What—and Why—the Neonatologist Should Know About Twin-To-Twin Transfusion Syndrome

Joseph M. Bliss, MD, PhD,*† Stephen R. Carr, MD,*‡ Monique E. De Paepe, MD,*§ Francois I. Luks, MD, PhD*¶

The Fetal Treatment Program of New England and the Divisions of †Neonatology, ‡Maternal-Fetal Medicine, §Pediatric and Developmental Pathology, and ¶Pediatric Surgery, Alpert Medical School of Brown University, Providence, RI

Education Gaps

1. Clinicians may not appreciate the unique risks and potential complications faced by monochorionic twins due to vascular connections in their shared placenta.
2. Clinicians need to understand contemporary fetal treatment modalities available to disrupt the pathophysiology of twin-to-twin transfusion syndrome.

Abstract

Twin-to-twin transfusion syndrome results from unbalanced vascular anastomoses in monochorionic twin gestations. This condition, affecting 2,500 pregnancies each year in the United States, is most commonly identified with ultrasonography on the basis of unequal amniotic fluid volumes in a monochorionic, diamniotic pregnancy. Hemodynamic alterations in the syndrome lead to oligohydramnios, intrauterine growth restriction, and frequently, anemia in the "donor" twin while the "recipient" has polyhydramnios and polycythemia. In severe cases, both twins are at risk of developing hydrops fetalis and death. The Quintero staging system is widely used to characterize the features and severity of the disease in a given pregnancy and to guide decisions regarding therapy. The advent of endoscopic fetoplacental surgery, which affords the possibility of laser photocoagulation of connecting placental vessels and thereby separation of the twins' circulation, has revolutionized the management of this condition and improved outcomes. The main risk of intervention is preterm premature rupture of membranes and subsequent preterm delivery of the twins. The outcomes for survivors of the syndrome are generally comparable to those of monochorionic, diamniotic twins in general and relate primarily to the degree of prematurity.

Objectives After completing this article, readers should be able to:

1. Summarize the pathophysiology and potential fetal and neonatal complications of twin-to-twin transfusion syndrome.

AUTHOR DISCLOSURE Drs Bliss, Carr, De Paepe, and Luks 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.

ABBREVIATIONS

AA	artery-to-artery
AV	artery-to-vein
BPD	bronchopulmonary dysplasia
FLOC	fetoscopic laser occlusion of chorioangiopagous vessels
MDA-PSV	middle cerebral artery peak systolic velocity
MoM	multiples of the median
PPROM	preterm premature rupture of membranes
TAPS	twin anemia polycythemia sequence
TTTS	twin-to-twin transfusion syndrome
VV	vein-to-vein

2. Describe the prenatal screening and staging criteria used in the diagnosis of twin-to-twin transfusion syndrome.
3. Explain how treatment modalities for twin-to-twin transfusion syndrome have evolved and the usefulness of fetoscopic laser therapy for the disorder.
4. Review the criteria and indications for fetoscopic laser therapy.
5. Discuss how the complications of twin-to-twin transfusion syndrome manifest in the newborn period and the likely neonatal outcomes.

INTRODUCTION

Twin-to-twin transfusion syndrome (TTTS) is a complication of monochorionic twin gestations. Because the twins are monozygotic and share a single placenta, vascular connections are virtually always present. Most often, blood flow through these placental anastomoses is bidirectional and balanced. In 10% to 15%, however, this inter-twin exchange is unbalanced: 1 fetus becomes the net donor, while the other becomes the net recipient. If the condition is severe and goes unchecked, both twins are at significant risk of dying in utero or sustaining severe cardiac, neurologic, and other complications. (1) The syndrome, which may affect as many as 2,500 pregnancies annually in the United States, is clinically relevant in the second trimester. If it occurs before 13 to 14 weeks of gestation, it is likely to be undiagnosed (but may present as single or dual intrauterine demise). In the third trimester, treatment for worsening TTTS is delivery.

Management of midgestation TTTS has changed dramatically over the last 2 decades, in large part because of the emergence of endoscopic fetoplacental surgery. Fetoscopic laser occlusion of chorioangiopagous vessels (FLOC) is the only treatment that can effectively halt the syndrome. It is also the most invasive, and may not be necessary in all cases of TTTS. (2) Prematurity is common in TTTS because of the cumulative effects of twin pregnancy, polyhydramnios, fetal intervention and, in some cases, rescue delivery for fetal deterioration. Neonatal management for infants affected by TTTS is, in many ways, similar to that of gestational age–matched unaffected twins. However, certain clinical findings and complications are specific to TTTS and its treatment.

