How can we diagnose and manage twin–twin transfusion syndrome?

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Severe mid-trimester twin–twin transfusion syndrome (TTS) complicates about 15% of monochorionic twin pregnancies. If left untreated, the mortality is 80–100%. The pathophysiological prerequisite for the onset of TTS is unequal blood flow via arteriovenous placental anastomoses from the so-called donor to the recipient twin. This can result in hypovolemia, hypotension and oligo- or anuria in the donor, and hypervolemia, hypertension, polyuria and finally heart failure in the recipient. Leading sonographic signs of TTS include severe oligo- or anhydramnios and a small or absent bladder filling in the donor in contrast to polyhydramnios with increased bladder filling in the recipient. Patients might present with clinical symptoms due to massive polyhydramnios. In severe mid-trimester TTS, fetoscopic laser occlusion of the anastomosing vessels on the placental surface under local anaesthesia plus subsequent amniodrainage is the most promising therapeutic option at present. In acute TTS after 26 weeks of gestation, amniodrainage is the therapy of choice. All patients suspected of this high-risk condition should be referred to a specialized fetal medicine centre.

Key words: twin–twin transfusion syndrome; endoscopic laser coagulation; amnioreduction; placental vascular anastomoses.

Compared both to dichorionic twins and to singletons, monochorionic twin pregnancies have an increased risk of serious pregnancy complications including miscarriage, perinatal death and intrauterine growth retardation.1 The incidence of monzygotic twinning is approximately 3.5/1000 pregnancies, of which approximately 25% are dichorionic–diamniotic, 75% monochorionic–diamniotic and less than 1% monochorionic–monoamniotic. Monochorionic–diamniotic twinning (a single placenta with two separate amnions) results from division of the early embryonic mass before day 8 of gestation. Apart from exceptionally rare cases2, all monochorionic pregnancies are monozygotic (MZ) and the twins are characterized...
as ‘identical’, as opposed to the so-called ‘fraternal’ twins that result from dizygotic twinning.

One of the major risks facing monochorionic twins is the development of twin–twin transfusion syndrome (TTS) during pregnancy, whereby blood shifts unequally from one fetus (the donor twin) via communicating placental anastomoses to its co-twin (the recipient). This condition complicates about 15% of mid-trimester monochorionic pregnancies.3,4

This article provides an overview of the pathophysiology, diagnosis and different treatment options in TTS, which depend on onset and severity.

PATHOPHYSIOLOGY

The placental anastomoses between the two fetuses, present in almost all monochorionic pregnancies5,6, are the basis of the onset of TTS. If the blood shift from one fetus to the other is unbalanced, the donor becomes progressively hypovolemic, hypotonic, often growth-restricted and oliguric, all of which lead to oligo- or anhydramnios in this twin’s amniotic sac. By contrast, the recipient fetus becomes hypervolemic, hypertonic, polyuric and might develop congestive heart failure because of the volume overload. As demonstrated in a model by Talbert et al7, after an initial phase of volume overload and subsequent polyuria, the recipient progressively acts ‘as a water pump’, passively absorbing water from the mother into its amniotic cavity as a consequence of its increased colloid osmotic pressure. If onset is prior to fetal viability, the condition is associated with a high mortality rate (about 90%)8 due to miscarriage/premature delivery either because of the recipient twin’s excessive polyhydramnios or because of intrauterine demise of one or both fetuses. Of equal importance, in instances of death of one twin in utero, the surviving twin has a substantial risk of subsequent intrauterine death or cerebral damage due to haemorrhage into the dead co-twin via open placental anastomoses.9

The fetuses of monochorionic twin pregnancies have been labelled ‘les liaisons dangereuses’ because of their high risk profile secondary to the vascular connections.3

