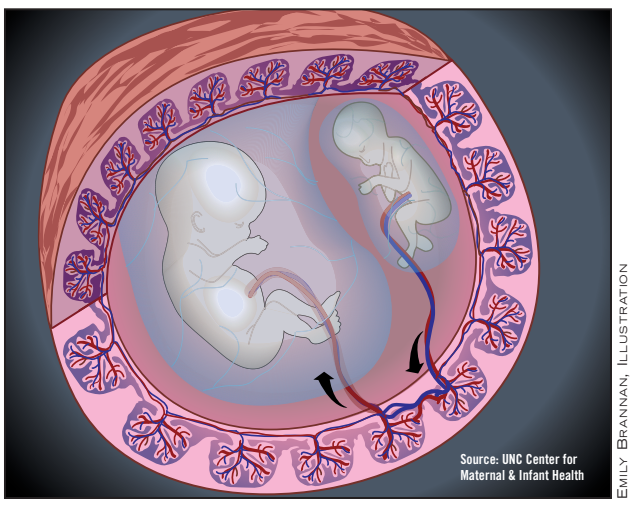
Master Class

Twin-to-Twin Transfusion Syndrome

E. ALBERT REECE, M.D., PH.D., M.B.A.

Despite the advances that have occurred in obstetrics over the years, who would have imagined that fetal surgery would be a viable therapeutic approach today? Well, indeed, this is where we are in the history of obstetrics.

Fetal evaluation has been conducted over the years using a variety of noninvasive techniques, most notably electronic fetal monitoring. More invasive techniques, such as amniocentesis, have also been used with very good success and with relatively low risk to mother and fetus. Certain conditions, however, cannot be addressed with noninvasive or slightly invasive approaches, but rather require either open surgery or more involved surgery of a minimally invasive nature.



Emily Brannan, Illustration

One of these conditions is twin-to-twin transfusion syndrome, in which one of the fetuses may succumb during intrauterine life. Over the years, amniocentesis has been used with limited success. However, newer techniques involving endoscopic laser therapy are being introduced with improved outcomes. In this Master Class, we review both modalities in the management of these patients, with careful attention to advances in fetal laser therapy.

We are pleased to introduce Dr. Ahmet A. Baschat, of the department of obstetrics, gynecology, and reproductive sciences at the University of Maryland School of Medicine, Baltimore, as our guest professor this month. Dr. Baschat is considered a national expert in fetal therapy, including laser and other intrauterine surgical procedures.

Dr. Reece, who specializes in maternal-fetal medicine, is vice president for medical affairs, University of Maryland, as well as the John Z. and Akiko K. Bowers Distinguished Professor and dean of the School of Medicine in Baltimore. He is the medical editor of this column.

From Amniocentesis to Selective Laser Coagulation

BY AHMET A. BASCHAT, M.D.

Compared with just a decade ago, twin-to-twin transfusion syndrome (TTTS) is a much more understood and treatable condition.

Our understanding of its causes and effects has expanded rapidly. We now know that a spectrum of disease can result when unequal placental sharing and/or unequal blood-volume sharing occurs in monochorionic pregnancies, for instance, and that a significant imbalance in blood-flow exchange between twins' circulations is the primary contributor to the development of TTTS. On the other hand, our knowledge is still quite simplistic: We have much to learn about the pathophysiology and the natural history and progression of the syndrome.

The observations we have made, however, are significant enough to justify the treatment of severe TTTS—especially given the advances in ultrasound assessment, which allow us to detect the syndrome early, as well as the dramatic improvements in technology for minimally invasive intrauterine therapy that have come about in recent years.

Endoscopic laser ablation (or laser coagulation) of placental anastomoses has been shown in numerous studies—including a multicenter, randomized trial comparing it with serial amnioreduction—to be an effective treatment for TTTS, and a preferable first-line approach for severe TTTS that is diagnosed before 26 weeks' gestation.

