Management of Twin–Twin Transfusion Syndrome (TTTS) is one of the most challenging clinical problems concerning multiple gestations. Approximately 20% of all twin pregnancies are monochorionic, and the incidence of TTTS in monochorionic diamniotic gestations is approximately 10% to 20%. TTTS is a phenomenon almost exclusively of monochorionic twin pregnancies. The natural history of severe TTTS is well established with mortality approaching 80% to 100% if left untreated, especially when it presents at less than 20 weeks' gestation. This is particularly troublesome given that two structurally normal fetuses are involved.

Diagnosis and Staging of TTTS

The lack of agreement on specific diagnostic criteria to define midgestation TTTS and the influence of older neonatal criteria have hampered understanding of its pathophysiology and slowed the development of more effective treatment strategies. The donor twin is characterized by oliguria, oligohydramnios, or anhydramnios, growth restriction, and abnormal umbilical artery Doppler velocimetry. The recipient, on the other hand, is characterized by polyuria, polyhydramnios, abnormal venous Dopplers, cardiac enlargement/failure, and eventually hydrops.

Clinicians caring for women with monochorionic pregnancies should have a strong clinical suspicion for TTTS (Fig. 1). Sonographic signs of monochorionic diamniotic twins include a single placenta, a thin dividing membrane, a “T”-sign, and gender concordance. Before ruling out monochorionic diamniotic twins in the case when no dividing membrane is seen, a diligent search for a thin membrane tightly wrapped around one twin should be performed. Although not all of the following sonographic criteria are necessary for a diagnosis of TTTS, the following findings are suggestive of the diagnosis: (1) monochorionicity, (2) discrepancy in amniotic fluid between the amniotic sacs with polyhydramnios of one twin (largest vertical pocket greater than 8 cm) and oligohydramnios of the other (largest vertical pocket less than 2 cm), (3) discrepancy in size of the umbilical cords, (4) presence of cardiac dysfunction in the polyhydramniotic twin, (5) characteristically abnormal umbilical artery or ductus venosus Doppler velocimetry, and (6) less specifically, significant growth discordance (often >20%). Although criteria for TTTS diagnosed in utero were initially derived from neonatal criteria relying on discordant weights (usually >20%) and hemoglobin levels (usually difference of >5 g/dL) between the twins, subsequent literature demonstrates that hemoglobin discordance is often not present in midgestation, and advanced TTTS may be present before the threshold of 20% weight discordance is reached.

In addition to careful sonographic follow-up, mothers of monochorionic diamniotic twins should be alerted that rapid uterine growth, premature contractions, and dyspnea may be symptoms of polyhydramnios. The differential diagnosis of TTTS includes uteroplacental insufficiency, growth distur-
Bances due to abnormal cord insertions, intrauterine infection, preterm premature rupture of membranes of one twin, and discordant chromosomal or structural anomalies of one twin.

Quintero and coworkers proposed a staging system for TTTS that considers a sequence of progressive sonographic features. The individual stages are described as follows: Stage I) polyhydraminos in the recipient, severe oligohydraminos in donor but urine visible within the bladder in the donor; Stage II) polyhydraminos in the recipient, a stuck donor, urine not visible within the donor’s bladder; Stage III) polyhydraminos and oligohydraminos as well as critically abnormal Dopplers (at least one of absent or reverse end diastolic flow in the umbilical artery, reverse flow in the ductus venosus, or pulsatile umbilical venous flow) with or without urine visualized within the donor’s bladder; Stage IV) presence of ascites or frank hydrops (fluid collection in two or more cavities) in either donor or recipient; and Stage V) demise of either fetus. This staging system was descriptive but had not been validated as prognostically important.

