Review Twin-to-twin transfusion syndrome

Authors Richard P Smith / Mark L Denbow

The management of twin-to-twin transfusion syndrome is continually evolving with the publication of new data. The rationale for treatment options and the authors’ current practice are discussed.

Keywords amnioreduction / laser ablation / selective feticide / septostomy / twin-to-twin transfusion syndrome

Please cite this article as: Smith RP, Denbow ML. Twin-to-twin transfusion syndrome. The Obstetrician & Gynaecologist 2006;8:1–6.
Introduction
Monochorionic twin pregnancies arise from a monozygous conception where the early cell mass splits later than four days after conception. If this split occurs between four and seven days, then monochorionic diamniotic (MCDA) twins occur, i.e. there is one placental mass but two amniotic sacs. Almost all MCDA twins have vascular anastomoses between placental vessels, and these have been implicated in the pathophysiology of twin-to-twin transfusion syndrome (TTTS). TTTS occurs in 15% of MCDA twins, therefore affecting about 1 in 1600 pregnancies. If left untreated, perinatal mortality exceeds 80%. If the cell mass splits prior to four days, dichorionic twins result. Between seven and 12 days, monoamniotic twins result, and after 12 days conjoined twins can occur.

Diagnosis
Chorionicity should be determined in the first trimester and this can easily be achieved in a non-tertiary centre. Fortnightly ultrasound assessment is recommended for monochorionic twins from the second trimester onwards and is necessary, usually between 15 and 25 weeks, to make the diagnosis. This should be done by a practitioner familiar with monitoring of monochorionic twins, which may involve tertiary referral. TTTS is defined as a sequence of oligo/polyhydramnios, with the deepest vertical pool of amniotic fluid in the donor measuring 2 cm or less and measuring 8 cm or more in the recipient. If TTTS develops, the donor (i.e. the twin with net volume loss) shows signs of hypovolaemia and growth restriction with oliguria (small or non-visible bladder), oligohydramnios and abnormal umbilical artery Dopplers. The recipient (i.e. the twin with net volume gain) shows signs of hypervolaemia and growth restriction with polyuria (large visible bladder), oligohydramnios and abnormal umbilical artery Dopplers. The recipient (i.e. the twin with net volume gain) shows signs of renal perfusion and urine production. Post-mortem studies have shown increased renin gene expression in the kidneys of donor twins and decreased expression in recipients. Increased renin secretion by the donor can lead to reduced renal perfusion and urine production.

Pathophysiology
Injection of dye into monochorionic twin placentas has demonstrated vascular anastomoses in 96% of cases, and these are broadly divided into two types. The first are superficial anastomoses, which lie on the placental surface. These are either arterio-arterial anastomoses (AAAs), which are present in 66% of cases, or veno-venous anastomoses (VVAs), which are present in 20% of cases. Superficial anastomoses connect the twins’ circulation directly and can result in net transfusional flow in either direction. The second are deep arterio-venous anastomoses (AVAs), which are present in 90% of cases, where a cotyledon receives its blood supply from one twin and drains its venous blood to the other. AVAs permit only unidirectional flow between the twins, i.e. from artery to vein, in the conventional manner.

There is extensive ex vivo and in utero evidence to support a vascular basis to TTTS. The characterisation of monochorionic placental vascular anatomy during postnatal injection studies has revealed a consistent trend in the presence of AVAs and absence of AAAs in cases affected by TTTS. It has been proposed, therefore, that AAAs have a protective effect against TTTS, probably by allowing equilibration of any unequal interfetal flow set up by the presence of unbalanced AVAs. These findings have been supported by in utero evidence, as AAAs can be identified antenatally using colour Doppler ultrasound imaging. Indeed, the absence of AAAs is associated with an increased risk of developing TTTS (61% versus 15%, odds ratio 8.6).

Post-mortem studies have shown increased renin gene expression in the kidneys of donor twins and decreased expression in recipients. Increased renin secretion by the donor can lead to reduced renal perfusion and urine production.