Because intrauterine procedures require a high level of expertise and infrastructure, it is likely that the management of these conditions will remain regionalized. Improved referral patterns and support for families, however, will promote the development of a nationwide network of designated centers, making such therapy more accessible.

Pathophysiology and Consequences

Identical twins are monochorionic, and these pregnancies present several potential risks: the risk that one baby will not get its fair share of the placenta, the risk that blood volume will be shared unequally, and an overall risk of vascular instability in each twin.

When the predominant issue in an identical twin pregnancy is unequal placental sharing, the growth of one baby becomes restricted and the other baby grows normally, resulting in a condition called selective intrauterine growth restriction (selective IUGR).

The other main issue—that of unequal blood-volume sharing—is what fuels TTTS. In uncomplicated pregnancies, blood is exchanged equally through the vascular anastomoses that characterize all monochorionic pregnancies. In complicated pregnancies, however, the exchange is unbalanced, and blood is shared in one direction without adequate return.

Arteries emanating from the placental cord insertion of one twin, for instance, can drain into a vein returning to the other twin. Such arteriovenous anastomoses are in the substance of the placenta and act as one-way valves for blood flow. If the amount of blood flow in one direction is not balanced by enough flow in the opposite direction—that is, if the magnitude of blood flow through unidirectional arteriovenous anastomoses is not compensated by vascular channels that permit flow in the opposite direction—then an imbalance develops that is potentially harmful to both babies.

In TTTS, which develops in about 15% of monochorionic pregnancies, the imbalance progresses to the extent that one twin becomes a "donor" of blood volume and the other becomes the "recipient" twin.

The donor twin moves blood across the anastomoses to the placenta and to the recipient twin, and does not receive an equal amount in return. A decline in blood volume leads to decreased urine output to the extent that, eventually, bladder filling in the donor twin virtually ceases. Under these circumstances, oligohydramnios may progress to anhydramnios, and the twin may become "stuck" in an essentially empty amniotic sac.

The recipient twin, in the meantime, receives an excess amount of venous blood volume. The increase in intravascular blood volume drives an increase of filtration in the kidneys, which results in excess urination. The increased urinary frequency, which may even result in constant bladder filling, leads to polyhydramnios.

When the sac of the recipient twin becomes distended by amniotic fluid, and the donor twin is no longer producing urine, the membrane between the twins may become wrapped so tightly around the donor twin that it is barely visible on ultrasound (See image below.) When the donor twin is "stuck" to the uterine wall in such a way, the ultrasound appearance resembles that of identical twins with one amniotic cavity (monoamniotic twins).

Courtesy Dr. Ahmet A. Baschat

The membrane is seen folding around the donor who becomes a "stuck twin."

Untreated TTTS has serious consequences for each twin and for the whole pregnancy. First, the resultant polyhydramnios can stimulate preterm labor because of uterine distention. Second, abnormalities in blood volume can lead to cardiac problems and cardiovascular compromise for the babies, most often for the recipient twin. The excess blood cells and volume overload that this twin faces can lead to cardiac failure and hydrops.

The donor twin, meanwhile, is at risk for abnormalities and long-term effects resulting from compression, failing placental function, malnutrition, and hypovolemia.

If one baby dies in utero, the placental anastomoses that cause TTTS in the first place—that is, the open vessel connections that exist between the twins—carry an additional danger. In artery-to-artery and vein-to-vein anastomoses, the direction of blood flow is determined by the difference in blood pressure on either side. If one twin dies, the resultant drop in blood pressure causes the surviving twin to lose a large amount of blood volume across the connecting vessels and into the dying twin. This puts the surviving twin at risk of hemorrhagic shock and a heart attack or stroke.

It is estimated that the risk for white-matter injury in the surviving twin at the time of birth may be as high as 50% following such an intrauterine event. The fates of both twins are thus essentially linked to each other through their placental anastomoses.

Although exact contributors still need to be determined, it is well established that, compared with nonidentical twins, identical twins have a higher incidence of cerebral palsy and other anomalies, and a higher rate of developmental delay at 2 years. Because the development of TTTS is one well-recognized contributor to these statistics, perinatal interventions in monochorionic pregnancies have primarily focused on its treatment.

