Thin dividing membrane (may be difficult to visualize)
Discordant fetal growth (at least 15% difference in estimated fetal weight)
Oligohydramnios/polyhydramnios sequence (maximum pool depth at least 10 cm in polyhydramniotic sac and donor twin may appear 'stuck' against uterine side wall)
Large bladder in recipient twin with often no bladder seen in donor twin
Larger twin may have hydrops, cardiomegaly and tricuspid regurgitation

al, 1995a; Lachapelle et al, 1997). The donor twin also demonstrates umbilical artery Doppler waveform changes consistent with diminished villous development (Bruner et al, 1998). Haemodynamic features in the recipient twin are suggestive of congestive heart failure caused by hypervolaemia. This twin can develop circulatory overload with hydrops, cardiomegaly and tricuspid regurgitation. Interestingly, an association with right ventricular outflow tract obstruction has been described in the recipient in utero (Zosmer et al, 1994).

The differential diagnosis includes discordant growth in a dichorionic twin pregnancy in which the smaller twin has reduced liquor volume. However, in this situation the larger twin would be expected to have normal, not increased liquor volume, and both twins would be expected to have normal cardiac parameters (Lachapelle et al, 1997). The determination of chorionicity and amnionicity is more difficult later in pregnancy, particularly if the smaller twin has minimal surrounding liquor, when gender is difficult to visualize and the dividing membrane may be impossible to see. The importance of allocating correct chorionicity/amnionicity of twin pregnancies at the initial booking ultrasound scan has been emphasized (Bajoria and Kingdom, 1997), although this has yet to be proven in a randomized controlled trial. Preterm rupture of membranes should be excluded and a detailed scan performed to exclude structural anomalies that are associated with abnormalities of liquor volume, such as urinary tract anomalies, upper gastrointestinal obstruction, neural tube defects and congenital heart disease.

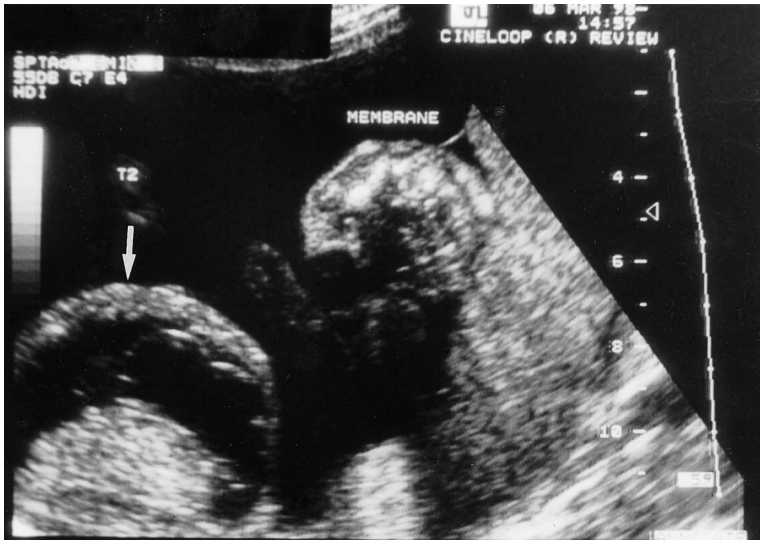

Figure 2. Ultrasound image of twin–twin transfusion syndrome in the second trimester. On the right, the body of the donor twin can be seen 'stuck' against the uterine side wall with closely adherent amniotic membrane. On the left (white arrow) is a transverse view of the abdomen of the hydropic recipient twin showing ascites.

PERINATAL OUTCOME

The high perinatal loss rate of untreated TTTS presenting under 28 weeks is mainly because of the incidence of preterm labour secondary to gross polyhydramnios. In addition, if one fetus becomes severely hypotensive or dies in utero in any MC twin pregnancy, the remaining twin is at risk because of the presence of vascular anastomoses. Shifts in the pressure gradient between the twins may allow an acute and significant transfer of blood from the normotensive to the hypotensive dying fetus. This leads to periods of hypotension and ischaemia in the surviving fetus (Fusi et al, 1991). The chance of immediate death in the co-twin is approximately 30%, and the risk of necrotic lesions developing in the brain, kidneys or distal limbs is comparable.