As long as blood flow via placental anastomoses between the fetuses is balanced, it represents a physiological fact. Four types of vascular connection are possible between the two circulations. Arterio-arterial anastomoses (AAA) and veno-venous anastomoses (VVA) are referred to as ‘superficial’ because they appear as a single vessel travelling without an interruption between the two cord insertions. Arterio-venous anastomoses (AVA) do not anastomose on the placental surface but rather at the villous level. They can run from the donor to the recipient or from recipient to donor. The arterio-venous connections from the donor to the recipient are known, from both in vivo and in vitro studies, to be responsible for the onset of TTS.5,10,11 By contrast, AAA are thought to play a protective role against the development of severe TTS12,13, which is underlined by the fact that AAA are found in about 30% on the placental surface in postnatal dye-injection as well as fetoscopically, whereas they are present in about 84% of placentas without TTS.11,14

Apart from the problems caused by imbalanced blood flow via placental anastomoses, the sharing of placental perfusion zones is often unequal (Figure 1) and can result in marked growth discordance.9
DIAGNOSIS

Sonographic assessment

As monochorionicity is the prerequisite for TTS, early sonographic demonstration of chorioicnicity is vital. The sonographic signs of monochorionicity are common placental mass, thin dividing intertwin membrane, T-sign and same sex. At the first-trimester screening between 11 and 14 weeks, discordant increased nuchal translucency and pathological flow in the ductus venosus can act as early predictors for an increased risk for development of TTS. All patients with monochorionic twin pregnancies should be counselled about the symptoms of polyhydramnios and should be seen approximately biweekly. If differences in the amniotic fluid volume are present, weekly scans should be performed.

If a patient with a monochorionic twin pregnancy complains of rapid growth of the uterus or even signs of premature contractions or dyspnoea, immediate ultrasound surveillance should be organized to exclude TTS.

TTS can occur at any time during pregnancy but is most common in the second trimester. As delivery is not an option in mid-trimester (<25 weeks of gestation), the main focus is on diagnosis and treatment options during that period before viability is reached.

Traditional neonatal criteria for the diagnosis of TTS are an intertwin haemoglobin difference of >5 g/100 ml and a birth weight discrepancy of >20%. These criteria do not apply in utero because fetal blood sampling shows that the majority of cases do

<table>
<thead>
<tr>
<th>Table 1. Characteristic sonographic signs of severe mid-trimester TTS.</th>
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<tr>
<td><strong>Recipient</strong></td>
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<tr>
<td>Massive polyhydramnios (deepest vertical pool &gt; 8 cm)</td>
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<tr>
<td>Signs of polyuria (distended bladder)</td>
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<tr>
<td>Optional signs of heart failure or hydrops</td>
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<td>Single monochorionic placenta; same sex</td>
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Figure 1. Monochorionic placenta with vascular anastomoses and unequal placental sharing (© Kurt Hecher, K. Dalkow ski, and Karl Storz GmbH).
not have an intertwin haemoglobin difference of $\geq 5$ g/100 ml.\textsuperscript{17} Rather, the diagnosis of TTS is made by demonstration of the characteristic sonographic features that result from the blood flow discordances in severe mid-trimester TTS (Table 1). Figure 2 shows the characteristic appearance of mid-trimester TTS, with the recipient surrounded by massive polyhydramnios and the donor being stuck to the uterine wall because of anhydramnios. A growth discrepancy is often noted (the donor being the smaller fetus) but is not a key criterion for the diagnosis of TTS.

In this situation the pregnancy is occasionally falsely described as being monoamniotic, because the donor’s amniotic membrane is wrapped so tightly around its body that it cannot be visualized. Although TTS occurs in monoamniotic pregnancies, one should check if the suspected donor with a small or absent bladder filling is able to move about freely (i.e. monoamniotic pregnancy) or appears to be a 'stuck twin' (i.e. diamniotic pregnancy) with reduced fetal movements due to the reduced amniotic fluid in its amniotic cavity.

