Twin-to-Twin Transfusion:
Part 3. Mortality and Neurodevelopmental Outcomes Following Intervention

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Author Disclosure
Drs Faye-Petersen and Crombleholme have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives
After completing this article, readers should be able to:
1. Compare and contrast the results of amnioreduction and laser therapy treatment of twin-to-twin transfusion syndrome (TTTS).
2. Discuss neurodevelopmental outcomes of infants delivered following treatment of TTTS.

Abstract
The high morbidity and mortality rates of twin-to-twin transfusion syndrome (TTTS) generally are related to sequelae of cardiovascular dysfunction or vascular disruption. Neurologic sequelae associated with TTTS are emerging concerns for survivors. A variety of clinical interventions, including amnioreduction, microseptostomy of the inter-twin membrane, and fetoscopic laser photocoagulation of placental anastomoses, have been used alone or in sequence to reduce the rates of mortality and morbidity. Because many of these specialized interventional procedures are performed at select centers in the United States, women may be treated at considerable distance from their primary obstetric care institutions and later return to deliver at their local facilities. Neonatologists may be unfamiliar with the relative efficacies and outcomes of the interventional procedures. In this review, we present a focused summary of the neurodevelopmental outcomes associated with these antenatal treatments.

Introduction
Chronic twin-to-twin transfusion syndrome (TTTS) is a gestational condition in which a sustained net imbalance of blood volume transfuses between twins of a diamniotic monochorionic (DiMo) placentation via placental anastomoses. It occurs in approximately 10% to 20% of all monochorionic twin gestations and has an 80% to 100% mortality rate, (1) if severe and left untreated, particularly if it is detected before 20 weeks of gestation. (2)(3) The pathogenesis of TTTS and its fetal and neonatal sequelae are discussed in Part 1 of this series on TTTS in this issue of NeoReviews. The clinical staging schemas of Quintero and associates (4)(5) and modifications (6)(7)(8) and various treatment modalities for TTTS (including amnioreduction [AR], microseptostomy of the inter-twin membrane, and nonselective and selective fetoscopic laser photocoagulation) are described in Part 2 in this issue. Also included in Part 2 are the efficacies of the various treatments and the pathologic examination of the DiMo placenta. In this review (Part 3), we discuss mortality and the neurodevelopmental outcomes of infants whose gestations were treated by antenatal AR and fetal laser photocoagulation interventions.

Clinical Interventional Procedures in TTTS: Comparative Analysis of Fetal/Neonatal Survival
The Eurofoetus trial (9) was the first prospective randomized trial to compare the efficacy and safety of treatment of TTTS with laser therapy or serial AR. Women presenting between 15 and 26 weeks’ gestation with polyhydramnios in the recipient twin and oligohydramnios in the donor twin participated in the trial. The patients were staged...
according to Quintero criteria: (4)(5) 52% 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 6 months of age (76% versus 51%, \( P=0.002 \)) in the laser group compared with the AR group. In addition, more infants were alive without neurologic abnormalities detected on neuroimaging studies in the laser group (52% versus 31%, \( P=0.003 \)). The overall survival in the laser arm was 57%, which was consistent with survival rates in previous reports of nonselective fetoscopic laser treatment (53%). (10)(11) This rate is significantly lower, however, than the survival reported with selective fetoscopic laser photoablation (SFLP) (64% to 68%). (12)(13) Of particular concern is the poor survival observed in the AR arm of 39%, which is significantly lower than previously reported (60% to 65%). (13)(14)(15) (16) Antenatal, peripartum, and neonatal care was provided by the referring hospital, and lack of standardization may explain some of these differences. (17) The decreased survival in the AR group may reflect the higher pregnancy termination rate in the AR 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. (13) Reliable assessment of neurologic outcome is critical when assessing efficacy of treatment for TTTS. Although the rate of abnormality on neurologic imaging was lower in the laser group (7% versus 17%), long-term neurodevelopmental assessment has revealed no difference in outcome between survivors treated by fetoscopic laser and those treated by AR.