Cranial ultrasonography is advocated in the neonatal period to detect cerebral lesions in both recipient and donor twin. Denbow et al (1998a) reported ultrasound evidence of antenatally acquired neurologic damage in 11 of 31 (35%) survivors, with a further seven (23%) babies showing lesions thought to be perinatal in origin. Long-term neurodevelopmental follow up is therefore indicated. Neonatal survivors of TTTS are at risk of additional complications — the recipient twin may develop right ventricular outflow obstruction (Zosmer et al, 1994), and episodes of haemodynamic instability related to hypertension.

PATHOGENESIS

Classically TTTS was attributed to transfusion of blood through placental anastomoses causing the 'donor' twin to be anaemic and the 'recipient' twin to be polycythaemic, with a neonatal cord

blood haemoglobin difference of 5 g/dl. This is now considered to be an oversimplification, as in-utero fetal blood sampling has shown that this haemoglobin difference is rarely found (Fisk et al, 1990). Another term used to describe this syndrome is therefore oligohydramnios-polyhydramnios sequence. It has been speculated that other aetiological events, such as occult fetal viraemia, may be associated with a significant number of these pregnancies.

More recently, the specific type and number of vascular anastomoses have been studied and implicated in the pathogenesis of TTTS. Anastomoses can be classified by their location (either superficial or deep within the chorionic plate) and by type — arterioarterial (AA), venovenous (VV) or arteriovenous (AV). Bajoria et al (1995), using perfusion experiments on placentae of MC twin pregnancies, showed that placental anastomoses are fewer in number in the pregnancies affected by TTTS compared with MC pregnancies unaffected by TTTS. The anastomoses in TTTS are also different, as they are more likely to be solitary and of deep AV type, flow being in one direction from smaller donor twin to larger recipient twin.

In contrast, in control cases unaffected by TTTS, there were multiple anastomoses of all three types that were more frequently superficial in location. Although intertwin transfusion is a normal feature of all MC pregnancies, in cases unaffected by TTTS the flow is likely to be in both directions, and net flow balanced by the presence of protective superficial anastomoses. The identification of superficial AA anastomoses is now possible in vivo using colour Doppler imaging (Hecher et al, 1995b). Denbow et al (1998b) have recently reported an association between TTTS and absence of these anastomoses, which may help in risk stratification of MC twin pregnancies in the future.

The actual severity of TTTS appears to be determined by the vascular anatomy (Machin et al, 1996; Bajoria, 1998b). The presence of a solitary unidirectional deep AV anastomosis is likely to be associated with more florid cases of TTTS, which are at a higher risk of hydrops and intrauterine death (*Figure 3*). The presence of a solitary superficial AA anastomosis is associated with milder TTTS (Bajoria, 1998b). In support of this theory, using a computerized model of dynamic fetal and placental physiological variables, Talbert et al (1996) proposed that the direction and symmetry of AV anastomoses determined the net hydrostatic and osmotic gradients in the model, and therefore the severity of TTTS.

MANAGEMENT OF TTTS

The fact that numerous therapies have been advocated for this syndrome suggests that the ideal treatment has yet to be determined (*Table 2*). The aim of treatment is to achieve survival of both

Vascular shunts are absent in dichorionic placentae. Placental anastomoses in monochorionic placentae are either superficial or deep. Superficial anastomoses are located on the surface of the chorionic plate and may be arterioarterial (AA) or venovenous (VV). These anastomoses are bidirectional and allow blood to flow between twins. In contrast, deep anastomoses which connect the artery of one twin to the vein of the other (arteriovenous, AV) allow unidirectional flow from the arterial to the venous end. Uncomplicated monochorionic placentae normally have multiple anastomoses of either superficial or deep type. Mild twin-twin transfusion syndrome (TTTS) has a single deep AV anastomosis and a single superficial AA anastomosis, while severe TTTS has a single unidirectional AV anastomosis. Monochorionic placentae with growth discordance have multiple deep anastomoses; the number of deep anastomoses (AV) from the smaller to the larger twin nearly always exceeds those running in the opposite direction (venoarterial, VA). Thick and thin lines represent arterial and venous channels, respectively