Staging
Until within the last 10 years the two main difficulties for the practising clinician confronted by a case of TTTS were the assessment of severity and the subsequent recommendation of appropriate treatment. To assess the severity of the condition, one group has developed a staging system for TTTS (Table 1). This group’s initial study suggested that survival was dependent on stage at presentation, but other studies suggest that worsening stage rather than stage at presentation is more important. However, as disease progression occurs in about 45% of cases, the stage at the time treatment is indicated is probably more important clinically. Also, this staging system takes no account of the presence or absence of AAAs, which are known to be an important prognostic indicator. Another group has therefore proposed a modified staging system incorporating the antenatal sonographic finding of an AAA into the TTTS stage, using an ‘a’ to indicate detection of an AAA, and ‘b’ if an AAA is not detected. Using this system, overall survival rates based on stage at treatment are: Ia 100%, Ib

Table 1 Quintero staging system for twin-twin transfusion syndrome

<table>
<thead>
<tr>
<th>Stage</th>
<th>Oligo/polyhydramnios sequence</th>
<th>Absent bladder</th>
<th>Abnormal Dopplers*</th>
<th>Hydrops</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>II</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>III</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IV</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>V</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>a, b</td>
</tr>
</tbody>
</table>

*a Absent or reversed flow in the umbilical artery, reversed flow in the ductus venosus, or pulsatile flow in the umbilical vein
63%, Ila 100%, IIB 59%, IIIa 83%, IIIb 44%, IVa 25% and IVb 50%.

Implications for the fetus and neonate
Monochorionic twins are at increased risk of cardiac anomalies, especially if TTTS is present (6.9%). Volume overload in the recipient can cause hypertension and myocardial hypertrophy and up to 10% of recipients have chronic cardiac problems; for example, right ventricular outflow tract obstruction. Renal failure can also occur (more commonly in donors), but this is usually transient.

Once abnormalities are seen on Doppler, i.e. absent or reversed end diastolic flow in the umbilical artery, reverse flow in the ductus venous, or pulsatile flow in the umbilical vein, the risk of death is high. The probability of at least one twin surviving is only 33% if there is absent or reversed end diastolic flow in the donor umbilical artery, or 37% when abnormal venous recordings are seen in the recipient. In survivors, there is a 20% chance of severe neurological impairment with cerebral palsy and a further 30% chance of minor neurological impairment and/or language delay. Death of one twin increases the risk of death and neurological impairment in the survivor; one review of single intratuterine deaths in monochorionic twin pregnancies showed only a 57% chance of a healthy survivor.

Treatment and outcomes
If TTTS is left untreated, the perinatal mortality rate exceeds 80%, with the donor at higher risk of death than the recipient. Several management options have been proposed for the treatment of TTTS; these include amnioreduction, septostomy, laser ablation and occlusive feticide. The options of non-intervention and, indeed, termination of pregnancy (prior to 24 weeks, as the prognosis is relatively poor) should also be offered to the parents.

Amnioreduction
Amnioreduction can improve outcome by reducing preterm delivery secondary to polyhydramnios (although there is a risk of preterm labour, membrane rupture, chorioamnionitis and abortion as a result of the procedure itself) and also by increasing blood flow to the uterus. Data from the International Amnioreduction Registry show that at least one fetus survived to four weeks after birth in 71% of cases and both survived in 48%. However, 25% of those survivors had abnormalities on neonatal cranial ultrasound (Figure 1). Amnioreduction is indicated in the presence of clinically tense polyhydramnios (usually when the amniotic fluid index is greater than 40 cm or the deepest vertical amniotic fluid pocket is greater than 12 cm³), but it does not treat the underlying cause of TTTS.

Septostomy
Septostomy allows excess fluid to pass from the recipient’s sac into the donor’s, where it can be swallowed or absorbed. It has been argued that at least some of any benefit seen after amnioreduction may be due to inadvertent septostomy during the procedure. Septostomy can be performed with a needle or laser, but there is no clear advantage with the more complex laser approach. A randomised trial of septostomy versus amnioreduction has shown no difference in overall survival (70%), but a decrease in the need for repeat procedures with septostomy (40% versus 70% with amnioreduction).