Doppler investigation demonstrates signs of congestive heart failure in severe cases due to hypervolemia in recipient fetuses (negative or reverse a-wave in the ductus venosus, pulsatile umbilical venous flow, tricuspid regurgitation) and signs of decreased venous return due to hypovolemia and increased placental resistance in donor fetuses.\textsuperscript{18,19} Fetal echocardiography should be performed in all fetuses to exclude myocardial hypertrophy or signs of right ventricular outflow tract obstruction in the recipient secondary to circulatory overload and hypertension. In a prospective study, Karatza et al\textsuperscript{20} found a 12% prevalence of congenital heart disease in recipient twins in severe TTS compared to 2.3% in uncomplicated monochorionic diamniotic twins. Lougheed et al\textsuperscript{21} retrospectively reviewed 73 pregnancies with mid-trimester TTS: 9.6% of the recipient twins in this series showed right ventricular outflow tract obstruction, whereas none of the donor twins had structural or functional heart disease. In a retrospective analysis of cases with intrauterine hypertrophic cardiomyopathy, Pedra et al\textsuperscript{22} found evidence of hypertrophic cardiomyopathy, a potentially reversible condition, in 18 of 37 (48.7%) recipient twins with severe TTS.

**Staging of severe TTS**

In 1999, Quintero and co-workers\textsuperscript{23} introduced a staging system to describe the pathophysiological cascade in the development of mild to moderate and severe TTS.
Stage I represents the most benign form of TTS with polyhydramnios of the recipient (deepest vertical pocket > 8 cm) and oligohydramnios of the donor twin (deepest vertical pocket < 2 cm) with its bladder still visible. In Stage II the donor is ‘stuck’ and its bladder is no longer visible. Stage III describes forms with severely abnormal Doppler flow patterns: absent or reverse end-diastolic flow in the umbilical artery of the donor twin and/or venous abnormalities in the recipient. (reverse flow in the ductus venosus or pulsatile umbilical venous flow, usually associated with marked tricuspid regurgitation). Stage IV is characterized by development of fetal hydrops. Stage V describes the fetal demise of either or both twins.

Several studies show that disease severity at presentation was one of the main determinants of fetal outcome and that progression to higher stage disease was associated with a poorer prognosis.

If TTS is suspected, the patient should be referred as soon as possible to a tertiary referral centre for appropriate evaluation including detailed sonographic assessment/echocardiography and Doppler sonography and counselling concerning treatment options.

**Differential diagnoses**

Rare differential diagnoses of TTS include other causes of discordant polyhydramnios (such as fetal anomalies and infections) and other reasons for discordant oligohydramnios [such as intrauterine growth retardation (IUGR), renal malformations and preterm prelabour rupture of the membranes (PPROM)]. If one fetus presents with severe growth retardation and oligo- or even anhydramnios due to placental insufficiency, this can give the impression of a ‘stuck twin’, as would be seen in TTS. In this condition, however, the co-twin does not show signs of hypervolemia or cardiac insufficiency and these cases represent a different entity.

**TREATMENT/PATIENT MANAGEMENT**

Two main treatment options are available in TTS: serial amniodrainage and fetoscopic laser coagulation of the communicating placental vessels.

**Serial amniodrainage**

Before the development of the laser coagulation technique serial amniodrainages (AD) had been the standard treatment option for severe TTS. The procedure aimed to relieve symptoms caused by the massive polyhydramnios and to allow prolongation of pregnancy by reducing the risk for miscarriage/preterm labour and PPROM. Uteroplacental perfusion increases as the intrauterine pressure is reduced. One amniodrainage is sufficient in about 20% of cases of severe mid-trimester TTS because a new equilibrium develops. In the majority of cases however, repeated amniodrainages are necessary.