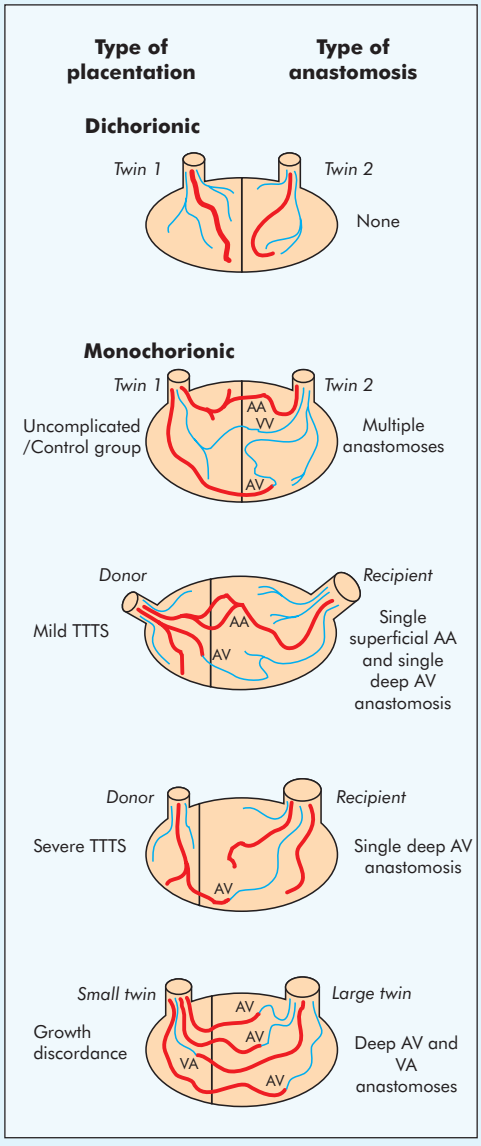

Figure 3. Diagram showing different types of vascular anastomoses in dichorionic and monochorionic placentae in relation to clinical outcome.

TABLE 2.
Management options in twin-twin transfusion syndrome

Termination of pregnancy
Digoxin therapy to improve cardiac function in recipient twin
Selective fetocide
Aggressive serial amnioreduction
Endoscopically-directed laser ablation of communicating vessels

twins with minimal morbidity. It is important that the couple are fully informed and counselled appropriately, preferably with referral to a fetal medicine unit. Contact with the Multiple Births Foundation may be helpful*. The management options to be considered include the following.

Termination of pregnancy

In view of the high perinatal morbidity and mortality rates associated with TTTS, and the fact that any treatment embarked upon is both physically and emotionally intensive in nature, the option of termination of pregnancy should be discussed.

Medical therapies

Indomethacin has been used to manage polyhydramnios in singleton pregnancies as it reduces fetal urine output. However, it is relatively contraindicated in TTTS because of the potentially adverse effects on an already oliguric donor fetus. Digoxin therapy may be used to improve cardiac contractility in a recipient twin with evidence of cardiomegaly and hydrops (Zosmer et al, 1994).

Selective fetocide

Selective fetocide of the donor twin has been advocated in severe cases of TTTS in an attempt to save one fetus. It requires the prior isolation of each twin's circulation because of the potential haemodynamic shifts when the blood pressure in one fetus acutely falls. The ultrasound-guided intracardiac insertion of thrombogenic coils (Bebbington et al, 1995), and the injection of histoacryl gel into the umbilical vein and fetal heart (Dommergues et al, 1995), have been described in an attempt to reduce perinatal loss. Fetoscopic cord ligation remains a therapeutic possibility, although it is associated with high rates of amniorrhexis (Deprest et al, 1997).