Taylor and coworkers applied the Quintero staging system to a population treated with serial amnioreduction, septostomy, and selective reduction alone or in combination. Taylor and coworkers found no significant influence of staging at presentation with survival in his conservatively treated group. Survival was significantly poorer where stage increased rather than decreased. These authors concluded that the Quintero staging system should be used with caution for determining prognosis at the time of diagnosis, but may be better suited for monitoring disease progression. A subsequent larger study from the same institution, however, showed that Quintero stage at presentation, at first treatment, and at worst stage did in fact predict both perinatal and double survival but not survival of any twin. Duncombe and coworkers also showed a correlation of Quintero stage at initial presentation and perinatal survival.

**Cincinnati Modification of the Quintero Staging System**

The Quintero staging system provides a useful shorthand to describe the progression of TTTS along a spectrum of severity. However, it has potential limitations in its use in guiding therapy. In patients who present at Stage I with only amniotic fluid discordance, it may be difficult to know with certainty if they actually have TTTS. Patients with Stage II are usually thought to be only in the early stages of the disease. The largest group of patients tends to fall into Stage III. This stage, however, comprises a very broad spectrum of severity. At one end are patients whose only hemodynamic derangement is abnormal Doppler velocimetry, and at the other end of the spectrum are patients in whom the recipient twin has severe twin–twin cardiomyopathy. The latter patients may be pre-morbid without the development of hydrops (which would be Stage IV disease). We have used fetal echocardiographic assessment of the recipient twin to stage these patients (Fig. 1).
2). This is in keeping with the view that, fundamentally, TTTS is a hemodynamic derangement. Fetal echocardiograms can distinguish degrees of severity among Stage III TTTS. Echocardiographic features include presence and severity of atrioventricular valvar incompetence, ventricular wall thickening, and ventricular function as assessed by the Tei index. In a recent small series of cases of TTTS, four of six Quintero Stage II patients were upstaged to Stage III disease based on echocardiographic findings. The upstaging of patients from Stage II to Stage III may influence counseling regarding treatment options. These echocardiographic features are also used to assess response to therapy. If a patient is initially treated with amnioreduction or microseptostomy, we use fetal echocardiography to assess progression of TTTS despite therapy as an indication to move on to selective fetoscopic laser photocoagulation (Crombleholme, unpublished observations).

**Pathophysiology**

The twin–twin transfusion syndrome is a complication primarily of monochorionic multiple gestations mediated through vascular communications and having differential effects on the cotwins; one twin is hyperdynamic whereas the other is hypodynamic. The etiology of TTTS is unknown, but vascular connections on the placenta between the twins are necessary for it to occur. The majority of monochorionic twins gestations have vascular anastomoses between the cotwins, although only a percentage, ranging from 4% to 17%, develop TTTS. Communications between the recipient and donor twin may be artery to artery (AA), vein to vein (VV), or artery to vein (AV) within a placental cotyledon. Depending on the number and type of anastomoses present, the exchange of blood may be balanced or unbalanced. Shifts in blood flow between the twins may be either acute, as in the case of cotwin demise, or chronic. A true transfusion from one twin to another is unusual in mid-gestation TTTS. For example, changes in the renin-angiotensin system compound the renal changes initiated by hemodynamic changes in the donor and recipient. Angiotensin II usually helps to compensate in the setting of volume depletion. In the setting of TTTS, however, the intrarenal vasoconstruction mediated by angiotensin II following up-regulation of renin synthesis and release may exacerbate oligohydraminos. Donor fetuses after demise have increased renin synthesis and renal tubular dysgenesis. Whereas recipient fetuses demonstrate down regulation of renin expression, glomerular and arterial lesions in the kidneys are suggestive of hypertension-induced microangiopathy. These findings suggest that hypertensive changes in the recipient twin may be due to vascular shunting of renin from the donor. It is not clear whether alterations in the renin-angiotensin system are primary or secondary effects of TTTS.