Laser ablation
Laser ablation of anastomotic vessels is usually performed between 18 and 26 weeks of gestation: it is seldom indicated later than this, as more advanced disease is likely to have presented prior to 26 weeks. It is the only treatment aimed at treating the underlying pathophysiology. The initial method developed (the so-called ‘non-selective’ technique) involves insertion of a fetoscope into the amniotic cavity of the recipient and photocoagulation of all vessels crossing underneath the origin of the interfetal septum by laser (Figure 2). In the UK, this is usually done under local anaesthetic, but it can be done under regional or even general anaesthetic. Preliminary experience with this technique in 45 cases of TTTS showed that 53% of fetuses survived to delivery and 71% of pregnancies had at least one survivor. Only one fetus died in the neonatal period and, encouragingly, all the survivors were described as developing normally at a median age of 12 months. However, a subsequent retrospective study of 24 twins (12 pairs) and 12 singleton survivors of laser therapy showed a cerebral palsy rate of 13% in the twins and 0% in singletons.
More recently the technique has been refined so that only fetoscopically suspected anastomoses are ablated rather than using the previous non-selective approach. In a study published in 2003 of 95 cases of this so-called ‘selective’ laser treatment, 83% of cases had at least one survivor, with a neurological morbidity of 4%.21

The Eurofetus study22 published in 2004 is a randomised comparison of serial amnioreduction versus laser therapy and single amnioreduction in 142 women presenting with TTTS before 26 weeks of gestation. The study was halted early after interim analysis showed laser therapy to be associated with improved perinatal outcome (Table 2). These improvements occurred despite an increased incidence of pregnancy loss within seven days of the initial procedure with laser (8% versus 2%).

The authors also concluded that staging of TTTS should not influence the choice of treatment. Since there was no difference in live birth rates, the results are likely to be in part due to the prolonged gestation in the laser group: median 33 weeks versus 29 weeks in the amnioreduction group. Furthermore, a previous retrospective multicentre study of stage-based treatment has shown no improvement in perinatal survival in pregnancies with stage I or II disease treated with laser therapy compared with amnioreduction, but better survival in those with stage III or IV disease.21 Since fewer than 10% of cases in the Eurofetus study were stage I or IV, it may be premature to conclude that laser ablation should be the first-line treatment in all cases. One important limitation of these multicentre studies is that equipment and methods of amnioreduction and laser were not standardised prior to the trials commencing.

Selective feticide

It is necessary that selective feticide is occlusive to obviate the risks of acute perimortem interfetal transfusion.23 Cord occlusion using bipolar diathermy can be performed up until approximately 26 weeks of gestation; thereafter the diameter of the umbilical cord becomes too large and occlusion is no longer possible. It can be offered where one fetus is deemed to be pre-terminal, or more recently to women where there is stage III/IV TTTS as an alternative to laser ablation because some parents may feel that a better prognosis for one twin is preferable to a guarded prognosis for both.2 In one study of 14 cases,24 survival rates for the remaining twin were 80–90% with no neurological abnormalities evident prior to discharge, despite an incidence of up to 20% of membrane rupture, due in part to the 3.3 mm port used to insert the bipolar diathermy forceps.

Stage-based treatment

Our approach to the treatment of TTTS at St Michael’s Hospital is constantly evolving as more data become available. Once the diagnosis is confirmed, the woman is counselled about the prognosis, but also the uncertainty of progression, including the possibility of spontaneous improvement or even resolution. Women are scanned weekly to look for worsening TTTS and to allow timely intervention. For stage Ia and IIa disease, women are offered amnioreduction if the amniotic fluid index is greater than 40 cm and/or there is significant maternal discomfort, a clinically tense uterus or cervical shortening. However, they need to be aware that they are likely to need repeated procedures and that laser treatment can be difficult or impossible after amnioreduction, especially if there is membrane separation or significant bloodstaining of the liquor (irrigation can be used, although it is likely to increase the complication rate). For those with stages IIIb, IVa and IVb TTTS, laser ablation with amnioreduction is offered. However, use of laser treatment for stage II disease, especially at earlier gestations, is equally acceptable.

Table 2

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Laser therapy (%)</th>
<th>Amnioreduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival of at least one twin</td>
<td>76</td>
<td>56</td>
</tr>
<tr>
<td>Periventricular leukomalacia</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Survivors free of neurological complications at age of six months</td>
<td>52</td>
<td>31</td>
</tr>
</tbody>
</table>