Aggressive serial amnioreduction

This is favoured in many centres including our own (Kilby et al, 1997). It involves the repeated removal of large volumes of amniotic fluid (1–4 litres) under ultrasound control using an 18-gauge needle. This is a relatively simple procedure to perform but is time consuming for patient and staff. The incidence of complications secondary to the procedure is small (less than 1%) but includes infection, preterm labour and abruption. The temporary control of polyhydramnios will hopefully reduce the risk of preterm labour and allow prolongation of the pregnancy so the fetuses achieve maturity.

Whether the fetal condition is improved by the reduction in amniotic fluid pressure is not known. Doppler ultrasound studies have noted an acute increase in uterine artery blood flow following decompression amniocentesis (Bower et al, 1995), and possibly an improvement in cerebral perfusion (Mari et al, 1992). The reappearance on ultrasound of a fetal bladder in the donor twin following amnioreduction has been suggested as a prognostic sign (Kilby et al, 1997). It has been proposed that this indicates improved fetal perfusion with increased renal blood flow and urine production.

Perinatal survival rates vary in published studies, ranging from 37% to 83% (Urig et al, 1990; Saunders et al, 1992; Pinette et al, 1993; Reisner et al, 1993; Elliott et al, 1994). Occasionally only a single amnioreduction is required. The reason for the wide variation in outcome between series in which similar protocols are used is unclear.

Recent work has shown that the success of amnioreduction depends on the presence or absence of superficial AA/VV anastomoses (Bajoria, 1998a). The authors proposed that following amnioreduction the haemodynamic imbalance caused by alteration in amniotic and vascular pressure allows, in the presence of superficial AA/VV shunts, a net flow in the compensatory recipient to donor direction. In contrast, in cases with isolated unidirectional AV channels, vascular and osmolality equilibrium are disturbed further as the decrease in amniotic fluid pressure perpetuates further transfer of blood from donor to recipient. Polyhydramnios appeared to reaccumulate following amnioreduction in the absence of superficial anastomoses and the likelihood of hydrops and cardiac failure was higher.

Laser therapy

A further therapeutic option in TTTS is laser ablation of the vascular anastomoses using fetoscopy (De Lia et al, 1995; Ville et al, 1998). A combination of direct vision and ultrasonographic guidance is used to systematically examine the chorionic plate along the whole length of the intertwin membrane to identify the crossing vessels requiring laser coagulation (*Figure 4*).

Controversy has occurred because the procedure is not selectively aimed at only the deep anastomoses. It is argued that irrespective of the vascular nature of the anastomoses, or their

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depth within the placenta, the efferent and afferent branches are superficial and can be seen on the chorionic surface of the placenta. Although the intertwin membrane does not necessarily overlie the common cotyledons, the systematic coagulation of all crossing vessels should inevitably include the branches of these anastomoses. Certainly the isolation of the two circulations would appear to be a logical aim of TTTS therapy. It is the only treatment that can potentially prevent the severe haemodynamic imbalance occurring when both twins are alive or in the case of single fetal demise, which is thought to be the main mechanism involved in perinatal handicap as previously described.

The main causes of fetal death include:

- Miscarriage, either secondary to the procedure or as a result of recurrent polyhydramnios
- In-utero fetal death, usually of the donor twin, which being growth restricted suffers the additional insult of sudden obliteration of part of its placenta as a result of coagulation of all vessels that cross the intertwin membrane
- In-utero demise of both twins, which may reflect failure to obliterate all anastomotic vessels and lead to further imbalance in perfusion between the twins.

In 1998, Ville et al reported the results of a multicentred study of endoscopic laser coagulation in the management of severe TTTS involving 132 pregnancies. Amniodrainage was also used at the time of the fetoscopy. The endoscopy was carried out at a median gestation of 21weeks. The total number of surviving infants was 144 (55%) and there was at least one survivor in 97 cases or 73%. At a minimum of 1 year neurological handicap was suspected in six survivors (4.2%). This appears lower than the figures for serial amniodrainage, with approximately 15–35% incidence of serious handicap in survivors (Pinette et al, 1993; Bajoria et al, 1995). Better methods of identifying the type and location of communicating channels to target laser ablation may be required to improve outcome further.