To accomplish amniodrainage, an 18-gauge spinal needle is inserted into the recipient’s amniotic cavity under ultrasound guidance and amniotic fluid is drained using a vacuum bottle system until the amount of amniotic fluid in the recipient’s sac appears to be normal. The procedure is carried out under prophylactic tocolysis. Possible procedure-related risks include rupture of membranes, premature labour, infection and placental abruption.
In a study by the International Amnioreduction Registry on 223 twin pairs with TTS diagnosed before 28 weeks of gestation, Mari et al. report an overall survival rate of 60% at 4 weeks of age. In 48.4%, both twins survived to 4 weeks after birth and in 70.8% at least one twin survived. However, at 4 weeks of age 24.5% of the infants showed abnormal brain scans and the prevalence of congenital cardiac malformations in neonatal survivors to 4 weeks was 3.6%. The overall procedure-related risk of complications per amnioreduction was 15% within 48 hours; this compares to 4.6% in the series by Duncombe et al.

In a systematic review of more than 20 literature reports, van Gemert et al. report an overall fetal survival rate of 57.3% in pregnancies with TTS diagnosed before 26 weeks, and neurologic sequelae in 15.3% of survivors. According to the Australian and New Zealand Registry, overall perinatal survival was 62.5%, with a median gestational age at delivery of 29 weeks. However, gestational age at diagnosis in this series was up to 34.6 weeks, when survival is no longer the main issue, and only 82% were managed with serial amnioreduction. The percentage of neonates with abnormal findings on cranial ultrasonography was 27.3%, a similar percentage to that found by Mari et al.; 10.8% had periventricular leukomalacia on postnatal headscan.

Cincotta et al. reported the results of 17 pregnancies with TTS, 12 of which were treated by serial amnioreduction. The survival rate was 68% but 22% of survivors showed significant handicaps. Haverkamp et al. found 40% of abnormal brain scans in surviving children after serial amnioreduction; 45% of the children had a normal neurologic outcome, 33% had mild neurologic abnormalities and 23% were severely handicapped.

**Laser therapy**

Unlike amnioreduction, which offers symptomatic relief but no causal treatment, endoscopic laser coagulation of the anastomosing vessels on the placental surface combined with a subsequent amnioreduction is a therapeutic approach aiming at the underlying pathophysiologic mechanisms. The procedure was first described by De Lia and co-workers in 1990, who performed a maternal laparotomy under general anaesthesia and fetoscopically coagulated the anastomoses on the placental surface using a neodymium-YAG laser. Subsequently, a minimally invasive approach was developed with percutaneous insertion of the fetoscope under local anaesthesia. The initial use of a non-selective coagulation of all vessels crossing the dividing membrane was replaced by selective coagulation along the vascular equator with growing operators experience. With this latter technique, vessels that cross the dividing membrane but do not anastomose with vessels of the co-twin are spared from coagulation.

**Technique**

Under local anaesthesia, a rigid 2-mm fetoscope is introduced percutaneously through a sheath using continuous sonographic control. The scope is directed into the amniotic cavity of the recipient twin. A 0.4-mm Nd:YAG laser fibre is passed down the working channel of the sheath. The base of the amniotic cavity on the chorionic plate is examined systematically along its whole length to visualize crossing blood vessels, which are followed along their course. Superficial anastomoses (direct connections between the two cord insertions: arterio-arterial or veno-venous anastomoses) or vessels from the donor's side meeting end to end with a corresponding vessel from the recipient's side (arterio-venous anastomoses at the villous level in both directions) are
coagulated by administration of repeated laser shots with an output of 50 to 60 W at a distance of 1 cm (Figure 3). The nature of the vessels can be determined with a fair degree of certainty because arteries usually cross over veins and are darker in colour than veins because of their lower oxygen saturation. After coagulation of all anastomosing vessels, the excess amniotic fluid in the recipient’s sac is drained through the sheath after removal of the fetoscope until normalization of the amniotic fluid volume is achieved.

Prophylactic antibiotic medication is administered, as is prophylactic tocolysis (magnesium and indomethacine) and analgesia. The patient is discharged from hospital after 24 to 48 hours if the postoperative period remains uneventful.

Fetoscopic laser coagulation is a causal treatment and reoccurrence is seen in only 4% of cases\(^{19}\), whereas in about 80% of the pregnancies managed with amnioreduction repeated amniodrainage is necessary.