The National Institutes of Health (NIH)-sponsored TTTS trial is the only other prospective randomized trial comparing survival among those receiving AR versus SFLP. (18) This trial differed from the Eurofoetus trial in several important aspects. First, to qualify for the NIH Trial, the TTTS had to fail to respond to a qualifying amniocentesis. The rationale for this requirement was to eliminate those who were more likely to respond to AR, the so-called “single amnio paradox.” Second, patients were candidates only if the TTTS presented earlier than 22 weeks of gestation, and no Stage I patients were candidates for the trial. These two requirements were substantially different from the Eurofoetus trial in which women were randomized into the trial up to 26 weeks of gestation, and 52% of those entered were Stage I. (9)

The NIH study was stopped early, after 42 women were randomized, when the Trial Oversight Committee detected a trend in adverse outcome affecting the recipient twin in one treatment arm and recommended to the Data Safety Monitoring Board that the trial be stopped to allow biostatistical analysis of the adverse trend. Results of the NIH TTTS trial showed no statistically significant difference in overall neonatal survival to 30 postnatal days (60% versus 43% \( p=NS \)) or neonatal survival of one or both twins in the same pregnancy (75% versus 65%, \( p=NS \)) in cases of severe TTTS treated by either AR or SFLP. Despite these overall results, a statistically significant worse fetal survival was observed among recipient twins in pregnancies treated by SFLP compared with those treated by AR. This apparent conundrum can be accounted for by recipient fetal losses in the SFLP arm being balanced by increased treatment failures among recipients in the AR arm. These results suggest that, in these highly selected cases of severe TTTS, neither treatment is superior to the other. Once TTTS reaches this degree of severity, the mortality among recipients is considerable, but the losses may occur at different times, depending on treatment. The impact of TTTS severity on fetal survival is supported further by the significantly worse fetal survival among recipient twins in Stages III and IV compared with those in Stage II. One of the strongest predictors of recipient demise is echocardiographic evidence of TTTS cardiomyopathy. The losses of fetal recipients treated by SFLP usually occur within 24 hours of the procedure. In contrast, the recipients treated by AR are not lost following the procedure, but there is progressive TTTS cardiomyopathy, as reflected by more recipients in the AR arm meeting criteria to be declared treatment failures. In every case, findings in the recipient twin met criteria for treatment failure. Taken together, these data suggest a disproportionate impact of TTTS cardiomyopathy on recipient survival in advanced stages of TTTS no matter what treatment they receive.

Recently, Rossi and D’Addario (19) reported a Cochrane review of TTTS with a meta-analysis that included data from both the Eurofoetus and NIH trials. The conclusion drawn from this analysis was that SFLP of TTTS is preferred over AR when it is available and AR is preferred when SFLP is not available. The results of this analysis likely are skewed toward fetoscopic laser based on the small numbers of individuals included from the NIH trial (\( n=40 \)) compared with the number included from the Eurofoetus trial (\( n=142 \)).

AR is readily available, less costly, and less invasive; laser therapy is only available at select institutions and requires specialized training. Although it makes sense to use AR where treatment options give similar results, it...
would be prudent to move promptly to laser therapy if rigorous studies can prove that this therapy has better short- and long-term outcomes in the setting of advanced disease.

For patients who respond to AR, the overall survival rate has been 88%. (20) In those cases in which echocardiographic progression is detected despite AR, the overall survival rate when SFLP is performed is 80%. The difference in survival between responders to AR and those who progress to SFLP are not statistically significantly different, suggesting that survival was not compromised by an initial trial of AR before progressing to SFLP.

Neurodevelopmental Outcomes in TTTS Versus Outcomes Following Interventions

Although much attention has focused on the effect of treatment on survival in TTTS, the neurologic morbidity among survivors is underappreciated. The International Amnioreduction Registry tracked 223 women who had TTTS diagnosed before 28 weeks' gestation and were treated with serial aggressive AR. (16) Of those infants who survived to 4 weeks of age and underwent clinically indicated cranial ultrasonography, 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, and 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 AR, the rate of abnormal cranial ultrasonography findings was similar at 27.3%. (13) 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 AR, the rate of abnormal neonatal cranial ultrasonography findings was as high as 58%. (21) It is important to recognize, however, that neuroimaging does not always correlate with neurodevelopmental outcome. An infant who has normal findings on head ultrasonography and magnetic resonance imaging can be neurodevelopmentally devastated, and an infant who has evidence of leukoencephalomalacia on imaging studies can be neurodevelopmentally intact.

Only a few studies have reported longer-term neurodevelopmental outcome. When interpreting these studies, it is important to appreciate the neurodevelopmental outcome in monochorionic twins who do not have TTTS. The incidence of severe neurodevelopmental abnormalities in monochorionic twins without TTTS is 6%. TTTS survivors who develop neurologic handicap and mental retardation do not always have abnormal neonatal ultrasonography results. Similarly, not all children who have abnormal ultrasonography findings have clinically significant neurodevelopmental deficits. In one small study that followed TTTS survivors for a mean of 6.2 years (range, 4 to 11 years), the incidence of cerebral palsy was 26% (5/19 infants) in the group treated by serial AR. All of these children had abnormal mental development in addition to motor deficits. Of note, three of the five children had normal findings on neonatal head ultrasonography. In the combined cohort of children whose mothers had been treated with AR or conservative treatment, 22% (5/23) who did not have 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 who receive AR and other treatment modalities, however, it is unlikely that such a cohort ever will be available for comparison.

