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THE FRONT LINE TWIN-TWIN TRANSFUSION SYNDROME (TTTS)

BY ROBERT CARPENTER, MD
Clinical Associate Professor, Obstetrics–Gynecology

Twin-twin transfusion syndrome (TTTS) occurs in 5 percent to 10 percent of monochorionic, diamniotic identical twins (or rarely, in higher order identical pregnancies). TTTS usually is first observed between 10 and 24 weeks of gestation and may vary in severity at different periods throughout the pregnancy. The condition is characterized by a pregnancy in which one fetus (donor) is smaller and is “stuck” inside the amnion, which is devoid of amniotic fluid, while the transfused fetus (recipient) exists in a large volume of amniotic fluid.

The polyhydramnios within the recipient sac is one of the most problematic issues for the obstetrical team. Commonly, the volume of fluid is measured in liters and often is associated with a tense maternal abdomen and a very uncomfortable mother. Complications of untreated polyhydramnios can be preterm labor and premature rupture of membranes; occasionally acute placental abruptions may develop. Traditional treatment has consisted solely of repetitive decompression amniocentesis where volumes of amniotic fluid (1 to 3 liters) may be removed as often as every several days.

Historically, TTTS was considered to have developed from an abnormal anastomosis of a donor artery with a recipient vein and increased blood flow from the donor fetus to the recipient fetus. However, studies in which labeled maternal

— See TTTS, page 2

BREAKING NEWS

Bhagavatula Moorthy, PhD, will serve as a member of the Xenobiotic and Nutrient Disposition and Action Study Section, Center for Scientific Review, at the National Institutes of Health (NIH) for a term that ends June 30, 2009.

“Membership on a study section represents a major commitment and is a unique opportunity to contribute to the national biomedical research effort,” said Toni Scarpa, MD, PhD, Director of the NIH Center for Scientific Review.



Members are selected on the basis of their demonstrated competence and achievement in their scientific discipline as evidenced by the quality of research accomplishments, publications in scientific journals, and other significant scientific activities, achievements, and honors.

“Service on a study section also requires mature judgment and objectivity as well as the ability to work effectively in a group,” Dr. Scarpa said, “qualities we believe Dr. Moorthy will bring to this important task.”

EDITOR'S CORNER

Advances in Fetal-Maternal Medicine

BY MICHAEL E. SPEER, MD
Professor of Pediatrics–Neonatology

Not all that long ago, the only clinical tools to assess a fetus were measuring uterine growth and auscultating fetal heart tones. Neither method could be accomplished before the second trimester. Now, however, potential fetal intervention runs the gamut from chorionic villus sampling to fetal surgery.

In this issue, Dr. Carpenter notes the advances made in twin-twin transfusion syndrome through carefully conducted clinical trials. Using fetal ultrasound, physicians are able to identify the presence of abnormal fetal development, including cardiac defects, early in gestation. Early pregnancy ultrasound also has helped to

- elucidate the causes of fetal hydrops,
- determine gestational age, and
- ascertain the presence of probable chromosomal anomalies.

Using a fixed detection rate of 85% for Trisomy 21 and a combination of maternal age, nuchal translucency, and biochemical markers, the false positive rate can be as low as 1% for the detection of this disorder.

Use of fetal transfusion for anemia is commonplace.

Stem cell therapy is in its infancy, as is fetal surgery.

The role of the placenta in contributing to developmental effects and fetotoxicology is enjoying renewed interest.

Additionally, over the next several years we will embark upon a new journey — functional genomics and proteomics. This is a systematic and comprehensive approach to the identification and description of the processes and pathways involved in physiological states. Using this technology, possible biomarkers of pre-eclampsia, preterm labor, and gestational trophoblastic diseases have been discovered.

The combination of advances in fetal-maternal medicine coupled with those in neonatology will improve not only fetal health but neonatal outcomes as well.

TTTS (continued from page 1)

red cells were injected into the donor umbilical vein have not demonstrated significant transfer of those cells into the recipient fetus several hours later, as determined by fetal blood sampling.

Recent findings have suggested that the renin-angiotensin system, human brain natriuretic peptide (hBNP), and endothelin-1 may cause a hypertensive vasculopathy, causing damage to the donor kidneys, which disturbs the regulation of amniotic fluid volumes and urine formation.