**Outcome**

A study\(^{28}\) comparing laser therapy versus amniodrainage in severe mid-trimester TTS (gestational age at diagnosis 17–25 weeks) showed overall survival rates of 61% and survival of at least one fetus in 79% after fetoscopic laser coagulation compared to 51% and 60%, respectively, in pregnancies treated with amniodrainage. The median gestational age at delivery in the laser group was 33.7 weeks compared to 30.7 weeks in the amniodrainage group. The risk for spontaneous intrauterine demise of both fetuses after laser therapy was significantly lower than after amniodrainage (3% versus 19%), as was the risk for abnormal neonatal brain scans (6% versus 18%).

With growing experience in the technique\(^\text{37}\), the overall survival rate after laser therapy at our institution recently increased to 70%, the percentage of pregnancies with survival of both fetuses reached 57% and those in which at least one fetus survived reached 83%. The median gestational age at delivery increased to 34.9 weeks.\(^\text{40}\) Our results are similar to those described by Martinez et al\(^\text{41}\), who report an overall survival rate of 68.6% and at least one survivor in 88.2%, and to those by De Lia et al\(^\text{42}\) who treated 69 pregnancies by laser under general anaesthesia after laparotomy and
achieved an overall survival rate of 69%, survival of both fetuses in 57% and survival of at least one twin in 82%.

Long-term neurodevelopmental outcome of surviving children after laser therapy shows 84% normal development, 8% minor and 8% major neurologic deficiencies. The initial results of a multicentre, randomized controlled trial by the Eurofoetus Study Group also clearly indicate that laser therapy is superior to serial amniodrainage in severe TTS before 26 weeks concerning survival, gestational age at delivery, birthweight and neurologic outcome; however, the final report of the study is not yet published.

Contraindications to laser therapy are amniotic fluid leakage, ruptured membranes and regular uterine contractions/labour with progressive cervical dilatation. Although the operation is technically more difficult with an anterior placenta, in experienced hands outcomes appear similar in pregnancies with anterior compared to posterior placentas, and only very rarely is one confronted with an extensive anterior placenta that does not permit fetoscopic access. New developments, such as a fetoscope with an angle of 30°, offer optimized visualization in cases where placental location is unfavourable. The risk for delivery within 4 weeks of the procedure is 8% in our population. Maternal complications have been described only rarely and patients should be counselled about the theoretical procedure-related risk of infection, damage to blood vessels or adjacent organs. No serious maternal complications have been observed in our population of 400 percutaneous fetoscopic laser procedures.

Parents should be counselled about termination of pregnancy in severe mid-trimester TTS before fetal viability is reached if the rates of survival and handicap associated with the condition and its treatment modalities seem unacceptable to them.

If the symptoms do not require emergency amniodrainage and sonography is not suggestive of a chromosomal abnormality, karyotyping/amniodrainage should not be performed before possible laser coagulation, as any invasive procedure increases the risks for unfavourable conditions for the intervention, such as amnion dissection or bleeding into the amniotic cavity.

Close sonographic monitoring should be instituted after laser treatment. Transient hydropic signs can develop in up to 25% of donor fetuses as a sign of relative volume overload following interruption of the transfusion process and are not associated with a poor prognosis. In our own series, 27% of donor twins showed absence or reversal of blood flow during atrial contraction in the ductus venosus one day after the procedure.

Absent or reverse end diastolic flow (AREDF) in the umbilical artery is present in 14–19% of donor fetuses preoperatively. Reappearance of end diastolic flow occurs in 30% of donor fetuses 1 day after the procedure and in up to 53% of donor fetuses 5 days after the procedure. Unlike with singleton or dichorionic pregnancies, these observations suggest that the pathological Doppler findings do not necessarily reflect high placental resistance and unequal placental sharing but might rather be attributed to fetal hypotension due to hypovolemia, which can be corrected by laser therapy.

