Twin–Twin Transfusion — As Good as It Gets?

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The twin-to-twin transfusion syndrome poses a major challenge for fetal therapy. Untreated, it results in inordinate perinatal mortality and morbidity. It affects two babies, both of whom are structurally normal. Because the connections mediating intertwin transfusion lie on the placental surface, they should be amenable to therapeutic interruption.

Although all monochorionic twins have vascular anastomoses and thus intertwin transfusion, the clinical syndrome develops in only 15 percent. This results in midtrimester discordance in amniotic-fluid levels and growth between the twins, with signs of hypovolemia and uteroplacental insufficiency in the donor and hypervolemia and cardiac dysfunction in the recipient (Fig. 1). Unbalanced intertwin transfusion is mediated by unidirectional arteriovenous anastomoses with inadequate or absent compensation along bidirectional superficial anastomoses,[1] resulting in up-regulation of the renin–angiotensin system in the donor and down-regulation in the recipient.[2]

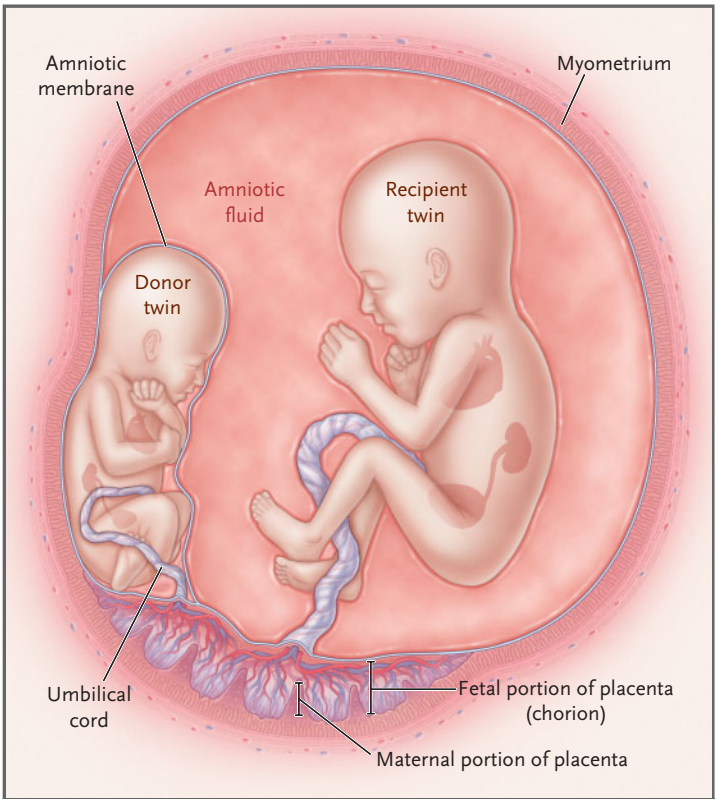

Figure 1. The Twin–Twin Transfusion Syndrome.
The twin–twin transfusion syndrome results in midtrimester discordance in amniotic-fluid levels and growth, with signs of hypovolemia and uteroplacental insufficiency in the donor twin and hypervolemia and cardiac dysfunction in the recipient twin.

There are several treatments. Amnioreduction and microseptostomy (puncturing the intertwin membrane) are intended to normalize the amniotic-fluid volume in an effort to prevent preterm labor from polyhydramnios. These treatments, however, do not primarily address the circulatory decompensation that occurs in severe progressive disease, and survivors are at risk for neurologic complications, particularly if one twin dies in utero, precipitating hypotension in the other twin from agonal intertwin transfusion. In cases in which fetal death is likely, cord occlusion by means of bipolar diathermy to terminate one twin allows the other twin to survive without neurologic complications.[3] The goal of endoscopic laser ablation of anastomoses is to resolve the syndrome by curtailing intertwin transfusion (Fig. 2), but there is a risk of fetal loss, owing to the nonselective destruction of blood vessels to normal cotyledons. The optimal therapy is unclear from the available observational studies, although both amnioreduction and laser surgery have resulted in perinatal survival rates of 60 to 65 percent in studies of large cohorts.[4-7]