Evolution of Management

It's most interesting to look at the evolution of management from a historical perspective. When TTTS was clinically recognized, before the days of multivessel Doppler assessment, patients would most often present with a massively distended uterus and preterm labor.

The natural management approach was amnioreduction, which involved the removal of large volumes of amniotic fluid in an effort to relieve uterine distention and prevent preterm delivery. Physicians recognized the need for serial amniore-

Continued on following page

Continued from previous page

duction, as the procedure leaves anastomoses open and does nothing to address the underlying problem.

This approach was often satisfactory when it was started at 26-27 weeks' gestation because chances to prolong pregnancy to 32-34 weeks with repeated drainage were reasonable. The patients who presented with massive polyhydramnios and severe TTTS at 20 weeks, however, were another story. Their outcomes with serial amnioreduction were poor; in fact, many physicians would offer pregnancy termination under these circumstances.

In the late 1990s several groups began to address the underlying problem by closing the problem vessels. Dr. Julian De Lia, at that time practicing in Utah, was the first to describe fetoscopic laser ablation of placental anastomoses. He and the team of Prof. Kypros Nicolaides in Europe used a nonselective technique that involved ablating blood vessels and the placental mass along a dividing line between the twins—essentially making the placenta functionally dichorionic—and then draining the amniotic fluid.

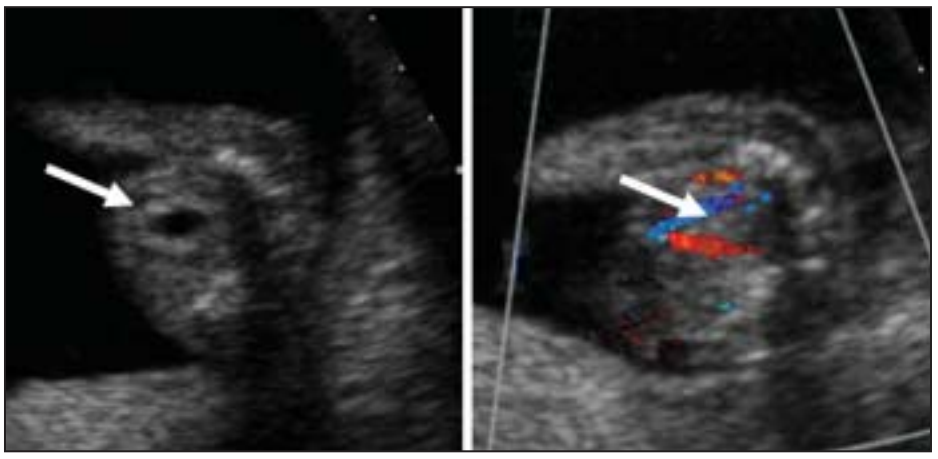
Developmental research on the equipment and modification of the technique proceeded. In 1999, Dr. Rubén A. Quintero in Florida published a five-stage classification system for the progression of TTTS, with stages I and II characterized primarily by imbalances in blood volume, stages III and IV signified by cardiovascular compromise, and stage V signified by the death of one or both twins.

This staging system marked a significant step in the management of TTTS because it established a unified diagnostic approach that was based on prenatal criteria. Until this point, the definitions of TTTS were based on an extrapolation of pediatric diagnostic criteria that were used at birth. The application of Dr. Quintero's staging system allowed a more objective comparison of treatment strategies, but required familiarity with arterial and venous Doppler techniques.

Dr. Quintero also argued that a nonselective approach with the laser—one that coagulates vessels that do not contribute to TTTS, as well as those that do—can rob one or both twins of placental territory that is vital for their survival. He developed a selective laser technique that involves identification and coagulation of the vessels that pass from one twin to the other, leaving normal placental territory and noncontributing vessels untouched.