If the pregnancy proceeds uneventfully and all anastomosing vessels have been coagulated by laser, the fact that the pregnancy was complicated by TTS is not a contraindication in itself to a vaginal delivery. In instances where some anastomoses might still be open due to impaired vision at laser therapy, delivery by caesarean section is recommended to avoid the risk of acute intrapartum TTS.

Whereas laser therapy is superior to amniodrainage alone in severe mid-trimester TTS, a comparative study by Quintero et al suggested more favourable outcomes in early stage disease for amniodrainage compared to early intervention by laser.
A randomized trial is now needed to improve our understanding and treatment regimens for mild to moderate stages of TTS. Table 2 shows the characteristics of laser therapy versus amniodrainage with the advantages and disadvantages of each therapeutic approach.

### Table 2. Laser treatment versus amniodrainage in severe stages of TTS.

<table>
<thead>
<tr>
<th>Laser treatment</th>
<th>Amniodrainage</th>
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<tr>
<td>Single procedure</td>
<td>&gt; One procedure in 80% of cases</td>
</tr>
<tr>
<td>Causal treatment</td>
<td>Symptomatic treatment (reduces the risks associated with polyhydramnios; improvement of placental blood flow)</td>
</tr>
<tr>
<td>Improved outcome (gestational age at delivery, survival and neurologic outcome)</td>
<td></td>
</tr>
<tr>
<td>Protection of the surviving twin if one fetus dies in utero</td>
<td>Substantial risk for death/damage to the surviving twin in case of intrauterine demise of its co-twin</td>
</tr>
<tr>
<td>More invasive</td>
<td>Less invasive</td>
</tr>
<tr>
<td>Referral to specialized centre required?</td>
<td>Widely available, technically easy to perform</td>
</tr>
<tr>
<td>Optimal treatment in early stages of TTS?</td>
<td></td>
</tr>
<tr>
<td>Randomized controlled trial required</td>
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**Septostomy**

This procedure aims at normalizing the amniotic fluid volume of the donor twin and has been suggested as a treatment option for TTS in combination with amnioreduction.\(^{49}\)

The fact that severe TTS also can occur in monoamniotic twin pregnancies where no intertwin membrane exists is a logical argument against the procedure. The different amniotic fluid volumes are the consequence of haemodynamic differences and not the cause for the development of TTS. Mathematical modelling has shown that whereas septostomy allows the donor to swallow amniotic fluid, there is only minimal effect on blood volume and growth, and is therefore unlikely to offer significant therapeutic success.\(^{50}\)

In contrast to the extreme difference in amniotic fluid volume, no differences are present in the amniotic fluid pressures in the amniotic sacs of both twins.\(^{51}\) Additionally, artificially creating a pseudo-monoamniotic pregnancy can lead to other problems, such as cord entanglement.

**Selective feticide**

In selected cases of severe TTS in which one twin has an extremely poor prognosis or shows signs of substantial intrauterine damage, selective feticide might be discussed with the parents. Apart from the ethical considerations surrounding this option, specific technical considerations must also be taken into account in a monochorionic pregnancy, including the fact that intracardiac application of potassium chloride is contraindicated because the substance would cross into the circulation of the co-twin via the placental anastomoses. Other methods have therefore been developed, such as bipolar cord coagulation of the umbilical cord.\(^{52,53}\)
INTRAUTERINE FETAL DEMISE OF ONE TWIN

If intrauterine fetal demise (IUFD) is diagnosed in a monochorionic twin pregnancy, the risk of the surviving co-twin dying or being severely damaged is substantial. In selective intrauterine growth retardation of one twin, the risk of the surviving twin dying as well has been estimated to be as high as 40%. The risk for serious cerebral morbidity has been estimated to be as high as 20–50% in the surviving twin of a monochorionic twin pregnancy after death of its co-twin.

Acute twin–twin transfusion from the surviving to the dying/dead co-twin is currently considered as the underlying pathophysiologic mechanism leading to hypovolemia, possible organ hypoperfusion and hypotension (which results in brain and tissue damage in the surviving twin rather than late-onset disseminated intravascular coagulation). In most cases, fetal death is not diagnosed during the actual event and immediate delivery of the co-twin at diagnosis would not prevent the hypotensive/hypovolemic episode in the survivor.