In this issue of the *Journal*, Senat et al.[8] report the results of a much-needed trial in this difficult area. They randomly assigned 142 women to undergo serial amnioreduction or laser therapy (concomitantly with a single amnioreduction procedure). Laser therapy was associated with improved survival, both perinatally and at six months, and a lower incidence of periventricular leukomalacia. Since there was no significant difference between groups in the rate of live births, these results are partly explained by the prolongation of gestation by 4 weeks in the laser group (median, 33 weeks, as compared with 29 weeks in the amnioreduction group).

The focus of the analysis was the perinatal survival of at least one baby,[8] a pragmatic acknowledgment that the majority of pregnancies complicated by the twin–twin transfusion syndrome involve the loss of at least one baby, whatever the treatment. Although the overall favorable effect of laser therapy

as compared with amnioreduction seems clear (relative risk of the death of both twins before the end of the perinatal period, 0.63), several aspects of the study warrant examination.

Patients in randomized trials generally have better outcomes than those in the general population. Yet survival in both study groups was worse than in previous studies, especially since only 2 of 142 women with "severe" cases had fetuses with hydrops. The somewhat lower than expected rate of perinatal survival in the laser group (57 percent, vs. 64 to 68 percent in other series with the use of selective laser techniques[4,5]) might reflect the semiselective technique used, in which the recipient's blood vessels to normal cotyledons were ablated if they coterminated in the donor's sac. More pronounced was the discrepancy in the amnioreduction group, with a 41 percent rate of perinatal survival, as compared with a rate of 65 percent in the amnioreduction group in a randomized septostomy trial[9] and rates of 60 percent and 61 percent in the two published registries involving more than 400 cases of the twin–twin transfusion syndrome.[6,7] This difference may be due to the lack of standardization in perinatal care, since pregnancies with ongoing twin–twin transfusion syndrome were allowed to continue as late as 37 weeks and the women to deliver vaginally. More likely, it reflects the high frequency of pregnancy termination in the amnioreduction group (16 percent, as compared with 0 percent in the laser group). We are not told whether cord occlusion (to allow one baby to survive) was offered to women electing double termination. Furthermore, six women (9 percent) who were randomly assigned to amnioreduction subsequently underwent laser treatment for cardiac decompensation in the recipient twin; it is not clear whether their fetuses survived the procedure. Alternatively, it is possible that these outcomes may be attributable to greater severity of the twin–twin transfusion syndrome in this cohort than in cohorts described in the observational literature.

The rate of neurologic complications among survivors was lower in the laser group than in the amnioreduction group (7 percent vs. 17 percent). This advantage would have been greater if six pregnancies in the amnioreduction group complicated by apparent fetal brain lesions had not been terminated. However, in the absence of a formal neurologic examination, the six-month morbidity end point essentially reflected differences in findings on imaging (grade 3 or 4 intraventricular hemorrhage and cystic periventricular leukomalacia) detected in the two weeks after birth. Long-term follow-up will be important, because cystic periventricular leukomalacia may not be apparent on ultrasonography in the first fortnight after birth, abnormalities identified on imaging are not necessarily associated with clinical handicap, and neurologic sequelae may develop in infants with normal ultrasonograms. One cohort of survivors of laser therapy had a similar incidence of abnormalities (6 percent) on neonatal imaging, yet 11 percent had cerebral palsy on neurodevelopmental assessment at one year or more.[10]