Consistent with the hypothesis that hypertensive mediators play an important role in TTTS is the finding by Bajoria and coworkers of elevated levels of endothelin-1, a potent vasoconstrictor, in the serum of recipient twins 2.5-fold higher than in donor twin. Moreover, plasma endothelin-1 levels were significantly higher in the recipient twins with hydrops than those with mild or no hydrops. Endothelin-1 may also be important for the regulation of amniotic fluid volume, both by itself and in the pathway leading to higher human brain natriuretic peptide (hBNP) levels in amniotic fluid. Both endothelin-1 and hBNP amniotic fluid levels correlate with amniotic fluid index in TTTS. Recipient twin amniotic fluid levels of endothelin-1 and hBNP are the highest, followed by amniotic fluid levels from non-TTTS monochorionic twins, followed by amniotic fluid levels from donor twins.

We believe that high levels of vasoactive mediators are preferentially shunted to the recipient twin, resulting in hypertension and hypertensive cardiomyopathy. Interruption of vascular communications by selective fetoscopic laser photocoagulation may eliminate the hypertensive stress in the recipient twin by preventing vasoactive mediators from crossing to the recipient. Consistent with this vasoactive mediator hypothesis, we have seen the development of hypertension and hypertensive cardiomyopathy in some donor twins following successful fetoscopic laser photocoagulation. Presumably, in these cases, selective laser photocoagulation results in an alteration in the venous drainage of the region of the placenta producing the vasoactive mediators shunting them from the placenta formerly drained by the recipient toward the donor twin. In twins with TTTS treated by selective laser photocoagulation, we have echocardiographically
observed postoperative resolution of these hypertensive changes in recipient twins over weeks to months.

**Echocardiographic Changes Associated with TTTS**

Cardiovascular compromise occurs in most recipient twins and is a major cause of death for these fetuses. In addition, cardiovascular disease in the recipient twin is a significant contributor to morbidity and mortality in the donor cotwin. When the recipient twin develops progressive cardiovascular compromise leading to death, the donor cotwin is also at risk for hemorrhage into the dead recipient from decreased placental resistance in areas of vascular communication between the twins. Echocardiographic examination of the twins is thus an essential component of the initial workup of TTTS as well as follow-up evaluation for progression of the disease. In addition, study of short- and long-term cardiovascular effects of various therapeutic interventions is critical.

Recipient twins can develop a progressive cardiomyopathy. Although both ventricular dilation and myocardial hypertrophy may occur, the latter predominates and typically only mild evidence of dilation is seen. Usually the right ventricle (RV) is compromised first and to a more significant degree than the left ventricle (LV). In one study of 28 women with TTTS who received echocardiographic evaluation before any intervention, either right or left ventricular hypertrophy was detected in 27% of recipient twins, and biventricular hypertrophy was observed in an additional 33% of recipient twins. Biventricular diastolic dysfunction was present in two-thirds of recipient twins, whereas right ventricular systolic dysfunction was present in 35%. Atrioventricular valve disease is also common with moderate insufficiency reported in 71% of recipient twins with structurally normal hearts. Moderate to severe tricuspid and mitral regurgitation is more common in Quintero stage III and IV patients. Peak velocity of tricuspid and mitral regurgitant jets suggests the presence of ventricular hypertension in echocardiographic data from 39 recipient twins. Estimates of RV systolic pressure based on tricuspid regurgitant jet velocity are commonly elevated to 60 to 80 mm Hg, and pressures in excess of 100 mm Hg can be seen in severe cases.

Finally, several cases of acquired pulmonary atresia/stenosis with intact ventricular septum have been described in the recipient twin. In our own series, we have seen five such cases with varying degrees of pulmonary stenosis or pulmonary atresia. Worsening RV hypertrophy, reduced RV systolic function, and severe tricuspid regurgitation result in progressively diminished flow across the pulmonic valve, resulting in stenosis or atresia. In one patient undergoing postnatal cardiac surgery, a structurally normal pulmonary valve with adhered valve leaflets was found. These observations are not consistent with primary structural heart disease but rather acquired valvular atresia/stenosis related to TTTS, a unique form of “acquired congenital” heart disease.