Senat et al have proposed fetal blood sampling to evaluate the condition of the survivor within 24 hours after the death of its co-twin in TTS. They found anemia in 6 of 12 surviving fetuses and performed intrauterine transfusion in case of anemia to reduce the risks of secondary damage. All fetuses found to have normal haemoglobin levels at examination had normal paediatric examinations up to 1 year of age, whereas two of the six anemic fetuses who had been treated with amniodrainages developed periventricular leucomalacia despite transfusion.

If death of one twin occurs after successful laser coagulation, the risk of damage to the surviving twin seems to be much lower, as exsanguination to the dead fetus is impossible once all anastomoses have been coagulated. This is confirmed by follow-up studies showing no significant difference in neurologic deficiencies between singleton and twin survivors.

SUMMARY

Twin–twin transfusion syndrome is a serious complication in monochorionic twin pregnancies. Vascular anastomoses on the placental surface result in a net blood flow from one fetus (the donor twin) to its co-twin (the recipient twin), resulting in hypovolemia and hypotension in the donor and hypervolemia and hypertension/cardiac failure due to volume overload in the recipient. Characteristic sonographic signs are polyhydramnios and a full bladder due to polyuria in the recipient, and severe oligo- or anhydramnios in the donor with small or absent bladder filling. If left untreated there is a high risk of adverse pregnancy outcome due to premature labour or PPROM as a consequence of the polyhydramnios or intrauterine demise of one or both fetuses. The unfavourable intrauterine conditions can result in subsequent neurologic damage in both fetuses and right outflow tract obstruction in the recipient. The two main treatment options are serial amniocentesis and fetoscopic laser coagulation of placental anastomoses. Whereas amniocentesis offers only symptomatic therapy by reducing the risk of premature labour or PPROM, laser therapy combined with a subsequent amniocentesis is a causal treatment option aiming at conversion into a haemodynamically dichorionic placenta. Outcome data after laser therapy are better than after amniocentesis and overall survival rates of approximately 71% can be achieved after laser therapy, with survival of both twins in 58%, survival of at least one twin in 83% and an overall rate for major neurologic abnormalities of 8%.
In severe mid-trimester TTS, fetoscopic laser therapy under local anaesthesia is regarded as the most promising and effective therapeutic option regarding favourable outcome and patients with the condition should be offered referral to specialized centres. In early stages of the condition, amniodrainage also offers favourable results and we recommend a randomized trial to compare the best treatment for pregnancies presenting in the early stages.

**Practice points**
- in multiple gestations, chorionicity should be determined sonographically in the first trimester and monochorionic pregnancies should be monitored closely with biweekly ultrasound examinations. Patients should be counselled about the clinical signs of TTS (rapid growth of the uterus, shortness of breath, contractions) and, if TTS is suspected, should be referred to a specialized centre for fetal medicine
- fetoscopic laser coagulation of anastomosing vessels on the placental surface plus subsequent amniodrainage offers a causal treatment option in severe TTS and is superior to serial amniodrainage alone in terms of survival, gestational age at delivery and neurologic outcome

**Research agenda**
- maternofetal interaction
- stage-based treatment for mild to moderate TTS (early intervention by laser or amniodrainage versus expectant management)
- the impact of TTS on later life/follow-up studies as planned in the Euro Twin-2-Twin-follow-up study (5th Framework Programme of the European Commission, Eurofoetus project contract numbers PL 962 383 and QLRT 2001-01632)
- natal detection of arterioarterial anastomoses and correlation with optimal treatment for different stages of TTS
- the influence of TTS and treatment modalities on vascular programming in utero according to the Barker hypothesis. In a recent study, Gardiner et al demonstrated that vascular programming is evident in monochorionic twins with TTS and can be altered, but not abolished, by intrauterine therapy

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