Selective feticide

It is necessary that selective feticide is occlusive to obviate the risks of acute perimortem interfetal transfusion. Cord occlusion using bipolar diathermy can be performed up until approximately 26 weeks of gestation; thereafter the diameter of the umbilical cord becomes too large and occlusion is no longer possible. It can be offered where one fetus is deemed to be pre-terminal, or more recently to women where there is stage III/IV TTTS as an alternative to laser ablation because some parents may feel that a better prognosis for one twin is preferable to a guarded prognosis for both.2 In one study of 14 cases,24 survival rates for the remaining twin were 80–90% with no neurological abnormalities evident prior to discharge, despite an incidence of up to 20% of membrane rupture, due in part to the 3.3 mm port used to insert the bipolar diathermy forceps.
Stages Ib and IIb fall into the treatment ‘grey zone’, with no clear evidence of which treatment is optimal. Our practice is to individualise these cases at the time of treatment, with factors such as gestational age, placental site, whether the donor is truly ‘stuck’ (i.e. where there is anhydramnios and absent bladder with restricted fetal movement) and parental choice playing an important part in the final decision.

Following treatment, women are initially scanned twice weekly with full Doppler assessment, and then scanned at least weekly throughout the remainder of the pregnancy. The exact frequency of follow-up is tailored to the response to treatment. If the initial treatment is performed after 24 weeks, steroids are administered prior to the procedure; otherwise, steroids are given prior to delivery.

Timing of delivery depends on the treatment. If repeated amnioreduction is required (either as primary treatment or following failed laser treatment) then the underlying disease has not been treated and we aim to deliver at around 32–34 weeks of gestation, depending on fetal condition and the availability of neonatal cots. The decision to deliver earlier will depend on the gestation and ultrasound findings, including persistent tricuspid regurgitation in the recipient, which is associated with postnatal cardiac morbidity and mortality. If laser treatment has been successful, then we aim to deliver at around 34 weeks of gestation, again depending on the availability of neonatal cots.

Future developments

The Eurofetus trial has indicated that laser appears to be the optimal treatment for the majority of cases. It remains, however, a high-risk procedure with survival rates quoted only in terms of ‘at least one neonate’. With increasing experience of performing the procedure the iatrogenic complications are likely to decrease. However, there remains a subgroup of apparently successfully treated laser cases where the disease appears to progress. Within the last couple of years it appears that our understanding of the vascular anatomy of monochorionic placenta may have been oversimplified. Placental cast work now indicates that, in addition to the ‘classic’ AVA where an artery from one twin enters the placental surface close by to a vein from its co-twin, there may also be additional AV anastomoses that are not readily detectible from the placental surface.

Obviously, this has major implications for laser treatment and, in particular, the targeted approach, where anastomoses are individually identified by their appearance on the chorionic surface. The answer to this is at present unclear, although any future technique must allow the identification of all anastomoses, either by imaging or by marker techniques, which will enable a true rendering into a dichorionic placenta with minimal destruction of viable placental territory.

Conclusion

TTTS affects approximately 15% of MCDA twins and is due to an imbalance of blood volume resulting from placental interfetal anastomoses. Various treatments are available that have been shown to improve outcome, but in most affected pregnancies there will be loss of at least one baby, with an approximately 10% chance of handicap in the survivor. Our unit’s current treatment is gestational age and stage-based, with amnioreduction and septostomy used for early disease and laser treatment or cord occlusion reserved for more severe disease.
TOG referees 2005

TOG could not exist without its referees. Thank you very much indeed to the following people who refereed articles for us in 2005:

Abdel-Fattah, Mohammed
Ash, Robin
Beattie, Bryan
Bentick, Bernie
Bewley, Susan
Blakeman, Peter
Cameron, Alan
Carr, Susan
Conlon, Orla
Cordiner, James
Coulson, Catherine
Cust, Mike
Davidson, Campbell
Dooley, Michael
Downes, Ellis
Gebbie, Ailsa
Hawthorn, Robert
Heasley, Noel

Hillard, Tim
Hughes, Rhona
Hunter, Alison
Keay, Stephen
Khan, Khalid
Kyle, Heather
Lamont, Ronald
Latimer, John
Louden, Keith
Lower, Adrian
Manhire, Adrian
Mayne, Christopher
McKenna, Daniel
McManus, Joanne
Mellows, Heather
Murdoch, John
Neilson, Jim
Packe, Geoffrey

Parvaneh Mohajer, Michele
Pirie, Alexander
Radley, Stephen
Robins, James
Shennan, Andrew
Steer, Philip
Stirrat, Gordon
Stones, R William
Thompson, William
Tof, Brian
Tooza-Hobson, Philip
Tufnell, Derek
van den Broek, Nynke
Wardle, Peter
Wilcox, Mark
Wilton, Tamsin