In the meantime, the Eurofetus research consortium had formed in Europe, and had begun designing a trial to compare laser therapy with amnioreduction, with one of their premises being that laser therapy would most benefit twin pregnancies that are complicated by TTTS before 26 weeks' gestation. Perinatal mortality for untreated severe TTTS, they knew, was as high as 90%, with significant handicap in the survivors.

Results of the multicenter randomized study were published in 2004 (N. Engl. J. Med. 2004;351:136-44). Complication rates were basically comparable (approximately 9% in each arm), but the rates of survival of at least one twin at 28 days and at 6 months of age were significantly better in the group that underwent selective laser coagulation than in the amnioreduction group (76% vs. 56% at 28 days, and 76% vs. 51% at 6 months).

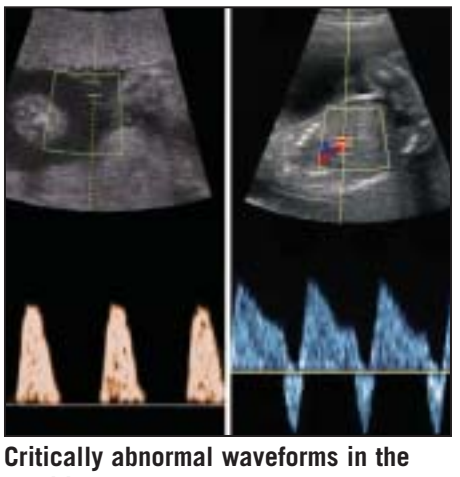


When bladder filling of the donor can no longer be demonstrated, progression to stage 2 TTTS is diagnosed. (Left arrow, small bladder; right arrow, empty bladder.)

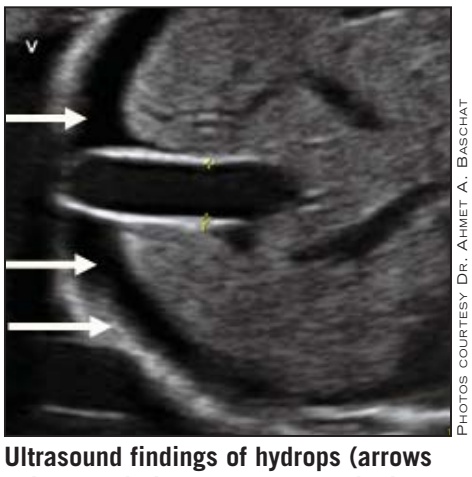
The differences existed in both the early and later stages of TTTS, although fetuses in the Quintero stages I or II had better outcomes than did those with higher stages in both treatment groups. (The study had been concluded early, after 72 women had been assigned to the laser group and 70 to the amnioreduction group, when an interim analysis demonstrated significant benefits.)

Gestational ages at the time of delivery were also significantly different: Patients in the laser group delivered, on average, at 33 weeks, whereas those in the amnioreduction group delivered at 29 weeks.

An intermediate-term look at neurologic outcomes favored laser surgery as well: At 6 months of age, infants in the laser group were more likely than those in the amnioreduction group to be free of neurologic deficits (52% vs. 31%, respectively).



Critically abnormal waveforms in the umbilical artery (left) and ductus venosus (right) indicate stage 3 TTTS.



Ultrasound findings of hydrops (arrows point to fluid in fetal abdomen) indicate stage 4 TTTS.

PHOTOS COURTESY DR. AHMET A. BASCHAT

At the center for advanced fetal care at the University of Maryland, Baltimore, which has served for almost a decade as a referral resource for minimally invasive fetal therapy, I have applied the identical technique utilized in the Eurofetus trial using a selective approach. Our treatment results have consistently mirrored the published statistics.

Our research, which we presented at the annual meeting of the Society for Maternal-Fetal Medicine, confirms that successful laser ablation corrects the abnormal blood volume distribution. This effect is first apparent for the donor twin and clinically presents with the reappearance of bladder filling, often on the day after the procedure.