Cardiovascular changes in the donor twin are usually less dramatic. Myocardial changes are rare, and ventricular function and atrioventricular valve competence are usually preserved. In several series of patients, absent or reversed end diastolic flow was noted before treatment in 12% to 39% of donor twins. The abnormalities in umbilical artery velocimetry are reversible; among survivors after laser therapy, 27% to 30% showed reappearance of end diastolic flow within 24 hours postoperatively. Abnormal umbilical artery Dopplers are more common in donor than recipient twins.

There is a paucity of information concerning the long-term cardiovascular implications of TTTS. In addition, data on the effect of various treatment modalities for TTTS on cardiovascular compromise and progression is lacking.

If treatment, whether amnioreduction or laser photocoagulation therapy, is successful, there should be an arrest in the progression of TTTS cardiomyopathy and even reversal of existent disease. Progression of the cardiac findings suggests treatment failure either due to lack of response to amnioreduction or to a missed vascular connection with fetoscopic laser treatment. Specifically, progressive changes noted after amnioreduction include worsening hypertrophy of the right, left, or interventricular septum. In addition, in one report, RV systolic function stayed or became abnormal in the majority of patients (15/19 patients, 79%), whereas RV systolic function normalized in one recipient only. On the contrary, one small study reported improved cardiac function following amnioreduction and another suggested altered progression of TTTS cardiomyopathy after laser photocoagulation. Finally, discordance of pulse wave velocity in brachial arteries of survivors of TTTS is altered with laser to be more similar to dichorionic controls, whereas the same alterations in vascular programming are not seen with survivors treated by nonlaser methods. Increased pulse wave velocity reflects increased vascular stiffness. This study suggests that in utero vascular remodeling may be altered by definitive laser therapy.

**Treatment Options in TTTS**

Numerous treatments for TTTS have been proposed, including selective feticide, cord coagulation, sectio parva, placental blood letting, maternal digitalis, maternal indocin, serial amnioreduction, microseptostomy of the intertwin membrane, and nonselective or selective fetoscopic laser photocoagulation. For decades in the United States, serial amnioreduction has been the most widely accepted therapy for TTTS, but in recent years, selective fetoscopic laser photocoagulation has become more accepted.

**Amnioreduction**

Amnioreduction was first employed for maternal comfort and as a means to control polyhydramnios in the hope of prolonging the pregnancy until the risks of extreme prematurity are lessened. In addition, amnioreduction improves uteroplacental blood flow, likely by reduction of pressure from the amniotic fluid. In uncontrolled series, amnioreduction improves survival compared with the natural history of
untreated TTTS. Moise, in a review of 26 reports dating from the 1930s of 252 fetuses, found an overall survival of 49%.24 The survival in more recent series, with more consistently aggressive serial amnioreduction to reduce amniotic fluid volume to normal, have ranged widely from as low as 37% to as high as 83%.25-30 However, these retrospective series are comprised of small numbers of patients from a range of gestational ages, as well as from a spectrum of severity of TTTS. Severity of TTTS and gestational age at diagnosis may have a profound impact on the observed mortality with any treatment strategy. The earlier in gestation TTTS presents, the worse the prognosis. Mari and coworkers found that patients presenting with advanced TTTS before 22 weeks’ gestation and absent end diastolic flow in the recipient umbilical artery had a survival of both twins with aggressive amnioreduction of only 13% and, with absent end diastolic flow in the donor umbilical artery, survival was 33%.36

**Microseptostomy**

The paradoxical resolution of oligohydramnios after a single amnioreduction was first suggested by Saade and coworkers to be due to inadvertent puncture of the intertwin membrane.31 Intertwin septostomy was specifically proposed as a treatment for TTTS to restore amniotic fluid dynamics without the need for repeated amnioreduction. One objection to this approach is the possibility it would result in a large septostomy, creating an essentially monoamniotic sac with the attendant risk of cord entanglement. For this reason, a fetoscopic “microseptostomy” has been proposed to prevent this complication. In a small multicenter series of 12 patients, Saade and coworkers reported an 81% survival with microseptostomy.32 However, not only was this series small and uncontrolled, there was no report of neurologic or cardiac morbidity. In a direct comparison, albeit a small retrospective single-institution series, of serial amnioreduction versus microseptostomy, Johnson and coworkers observed no survival advantage with either therapy.33 This was confirmed by Saade and coworkers who reported the results of a multicenter prospective randomized clinical trial comparing amnioreduction to septostomy. The survival in each arm of the study was 65%,34 consistent with the notion that the effect of amnioreduction may be inadvertent septostomy. These studies, however, cannot prove this theory.