Pregnancy complications included spontaneous miscarriage (9.8%), preterm prelabour rupture of membranes (9.8%) and reaccumulation of polyhydramnios (9.1%). Intraperitoneal haemorrhage or loss of amniotic fluid occurred in four women (3%). There are thus implications for significant maternal morbidity. The only accepted way of comparing endoscopic treatment with serial drainage is within the confines of a randomized study. Eurofetus has been funded by the European Union to answer this question (contact the Harris Birthright Centre, King's College Hospital, Denmark Hill, London SE5 9RS: 0171 924 0714).

CONCLUSION

Recent theories regarding the pathophysiology of this severe complication of MC twin pregnancies have been described, although the scientific basis of TTTS is poorly understood. It is acknowledged that without treatment the fetal survival is extremely poor.

Current management options remain suboptimal. Serial amnioreduction has been a standard therapy but recent evidence has suggested a reduction in neurological morbidity with similar survival rates if fetoscopic laser ablation of the vascular anastomoses is performed. A multicentred randomized trial of these two treatments is now required. In addition, further studies are needed to elucidate the vascular aetiology of the condition and to determine how to identify the responsible communicating vessels that require laser ablation. HM

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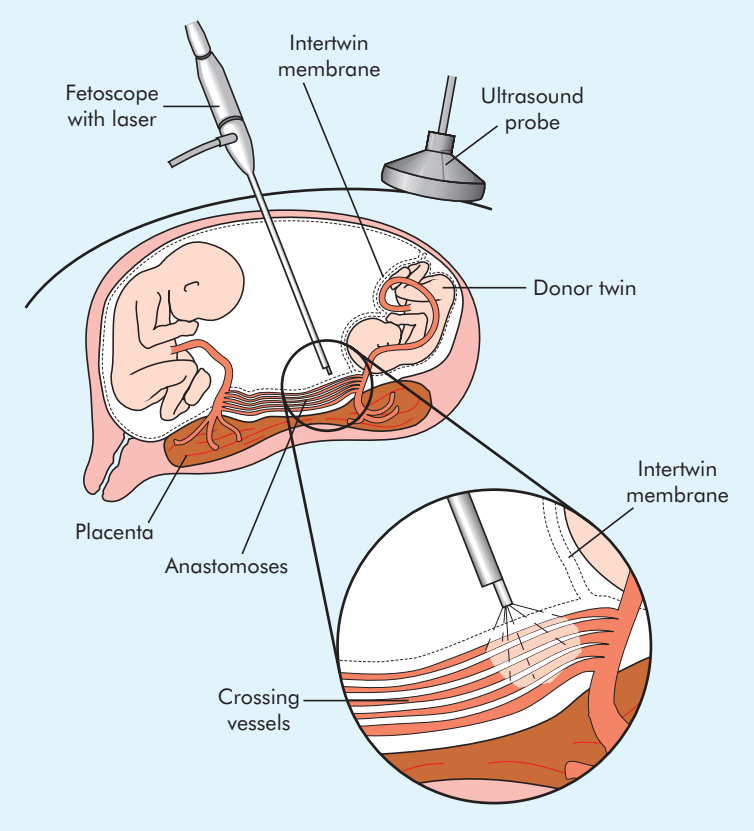

Figure 4. Diagram of the spatial organization for endoscopic laser coagulation.

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KEY POINTS

- Twin–twin transfusion syndrome (TTTS) is a serious complication affecting monochorionic diamniotic twin pregnancies in the second trimester, and has a 95–100% mortality rate if left untreated.
- Even with treatment, there is a significant risk of neonatal morbidity because of associated prematurity, growth restriction, cardiac, neurological and renal sequelae.
- The pathophysiology of TTTS is not fully understood but it may involve differences in vascular anastomoses between the fetoplacental circulations of each twin.
- Aggressive serial amnioreduction is often offered, which is an intensive therapeutic option and is associated with mortality rates ranging between 37% and 83%.
- More recently, use of endoscopic laser ablation of vascular anastomoses has been associated with slightly worse survival rates to amnioreduction, but with a lower incidence of neurological morbidity.