

TTTS: What do we know?

by Sharon Withers

Ask any parent—or any obstetrician, for that matter—who has faced twin-to-twin transfusion syndrome what makes TTTS so tough to treat and they will tell you that one thing is how little we know.

“There are so many questions we don’t have answers for; as a clinician it is very frustrating for me,” said Dr. Timothy Crombleholme, director of the National Institutes of Health-funded Twin-Twin Transfusion Trial and of the Fetal Care Center of Cincinnati at Cincinnati Children’s Hospital. “This field [study of TTTS] doesn’t lend itself to concrete answers. Like a lot of things in life, it is not black or white, but a big swath of gray.”

We do know that TTTS is a disease of the placenta, while the twins themselves are normal. Unborn babies, however, get their oxygen and nutrition from the placenta, and any disease of the placenta affects their well being.

We know that it is critical to catch the disease early. “Can we pick up the ones who will suffer TTTS earlier?” asked pediatric and fetal surgeon Dr. Francois Luks of the Brown Fetal Medicine Program and lead investigator of the Eurofoetus study at Rhode Island Hospital’s pediatric division, Hasbro Children’s Hospital. “We can stop the syndrome but we can’t turn back the clock. One or both fetuses may already have suffered from the condition.”

We also know what happens in a TTTS pregnancy. And we know several treatments that may help.

But we don’t know why 15% or so of monochorionic (MC) pregnancies develop problems with vascular communication when all MC pregnancies share placental blood vessels. Or why TTTS can show up at any point in a pregnancy, although the severe cases usually surface before 26 weeks. Dr. Luks believes that when the syndrome appears later in pregnancy, it was latent but we don’t know what makes it flip.

And we are not always certain which treatment is best for which patient. Two studies examining the treatment of TTTS may provide some answers.

The Eurofoetus study

Performing laser surgery in utero on identical twins suffering from twin-to-twin transfusion syndrome leads to significantly better outcomes than traditional treatment, according to a study conducted by physicians from Rhode Island Hospital, Women and Infants’ Hospital and Brown

Medical School. The results of the study, led by investigators in France and Belgium, appeared in the July 8 issue of the *New England Journal of Medicine*.

The Fetal Treatment Program, a joint venture of Rhode Island Hospital’s Hasbro Children’s Hospital, Women and Infants’ Hospital and Brown Medical School, is the only site in North America that performed fetal surgery as part of the study. Principal investigators for Rhode Island site were Stephen R. Carr, M.D., Women and Infants Hospital, and Dr. Luks.

But we don’t know why 15% or so of monochorionic (MC) pregnancies develop problems with vascular communication when all MC pregnancies share placental blood vessels.

This is the first prospective randomized trial to show an advantage of fetal surgery. A computer randomly assigned 142 pregnant women with severe TTTS before 26 weeks gestation to laser surgery or amnioreduction treatment. In this study, fetoscopic laser coagulation improved survival chances by 25% and reduced the risks of neurological problems by half, compared with drainage of amniotic fluid alone.

One or both babies survived in only half the mothers who were treated with amniodrainage only. Babies were also born very prematurely, about 29 weeks on average. While this is certainly better than without any therapy at all, it leaves room for improvement.

On the other hand, 76% of pregnancies treated with fetoscopic surgery ended up with one or two babies; this is an improvement of 25% when compared with amniodrainage alone. In addition, the study reported that laser therapy reduced the occurrence of serious brain damage by the age of 6 months from 10.3% to 4.5%. This may be attributable in part to the later gestational age at birth (babies in the laser group were born at a mean of 33 weeks) or a difference in imaging studies done at 6 months. (Studies have shown that an infant who shows significant abnormalities on head ultrasounds at 6 months can still have normal neurodevelopmental outcome. Conversely, an infant who has a normal imaging

study can be neurologically impaired.)

The results of this study suggest that patients diagnosed with severe TTTS should be offered the opportunity to have laser intervention. Since the study ended in 2003, the surgery is now offered to any patients who qualify at Rhode Island Hospital and Women and Infants' Hospital. The results appear to be comparable to, or better than, the trial results.

The Twin-Twin Transfusion Trial

The purpose of the ongoing NIH-funded Twin-Twin Transfusion Trial is not to say that one treatment is always superior to another, but to determine under what circumstances which therapy is best.