**Fetoscopic Laser Photocoagulation**

The first treatment for TTTS that attempted to treat the anatomic basis for the syndrome was reported by DeLia and coworkers35,36 who described fetoscopic laser photoagulation of vessels crossing the intertwin membrane. At least in theory, this treatment option should be superior since it not only arrests shunting of blood from the donor to recipient, but also halts transfer of potential vasoactive mediators. In his first small series, DeLia reported a survival of 53% in 26 patients.36 Although survival was not significantly better than previous reports with serial amnioreduction, the “neurologic outcome” in 96% of survivors was “normal” as assessed by head ultrasounds. Other groups from Europe have reported similar survival with nonselective laser photoagulation. Ville and coworkers reported 53% survival with a fetoscopic laser technique, which was better than the survival observed with historical controls at the same center with serial amnioreduction (37%).37 They also observed a lower incidence of abnormalities dictated by neonatal head ultrasound compared with historical controls.

The nonselective fetoscopic laser technique photoagulates all vessels crossing the intertwin membrane. This approach may be problematic, as the intertwin membrane often bears no relationship to the vascular equator of the placenta. This nonselective laser photoagulation of all vessels crossing the intertwin membrane may sacrifice vessels not responsible for the TTTS, resulting in a higher death rate of the donor twin from acute placental insufficiency.38 More recently, a selective approach to fetoscopic laser photoagulation in TTTS (Fig. 3) has been described by Quintero and coworkers.38 Unlike the nonselective coagulation technique initially described by DeLia, the selective technique does not photoagulate every vessel crossing the intertwin membrane. Only direct, arterial–arterial and veno-venous connections are photoagulated along with any unpaired artery going to a cotyledon with the corresponding vein (and vice versa) going to the opposite umbilical cord. Vessels on the chorionic plate can be differentiated endoscopically because arteries usually cross over veins and are darker in color due to lower oxygen saturation (Fig. 4).

In a nonrandomized comparison of patients treated by serial amnioreduction at one center and selective laser photocoagulation at another, the overall survival was not statistically significantly different (61% for laser versus 51% for serial amnioreduction).39 However, the survival of at least one twin with laser photoagulation was 79%, whereas survival of at least one twin with serial amnioreduction was only 60% (P < 0.05).39

The Eurofoetus trial conducted by Senat and coworkers40 is thus far the only prospective randomized trial that com-
compares the efficacy and safety of treatment of TTTS with laser therapy versus serial amnioreduction. Women presenting between 15 and 26 weeks gestation with polyhydraminos in the recipient twin and oligohydraminos in the donor twin were allowed to participate. Fifty-two percent of patients were stage I or II, 47% were stage III, and 1% were stage IV. Enrollment was halted after a planned interim analysis revealed a significantly higher likelihood of survival of at least one twin to 28 days of age (76% versus 56%, \( P = 0.009 \)) and to six months of age (76% versus 51%, \( P = 0.002 \)) in the laser group compared with the amnioreduction group. More infants were alive without neurologic abnormalities detected on neuroimaging studies in the laser group as well (52% versus 31%, \( P = 0.003 \)). The overall survival in the laser arm was 57%. This is consistent with previous reports of nonselective fetoscopic laser (53%). This is significantly lower, however, than the survival reported with selective fetoscopic laser (64-68%). Of particular concern is the poor survival which was observed in the amnioreduction arm. The overall survival was only 39%, which is significantly lower than previously reported (60-65%). Antenatal, peripartum, and neonatal care was provided by the referring hospital, and lack of standardization may explain some of these differences. The decreased survival in the amnioreduction group may reflect the higher pregnancy termination rate in the amnioreduction group (16% versus 0% in the laser group). The terminations were requested after the diagnosis of severe fetal complications; it would be instructive to know whether these women were offered cord coagulation as a means of rescuing one baby. Reliable assessment of neurologic outcome is critical when assessing efficacy of treatment for TTTS. Although there was a lower rate of abnormality on neurologic imaging in the laser group (7% versus 17%), there was no long-term neurodevelopmental assessment.