Urination gradually normalizes in the recipient twin, typically over 1-2 weeks after the procedure. The mother feels better immediately after the procedure and continues to improve as fetal status normalizes.

Longer-term follow-up of neurologic abnormalities in the Eurofetus trial is underway. For now, however, an analysis of a series of patients who received intrauterine laser treatment for TTTS has shown that 78% of 89 surviving children had a normal neurodevelopmental status at about 2 years of age, whereas 11% had minor neurologic deficiencies and 11% had major neurologic deficits (Am. J. Obstet. Gynecol. 2003;188:876-80).

Although comparisons of patients managed in the randomized trial are pending, these rates of neurologic handicap compare favorably with those seen after amnioreduction.

Two large series indicate that severe TTTS is associated with poor neurodevelopment, and that up to 27% of survivors may have abnormal brain ultrasounds at the time of delivery. It is therefore widely accepted that the neuroprotective benefit of laser therapy is most marked in early onset TTTS (prior to 26 weeks), and that the difference in outcomes is attributable to lower rates of preterm delivery and prematurity-associated complications as well as to the elimination of the risks of ongoing TTTS.

Moving Into the Future

In Europe, the randomized trial basically brought the controversy over optimal treatment for TTTS to a close. In the United States, there are some who still lean toward performing an initial amnioreduction and moving on to laser surgery if necessary.

There are disadvantages to such an approach. An initial amnioreduction removes the amniotic fluid pocket that is necessary to successfully maneuver the fetoscope. Decompression of the placenta not only unpredictably affects shunt dynamics but also can create placental "valleys" that can impair visualization of anastomoses. Potential bleeding from the procedure, as well as advancing gestational age until a suitable fluid pocket has reestablished, can also make the fluid cloudier.

Investigators who have looked at the factors that influence outcomes of selective laser coagulation of placental anastomoses have reported that those who do poorly have more advanced TTTS; have shorter cervical length, and thus a higher incidence of preterm labor; have a history of prior amnioreduction; and have technically difficult laser procedures with poor visualization of anastomoses as contributing factors.

Amnioreduction still has a role, however, particularly for patients who present with TTTS beyond 26 weeks' gestation. These patients are not candidates for laser therapy because the efficacy and safety of the procedure at this gestational age has not been studied.

Even with the improved outcomes, the therapies are still not optimal, and our knowledge of TTTS is still full of gaps and differences in opinion. Some experts believe, for instance, that with selective laser therapy there is a risk of recurring TTTS—that is, as visible anastomoses are closed, intravascular pressures are diverted to very small vessels that are barely visible at the time of the laser procedure. Over time, it is believed, these vessels may expand and therefore become hemodynamically relevant contributors to recurring TTTS.

At this time, I believe it's important to keep an open mind after presumably successful laser therapy, and to follow the fetuses closely after surgery for TTTS. Continued evaluation of bladder filling, amniotic fluid volumes, and placental and venous Doppler studies may be necessary over extended periods of time.

It is also important to inform neonatologists and referring obstetricians of the special circumstances of these babies, who behave very differently—both in the NICU and beyond—than do other babies of similar size or with other underlying conditions.

Babies who matured in utero as TTTS "recipients" are chronically hypervolemic and will not respond well, for instance, to dopamine given in the NICU as the primary agent to boost blood pressure. Careful attention to fluid balance is essential to prevent neonatal complications under these circumstances.

Fortunately, technologic advances in equipment are making intrauterine therapy much more minimally invasive. The development of fetoscopes with a 2-mm lens offers superior visual resolution and facilitates a minimally invasive approach. Digital camera technology also enhances the visualization of the smallest blood vessels. Steerable and angulated optical devices tackle the problems of anterior placenta. The smaller caliber of the entry site also decreases the risk for complications.

Today, laser surgery is typically performed under local anesthesia that requires minimal hospitalization with only perioperative tocolysis. The average length of patient stay is 1 day at the University of Maryland Medical Center.

The initiation of the North American Fetal Therapy Network (NAFTNet), a research consortium, is a significant development in the United States. ■