"We take the sickest patients we can get," Dr. Crombleholme said. With blinded review of tests that patients undergo, doctors can chart the differences in responses to a specific treatment.

The trial is a large study that randomizes women pregnant with TTTS babies into either an amnioreduction or a laser surgery group. Thirteen medical centers in the United States participate in the study, but only three—Cincinnati Children's Hospital Fetal Care Center of Cincinnati, Children's Hospital of Philadelphia and University of California at San Francisco—perform the surgery. All fetoscopic recordings are compared with placentas that undergo pathology studies, correlating fetoscopic surgery with pathologic findings for the first time ever.

Furthermore, the study follows babies for three years, monitoring neurodevelopment and evaluating the long-term outcome of the treatments. "It is far more complex than imaging studies at birth or in the first six months," Dr. Crombleholme explained, adding that the earliest age at which neurodevelopment measurements are reliable is 18 to 22 months. The comprehensive battery of tests and the follow-up are necessary to unlock the mysteries of this very complex disease.

"Even if you are a laser advocate, there is so much we still need to know. We don't know why a certain subset respond to laser and another to amnioreduction," Dr. Crombleholme said. "The only way to tease that out is with a large multi-center clinical trial."

To illustrate the purpose of the trial, Dr. Crombleholme told of a woman who was randomized into the amnioreduction arm of the trial, but was declared a treatment failure. When the amnioreduction did not work, she was given her choice of treatments. After evaluating her case, doctors were certain she would lose one twin if she had laser surgery. In her case laser amniotic septostomy (perforating the interfetal membrane septum) equalized the fluid volumes and saved both twins.

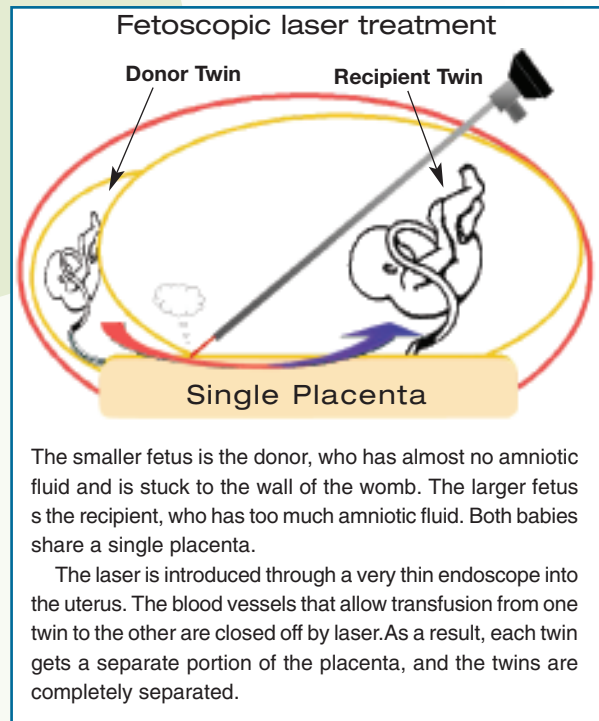


ILLUSTRATION BY FRANCOIS LUKS, M.D.

This case also illustrates how randomization works. "Randomization does not take any options off the table. You are not locked into a therapy that doesn't work," Dr. Crombleholme explained. "We have a mechanism to declare a patient a treatment failure." If a patient in the trial is declared a treatment failure, she receives the therapy that is best suited to her babies. "We do everything we can to optimize a mother and babies' outcome."

The future

While these studies are investigating the treatments, much work remains. "Some researchers around the world have great mathematical models of TTTS," Dr. Luks said. "Imaging will get better," he continued. "We will be able to see the individual vessels on imaging. We have a little further to go to see individual vessels and flow."

Dr. Luks also offers this advice to mothers: "It is tragic how so many people are told, 'There is nothing we can do for you.' Don't take 'no' for an answer."

The Twin-Twin Transfusion Trial will run for another two to three years. "Most monochorionic placentas have the communications necessary for TTTS to develop, but communications don't cause the disease. Something triggers it," Dr. Crombleholme said. Through the comprehensive Twin-Twin Transfusion Trial he hopes to not only establish the best treatment for a given situation, but also to find that trigger. ♥