Quintero and coworkers retrospectively examined data from 78 patients treated by serial amnioreduction and 95 patients treated with selective laser photocoagulation with no significant difference in the distribution of patients by stage. Perinatal survival was not significantly different in the laser versus amnioreduction group (64.2% versus 57.7%). However, there was an inverse relationship between fetal survival and stage in the amniocentesis group but not in the laser group. For stage IV disease, there was a significantly lower fetal survival in the amnioreduction group compared with the laser group (20.6% versus 63.6%, \( P = 0.001 \)). This information has important implications for evaluation of treatment options and the development of stage-based treatment protocols. Amnioreduction is easily available, less costly, and less invasive; laser therapy is only available at select institutions and requires specialized training. Although it makes sense to use the former where treatment options give similar results, it would be prudent to move promptly to laser therapy if rigorous studies can prove laser has better short- and long-term outcomes in the setting of advanced disease.

One potential limitation to the success of laser treatment is the presence of deep vascular AV anastomoses that cannot be identified endoscopically. In 1 study, vascular casts of 8 of 15 placenta (53%) demonstrated potentially significant atypical AV anastomoses such that 2 apparently normal cotyledons were actually communicating below the chorionic surface. A second type of atypical AV anastomoses was noted in 11 of the 15 placenta (73%) in which shared cotyledons arise within larger apparently normal cotyledons. One would be able to see these anastomoses as shared cotyledons on endoscopy; ablating these has the potential to destroy some surrounding normal cotyledon which, in the donor’s territory, could contribute to placental insufficiency.

Fetoscopic Cord Coagulation

Some centers have taken the view that the most definitive approach to treating TTTS is selective reduction using fetoscopic cord ligation or coagulation. The rationale for this approach is that cord occlusion and sacrifice of one twin arrests the syndrome, prolongs the gestation, and maximizes the outcome for one twin. We have reserved this approach for instances where advanced TTTS cardiomyopathy has irretrievably compromised the recipient twin with no hope for salvage. In such cases, due to unequal sharing between the donor and recipient, the selective fetoscopic laser procedure may result in death of the donor twin from acute placental insufficiency within hours of the procedure and a recipient twin that dies from progressive TTTS cardiomyopathy. In this situation, fetoscopic cord coagulation may be the best option available. Cord coagulation preserves the vascular communications between the donor twin and the placenta in the recipient twin’s domain. In 16 of 17 such cases, we have observed rebound fetal growth, restoration of amniotic fluid volume, and delivery of neurologically intact donor twin at a mean gestational age of 34 weeks. One survivor had grade I intraventricular hemorrhage, but is otherwise doing well.

Sequential Treatment

Our approach has been to offer sequential therapy tailored to the needs of a given set of twins based on gestational age at
presentation and evidence or progression of hemodynamic compromise as reflected by Doppler velocimetry and echocardiographic changes. In this approach, only those cases in which less invasive approaches have failed are offered the more invasive fetoscopic treatments.

In patients who present later than 24 weeks gestation, we have favored amnioreduction or microseptostomy based on the much more favorable prognosis in these patients. In patients presenting prior to 24 weeks without advanced cardiac changes in the recipient, we have tended toward amnioreduction as an initial therapy. This group of patients presenting earlier in gestation tends to develop signs of hemodynamic progression of TTTS despite normal amniotic fluid dynamics. For this reason, all pregnancies undergo close serial sonographic and echocardiographic surveillance for progression in cardiac and hemodynamic changes which would be indications for selective fetoscopic laser surgery.