The view has emerged that simpler, safer, but less effective procedures such as amnioreduction and septostomy are preferred for cases with a good prognosis and that technically challenging procedures such as cord occlusion and laser therapy, seemingly more effective but with a higher rate of fetal loss, should be reserved for cases with a poor prognosis. Favorable prognostic factors include an early stage of disease and Doppler detection of compensatory anastomoses.[11] In a previous study comparing amnioreduction with laser therapy for cases categorized according to severity, laser therapy resulted in worse perinatal survival among pregnancies with amniotic-fluid imbalance only (Quintero stage 1 or 2 disease; odds ratio for death, 2.7) but in better survival among fetuses who also have cardiovascular dysfunction (Quintero stage 3 or 4 disease; odds ratio, 0.4).[4,12] In contrast, the results of Senat et al. were not influenced by the Quintero stage. Because less than 10 percent of pregnancies were in Quintero stage 1 or 4, however, it is premature to conclude that laser coagulation should be

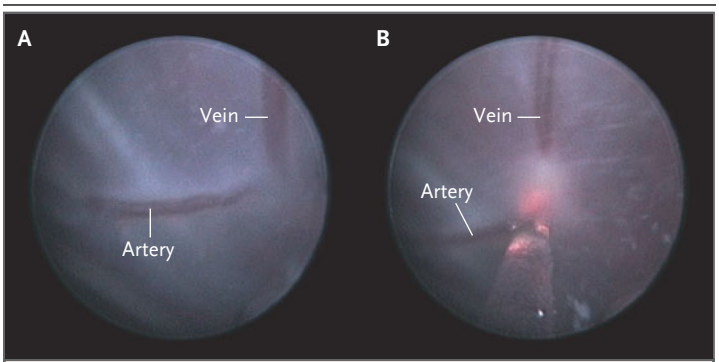

Figure 2. Endoscopic Views of a Typical Arteriovenous Anastomosis (Donor Artery to Recipient Vein) before (Panel A) and after (Panel B) Laser Therapy.
Identification of artery-to-vein anastomoses depends on tracing each unpaired vessel to its respective umbilical-cord origin.

the first-line treatment in all cases. An initial trial of amnioreduction leads to the resolution of disease in 20 percent of cases and may spare some patients from laser-related fetal loss.

An advantage of amnioreduction is that it is widely available. However, abnormalities in arterial compliance have been reported in children who were treated in utero with this approach. By curtailing intertwin transfusion and thus aberrant vascular remodeling in utero, laser therapy prevents this complication.[13] Laser therapy may also reduce the need for subsequent monitoring during pregnancy, although follow-up is indicated to detect persistent disease and the rare case of chronic reverse transfusion (recipient to donor). However, pregnancies involving an anterior placenta pose a technical challenge, because of the need to approach the chorionic plate intraamniotically with an instrument inserted transabdominally. Suggested solutions include the use of curved introducers, flexible scopes, and side-firing lasers. Without resorting to laparotomy, Senat et al. reported equally good results among women with an anterior placenta and those with a posterior placenta.

A discouraging aspect of this study is that only a third of affected pregnancies resulted in two healthy survivors. Perhaps we should counsel mothers with the syndrome that even with the better therapy, they still have a two-out-of-three chance of delivering a dead or brain-injured baby. Is this as good as it gets? The use of placental injection of vascular tracers to validate visually identified anastomoses may improve outcomes by reducing the number of false positive vessels ablated inadvertently and the number of false negative arteriovenous anastomoses left intact.[14] However, laser approaches remain inherently limited by poor placentation in the donor and hidden arteriovenous anastomoses that cannot be identified endoscopically.[15] The lack of an animal model and the difficulties involved in investigating human fetal pathophysiology further hamper therapeutic advances.

Should all fetal-medicine services now offer endoscopic laser coagulation? Although the report by Senat et al. suggests the real possibility of a benefit, before this approach can be generally recommended, further study is needed in other populations, particularly those with early-stage disease, and with assessment of long-term neurodevelopmental end points. An ongoing randomized trial conducted by the National Institutes of Health is comparing amnioreduction with laser therapy for refractory Quintero stage 2, 3, or 4 disease. Meanwhile, the widespread adoption of this challenging and difficult procedure by fetal specialists without training in endoscopy and placental vascular anatomy has the potential to do more harm than good.

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