Other explanations for the pathophysiology of TTTS concern critical pressures (hemodynamic and/or hydrostatic) rather than the pure “transfusion” volume exchanged between donor and recipient. Those pressures may represent both the abnormal vascular communication present in many identical twins and the hydrostatic forces that apply pressure to the chorionic plate and subjacent vessels by the membranes of the expanded polyhydramniotic recipient sac against the placental or chorionic plate of the donor. In the last 20 years, multiple centers reported resolution of the acute changes normally noted in TTTS after a decompression amniocentesis. Amniotic fluid was subsequently seen in the donor sac with a free-floating amnion between the two fetuses. Following this serendipitous event associated with decompression amniocentesis, the donor twin often demonstrated evidence of improved renal function with urine production and subsequent maintenance of amniotic fluid volume.

A protracted study was performed using septostomy to introduce holes within the intervening membrane either with or separate from decompression amniocentesis. While this procedure was shown to help in some patients, it does not help in all circumstances.

Using laser photocoagulation, Dr. Julian E. De Lia coagulated the traversing vessels found at the interface of the compressed membrane within the polyhydramniotic recipient sac. In some cases, the TTTS process stopped; however, a significant loss of one or both fetuses continued. The Eurofetus Trial demonstrated efficacy of the laser method with improved survival: 76% of treated fetuses compared with 56% of the serial amniocentesis treated group. Additionally, fewer neurological abnormalities (48%) were present in the laser treated group compared with those seen in the amniocentesis treated group (79%) by neuroimaging techniques.

Because of the unacceptably high mortality and morbidity in TTTS, some form of therapy is indicated. Even with treatment, however, the outcome often is death of one or both of the fetuses. If only one fetus dies, cerebral embolic phenomenon may occur in the surviving co-twin (often the donor) with significant destruction of cerebral and other tissues. On the other hand, many recipients die of congestive heart failure, a component part of the increased plasma volume present in that twin.

Most randomized controlled trials have not had the power to definitively state which treatment option is the best to improve fetal outcome (decompression amniocentesis, obliteration by laser photocoagulation of traversing vessels, or septostomy). The most important issues in TTTS are recognizing the disease process, close follow-up, and intensive education of the parents concerning different treatment modalities. For many patients, admission to a randomized therapeutic trial to allow scientific evaluation to determine the best method of treatment is appropriate. Since the gestational age of patients at delivery is 28 to 29 weeks in many patients experiencing TTTS, randomized experimental therapy may provide information that might benefit others who develop this syndrome.

JOURNAL REVIEW

BY MICHAEL E. SPEER, MD
Professor of Pediatrics–Neonatology



Elliott JP, Miller HS, Coleman S, et al. A randomized multicenter study to determine the efficacy of activity restriction for preterm labor management in patients testing negative for fetal fibronectin. *J Perinatol* 2005;25:626–630.

Introduction: Bed rest or other activity restriction has not been demonstrated to prolong gestation and may lead to complications such as fetal growth restriction, maternal bone mineral loss, or maternal thromboembolic disease. Nonetheless, more than 700,000 women per year are prescribed bed rest. The presence of fetal fibronectin (fFN) is identified with an increased risk of preterm delivery; the converse is not necessarily true. This study examined the impact of activity restriction on the preterm birth rate among women experiencing preterm labor with a negative fFN.

Methods: Entry criteria were successful tocolysis with magnesium sulfate, a negative fFN, >14 years of age, intact membranes, documented uterine contractions >6 hours at admission, 23–33 6/7 weeks' gestation, and <3 cm cervical dilation at the time of fFN testing. Exclusion criteria were conditions that required immediate delivery, prolonged hospitalization, or major fetal malformations. After randomization, all patients were treated with restricted activity. Following discharge, the treatment group (AR) continued restricted activity (bed rest with bathroom and showering privileges plus travel from home to physician's office); the control group (NAR) was allowed to return to normal daily activities. All patients received information about the signs and symptoms of preterm labor.