**Neurodevelopmental Changes Associated with TTTS**

Whereas much attention has focused on the effect of treatment on survival in TTTS, the neurologic morbidity among survivors is often under-appreciated. Due to the shared placental circulation, if death of one cotwin occurs there is an acute fall in blood pressure causing the placental resistance to fall. This drop in resistance across the placental vascular connections can result in a decrease in the cerebral perfusion pressure and ischemic injury in the brain of the surviving twin. Quintero and coworkers reported endoscopic evidence of feto-fetal hemorrhage from a recipient to donor twin within 3 hours of the spontaneous demise of the donor; these authors noted endoscopic and middle cerebral artery Doppler evidence of paradoxical anemia in the recipient and polycythemia in the donor. Brain injury, however, can occur in TTTS even when both twins survive. In the recipient with both surviving twins, neurologic damage could be related to polycythemia and venous stasis. In the donor, neurologic injury may be due to anemia and hypotension.

The International Amnioreduction Registry tracked 223 women with TTTS diagnosed before 28 weeks gestation who were treated with serial aggressive amnioreduction. Of those infants who survived to 4 weeks of age and underwent clinically indicated cranial ultrasound, 24% of recipient (26/109 scanned) and 25% of donor twins (22/88 scanned) had abnormal findings. Findings included severe intraventricular hemorrhage, ventricular dilation, cerebral echogenic foci, cerebral cysts, and periventricular leukomalacia among other less common lesions. Eighty infants died before reaching 4 weeks of age; how many of these would have had abnormal imaging if cranial ultrasonography had been performed is unknown. Among patients in the TTTS Registry from Australia and New Zealand, most of whom had been treated with amnioreduction, the rate of abnormal cranial sonography was similar at 27.3%. The rate of periventricular leukomalacia in this group was 10.8%, which is particularly important due to the association of this lesion with cerebral palsy. In another small series of patients treated with amnioreduction, the rate of abnormal neonatal cranial ultrasonography was as high as 58%.

Few studies report longer term neurodevelopmental outcome. Importantly, survivors who develop neurologic handicap and mental retardation do not always have abnormal neonatal ultrasonography. Similarly, not all children with abnormal ultrasonograms have clinically significant neurodevelopmental deficits. In one small study that followed TTTS survivors for a mean of 6.2 years (range 4-11 years), the incidence of cerebral palsy was 26% (5/19 infants) in the group treated by serial amnioreduction. All of these children had abnormal mental development in addition to motor deficits. Of note, three of the five children had normal neonatal head ultrasounds. In the combined cohort of children whose mothers had been treated with amnioreduction or conservative treatment, 22% (5/23) of the children without cerebral palsy or abnormal mental development had mild speech delay and required special education. One limitation to this and other studies is the lack of a comparable conservatively treated cohort group. Given the improved survival of TTTS babies with amnioreduction and other treatment modalities, however, it is unlikely that we will ever have such a cohort for comparison.

Studying infants from pregnancies complicated by TTTS and treated with amnioreduction, Mari and coworkers detected a rate of cerebral palsy of 4.7% (2 of 42 infants) in those children who survived to more than 24 months of age. One reason for the lower incidence of cerebral palsy than in the study by Lopriore and coworkers may be related to the latter study group having more severe disease, given that all the patients were diagnosed before 28 weeks versus up to 33 weeks in Mari and coworkers’ study. Of note, Mari and coworkers’ study also detected nine survivors with mild speech and/or motor delay.