Studying infants from pregnancies complicated by TTTS and treated with AR, Mari and associates (16) 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 colleagues (22) may be related to the latter study group having more severe disease, with all the patients diagnosed before 28 weeks' gestation versus up to 33 weeks' gestation in the study by Mari and colleagues. Of note, in the Mari study, nine survivors had mild speech or motor delay.

Wee and associates (23) studied the long-term neurologic outcome of 52 children from 31 TTTS pregnancies who survived to more than 18 months, most of whose mothers had been treated with AR. The comparison was a regional cohort of term and preterm infants, with most born very preterm. In addition, the TTTS babies were compared with matched singleton and twin control groups. The mean intelligence quotient (IQ) of TTTS survivors was significantly lower than the comparison cohort, due primarily to a 13-point IQ reduction in those children born before 33 weeks' gestation. There was no difference in the rate of cerebral palsy (5.8% for TTTS versus 4.9% for very preterm twins versus 3.3% for very preterm singletons) or behavioral test results in the TTTS survivors. This was a small study, however, and not sufficiently powered to demonstrate differences in cere-
bral 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 generally are more likely to experience neurologic compromise.

Even fewer studies have examined the long-term outcome of survivors of TTTS treated with intrauterine laser photocoagulation therapy. Banek and colleagues (24) reported that in 89 such children, 78% showed normal development at a median age of 22 months. 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, two infants from the most severely affected group had abnormal brain scan results before laser treatment. The findings of this study are consistent with those of Sutcliffe and associates, (25) who reported a cerebral palsy rate of 9% in children after in utero treatment with laser therapy for TTTS. Graef and coworkers, (26) in a report of 167 TTTS survivors who had been treated by fetoscopic laser, found normal neurodevelopmental testing results in 86.8% of cases, with 7.2% of infants having minor neurologic deficiencies and 6% having major neurologic deficiencies such as cerebral palsy, hemiparesis, and quadriplegia. These findings were not unlike those in follow-up of monochorionic twins without TTTS, and the most severely affected children were delivered prior to 28 weeks’ gestation, suggesting an important influence of gestational age on neurodevelopmental outcome. Similarly, Ortqvist and colleagues (27) reported the neurodevelopmental outcome of 114 survivors treated in the Eurofetus trial in which 13.2% had evidence of a major neurodevelopmental abnormality. However, there was no difference between those who had been treated by laser and those treated by AR. Perinatal factors, including gestational age at delivery and Apgar score, correlated with adverse outcome.

Of note, earlier and more sensitive antenatal detection of central nervous system injury (1) (28) has been reported recently with the adjunct use of magnetic resonance imaging (MRI) techniques. MRI has enabled the detection of cerebral venous sinus and urinary collecting system dilatation and more clearly delineated central nervous system lesions. The improvements in antenatal detection may result in further improvements in clinical management (1) and reduced morbidity and its severity in survivors.

**Summary**

The survival of one or both twins of a gestation complicated by TTTS is dependent on the gestational week of onset of TTTS, the rapidity of its progression, the cardiac status of the recipient, the gestational week of clinical intervention, and gestational age at birth. Both AR and SFLP are important means of increasing the duration of time for intrauterine development and, thereby, improving outcomes for the infants, but the use of MRI may become a key diagnostic means to enable earlier detection and mitigation of the deleterious effects of TTTS. However, central nervous system lesions or functional deficits may not be detectable at the time of birth or in the newborn period for a twin from a gestation with TTTS. Thus, as for the risks for long-term cardiac or renal dysfunction, long-term follow up to detect neurologic sequelae should be communicated to the pediatricians and staff caring for these infants.

**References**

6. The twin-to-twin transfusion syndrome (TTS) trial sponsored by the National Institutes of Health has examined the effect of treatments such as amnioreduction and selective fetoscopic laser photocoagulation on the mortality of one or both twins. Of the following, the strongest predictor of demise of the recipient twin in TTS is:

A. Echocardiographic evidence of cardiomyopathy.
B. Gestational age of twin at birth.
C. Gestational week of clinical intervention.
D. Gestational week of onset of TTS.
E. Rapidity of progression of TTS.

7. The TTS Registry from Australia and New Zealand has examined the effect of treatments such as amnioreduction and selective fetoscopic laser photocoagulation on the neurologic outcome among surviving twins. Of the following, the most common abnormality on cranial ultrasonography among twins treated for TTS reported by this TTS Registry is:

A. Cerebral cysts.
B. Cerebral echogenic foci.
C. Intraventricular hemorrhage.
D. Periventricular leukomalacia.
E. Ventricular dilation.