Treatment failures were considered to be (1) recurrent preterm labor, defined as >6 contractions per hour and (2) cervical advancement of >1 cm or >25% effacement from the previous exam. Patients with treatment failures received identical treatment as at study entry. If stabilization occurred, subjects resumed their original group assignment. The study was discontinued when the pregnancy reached 37 weeks' gestation or delivery occurred. The primary study endpoint was the prolongation of pregnancy.

Results: A total of 882 women were screened; 246 were eligible and 73 were enrolled (36 into the AR group and 37 into the NAR group). There were no differences in regard to either neonatal or maternal outcomes. Prolongation of pregnancy in both groups averaged 43.5 days. Preterm delivery occurred in 44.4% of the AR group and in 35.1% of the NAR group ($P = 0.478$). Overall, delivery occurred within 7 days in 3% and within 14 days in 9.6%.

Discussion: The sample size calculation for pregnancy prolongation had determined that 1625 patients should have been enrolled to find a difference of 7 ± 20 days between the 2 groups. Thus, the finding of no pregnancy prolongation with AR, while consistent with other reported studies, is not helpful in clarifying either the positive or negative value of this treatment method. What is of interest was the finding that the previously reported negative predictive value of a negative fFN may not be valid, particularly in certain high-risk women. Previous reports suggested that women with a negative fFN were at minimal risk of delivery within 7 days (<1%), within 14 days (<3%) or before 37 weeks' gestation (<10–12%), percentages that are far less than those reported from this study. Further large-scale trials may be warranted to re-examine the value of a negative fFN in predicting the incidence of early and overall preterm delivery.

Contact Us

The Baylor College of Medicine
Section of Neonatology has staff
at hospitals in Houston's
Texas Medical Center
and in the local community.

*To request a neonatal consultation
at any of our locations, call*

**1.877.NEONATE
(1.877.636.6283)**

Texas Medical Center locations

Texas Children's Hospital

6621 Fannin Street, Houston TX 77030
Director of Nurseries: James M. Adams, MD

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St. Luke's Episcopal Hospital

6720 Bertner Avenue, Houston TX 77030
Director of Nurseries: Michael E. Speer, MD

The Methodist Hospital

6565 Fannin Street, Houston TX 77030
Director of Nurseries: Michael E. Speer, MD

Ben Taub General Hospital

1504 Taub Loop, Houston TX 77030
Director of Nurseries: Joe Garcia-Prats, MD

Community locations

East Houston Regional Medical Center

13111 East Freeway, Houston TX 77015
Director of Nurseries: Dilcia A. McLenan, MD

Methodist Willowbrook Hospital

18220 Tomball Parkway, Houston TX 77070
Director of Nurseries: Elaine Sillos, MD

St. Luke's Community Medical Center- The Woodlands

17200 St. Luke's Way
The Woodlands TX 77384
Director of Nurseries: Charles T. Hankins, MD

Twelve Oaks Medical Center - Sharpstown

6700 Bellaire Blvd, Houston TX 77074
Director of Nurseries: Tommy Leonard, MD

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6TH REBA MICHELS HILL AWARD



The sixth annual Reba Michels Hill Award was presented in November 2005 to two deserving recipients at Texas Children's Hospital—**Elizabeth "Charley" Elliott** (top), Assistant Director of Nurses, Neonatal Nurse Practitioner Service, and **Sandy McElligott** (bottom), Director of Community Initiatives.



Nominations are made by Newborn Section faculty, fellows, and staff each year. Those eligible are the Section's non-physician employees "whose contributions have made a significant difference toward achieving the ideals and goals of Dr. Hill (1930–1994), including her compassionate commitment to education, patient care, research, and family."

photos by Allen Kramer, Texas Children's Hospital

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- **March 5–8, 2006, Neonatal Nutrition Conference.** Details, as available, will be at www.neonate.net/education/nutrition/
- **March 27–29, 2006, 15th Texas Children's Hospital International Colloquium.** Details, as available, will be at www.texaschildrenshospital.org/allabout/international/
- **April 22-29, 2006, National Infant Immunization Week.**
For more information, see www.cdc.gov/nip/events/niiw/

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Neonatal Nutrition Fellowship

for Registered Dietitians with clinical experience
accepts applications year-round for two training periods
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