Dickinson and coworkers studied the long-term neurologic outcome of 52 children from 31 TTTS pregnancies who survived to more than 18 months; a majority of the mothers had been treated with amnioreduction. The comparison was a regional cohort of term and preterm infants, with the majority having been born very preterm. In addition, the TTTS babies were compared with matched singleton and twin control groups. The mean IQ of survivors with TTTS was significantly lower than the comparison cohort, mainly due to the decreased IQ of 13 points in those children born less than 33 weeks. There was no difference in rate of cerebral palsy (5.8% TTTS versus 4.9% very preterm twins versus 3.3% very preterm singletons) or behavioral tests in the TTTS survivors. This was a small study, however, and not sufficiently powered to demonstrate differences in cerebral palsy. Still, these researchers appropriately raise the issue that studies evaluating long-term neurologic outcome in TTTS need to consider that most TTTS pregnancies are delivered very preterm as well as the fact that twins in general are more likely to be neurologically compromised.

Even fewer studies have examined the long-term outcome of survivors of TTTS treated with intrauterine laser photocoagulation therapy. Banek and coworkers reported that, in 89...
such children, 78% showed normal development at a median age of 22 months.\textsuperscript{30} Eleven percent had minor neurologic abnormalities, including strabismus, mildly delayed motor development, or mildly abnormal speech. The remaining 11% suffered significant neurologic deficiencies including cerebral palsy, hemiparesis, and spastic quadriplegia. Of note, significantly more children in the neurologically impaired groups were born very preterm. Also of importance is that of the most severely affected group had abnormal brain scans before laser treatment. The findings of this study are consistent with those of Sutcliffe and coworkers, who reported a cerebral palsy rate of 9% in children after in utero treatment with laser therapy for TTTS.\textsuperscript{51}

\textbf{Conclusion}

The recently reported Eurofoetus Trial,\textsuperscript{40} the only prospective randomized clinical trial published comparing serial amnioreduction to laser photocoagulation for the treatment of TTTS, suggests that laser therapy improves survival and neurologic outcome at 6 months of life. However, questions still remain in regards to which patients will benefit most from laser as well as how amnioreduction and laser therapy affect short- and long-term cardiac and neurodevelopmental outcomes. It is unfortunate that opinions regarding the best treatment for TTTS often go further than the existing data support. An example is the assertions by Roby et al.\textsuperscript{32} that there is no place for stage based treatment in this disease and that amnioreduction is illogical when the diagnostic criteria for TTTS are met even though they acknowledge that up to 20% of cases will respond to amnioreduction. We would suggest, that for early stage TTTS, a trial of amnioreduction is an option, as long as it is combined with careful serial echocardiographic surveillance to detect subtle signs of progression which would indicate treatment failure and the need to go on to fetoscopic laser. We believe that there is insufficient data at present to conclude that laser treatment is across the board the best first line treatment for TTTS.

Crombleholme and coworkers conducted a National Institutes of Health (NIH) sponsored multicenter prospective randomized controlled trial comparing aggressive amnioreduction with selective fetoscopic laser photocoagulation for severe TTTS before 22 weeks gestation. Only patients who failed to respond to initial amnioreduction qualified for the NIH sponsored trial. Recently, randomization was halted by the investigators when it became apparent that recruitment of 150 patients was unrealistic. The availability of fetoscopic laser at multiple centers outside the trial, reluctance to submit to randomization, and the impression among lay public and obstetricians alike that fetoscopic laser therapy may be superior contributed to poor recruitment. Entry into the trial was closed after 42 patients were randomized, but follow-up of all patients treated in the trial will continue until their neurodevelopmental assessment at 18 to 22 months in the NICHD Neonatal Network. The survival data, blinded sonographic data, echocardiographic data, MRI data, placental pathology, and neonatal morbidity data of all patients randomized in the trial and in the observation arm of the study are currently being analyzed. Although the trial was not completed, publication of important data is anticipated this year. The NICHD is currently considering conversion of this trial to a prospective cohort study focusing on a comprehensive neurodevelopmental outcome.

So where do we go from here? A thoughtful approach to the management of TTTS requires consideration of every aspect of the presentation, including gestational age, stage, Doppler findings, echocardiographic findings, concomitant placental insufficiency, and maternal risk factors. Until we have an effective medical therapy for TTTS, a judicious application of invasive procedures should be employed to optimize risk/benefit ratios for the mother and fetuses.

\textbf{References}