DIAGNOSIS OF TWIN-TO-TWIN TRANSFUSION SYNDROME

TTTS is most often suspected in the presence of amniotic fluid volume discordance in a monochorionic, diamniotic gestation. A definitive diagnosis of TTTS requires the determination of monochorionicity (concordant gender, absence of a "lambda" or "delta" sign where the double-layer inter-twin amniotic membrane inserts on the placenta) and concomitant oligohydramnios in 1 twin (the donor) and polyhydramnios in the co-twin (the recipient). (3) The degree of oligohydramnios may vary, but if there is little to no amniotic fluid in the donor sac, the fetus is "stuck" between its membranes and the placenta—a particularly striking finding if the placenta is anterior. Similarly, polyhydramnios can sometimes be severe, causing significant discomfort and even respiratory difficulty in the mother. The differential diagnosis of isolated oligo- and polyhydramnios is extensive, and one must distinguish between discordant growth from placental insufficiency (leading to oligohydramnios in the affected twin, but normal amniotic fluid volume in the co-twin) and TTTS; however, it is not uncommon to have TTTS and concomitant growth restriction in the donor twin. (4)

It is important to note that TTTS is diagnosed based solely on ultrasonographic criteria. Although the donor is usually anemic and the recipient is polycythemic, this is not a universal finding. Fetal blood sampling with hemoglobin determination is never indicated for the diagnosis of TTTS, and indirect measurements of anemia, like middle cerebral artery peak systolic velocity, are not necessary and sometimes confusing. (5)

PATHOPHYSIOLOGY OF TWIN-TO-TWIN TRANSFUSION SYNDROME

The pathogenesis of TTTS remains incompletely understood. If virtually all monochorionic twin fetuses share communicating placental vessels, why do only some develop the syndrome? The most simplistic explanation is a final common pathway that results in unidirectional net blood flow across the anastomoses, with a small number of anastomoses increasing the risk of imbalance: the donor twin gives away more blood than it receives, leading to hypovolemia and anemia, while the recipient develops

polycythemia and hypervolemia. However, this long-held notion has come under scrutiny.

Vascular communications can be artery-to-artery (AA), vein-to-vein (VV), or artery-to-vein (AV). AV anastomoses are deep and represent cotyledons shared by both fetuses (arterial supply from 1 twin and venous drainage to the other). AV anastomoses can be donor-to-recipient or recipient-to-donor, and typically, both types coexist. TTTS develops when the net flow across these multiple AV anastomoses favors a donor-to-recipient direction. AA and VV anastomoses are superficial and connect both umbilical cords directly without an intervening capillary bed. The frequency of AA anastomoses is lower in pregnancies complicated by TTTS than in non-TTTS pregnancies (25% to 57% in TTTS vs >85% in non-TTTS). (6) This relative paucity of AA anastomoses in TTTS placentas has led some to believe that they act protectively (7)—a notion supported by mathematical computer models of TTTS. (8) However, this protective theory does not account for the presence of AA in a substantial percentage of cases with TTTS.

In addition to choriovascular inter-twin anastomoses, peripheral cord insertion and uneven placental sharing have been linked to an increased risk for TTTS development in monochorionic gestations. The reported frequency of peripheral (velamentous or marginal) cord insertion of at least 1 twin is significantly higher in TTTS gestations than in non-TTTS gestations (52% vs 31%). (9) In TTTS gestations with discordant cord insertion types, it is virtually always the donor twin who has the peripherally inserted cord. (6) Markedly uneven placental sharing, traditionally defined as more than 25% inter-twin difference in distribution of placental territory, is seen in about half of TTTS gestations compared with one-quarter of non-TTTS gestations. Almost always, the donor twin has the smaller placental share.

In the recipient twin, various mediators may be modulated in response to increased blood volume, including atrial natriuretic peptide, brain natriuretic peptide, antidiuretic hormone, endothelin-1, and others. (10) Although their exact mechanisms of action remain incompletely understood, these various hormonal and related mediators may play a role in what some have called an exaggerated cardiovascular response to hypervolemia.

Either twin can develop hydrops fetalis: the donor because of anemia and high-output heart failure and the recipient because of hypervolemia. The recipient twin can also exhibit hypertension, hypertrophic cardiomegaly, pulmonic stenosis, and disseminated intravascular coagulation.

Both fetuses affected by TTTS are at risk for dying; in 66% of cases, the donor twin dies first. (11) Because of the existing fetofetal shunts, the sudden drop in arterial perfusion pressure in the dying twin may result in a steal phenomenon from surviving to dying twin, leading to profound hypotension in the survivor. Death of the co-twin is common (>30%) and often follows death of the first twin within hours; surviving twins with chronic TTTS have a 25% to 30% risk of severe neurologic or cardiac anomalies. (12) Periventricular leukomalacia is the most common brain anomaly found in survivors of TTTS and may occur even in the absence of co-twin death. Other complications include vascular thromboembolic events; limb defects and intestinal atresia almost always occur in the recipient, and have been attributed to a combination of low flow and polycythemia. (13)(14)

STAGING OF TWIN-TO-TWIN TRANSFUSION SYNDROME

Treatment options and prognosis of TTTS depend on accurate staging of the disease. Once the diagnosis of TTTS is suspected, a detailed ultrasonographic assessment, including Doppler studies of both twins, is made to further categorize the disease. Many detailed staging systems have been proposed, often involving complex echocardiographic criteria to predict the true hemodynamic impact on the twins. (15) Nevertheless, the staging system described by Quintero et al (16) in 1999 is still the most widely used today (Table 1). Its advantage is its relative simplicity, which facilitates referrals and communication between health care providers.

Stage I describes the amniotic fluid volume discordance—a deepest vertical pocket less than 2 cm in the donor sac and greater than 8 cm (or 10 cm, after 20 weeks' gestational age) around the recipient. In stage I, donor hypovolemia is still mild, and urine production is still adequate: the bladder fills and is visible on ultrasonography. Once oliguria occurs and the bladder is no longer observed to fill, the disease is classified as stage II.

In stage III, one of the following is present: absent or even reversed end-diastolic umbilical artery flow in the donor, indicating high systemic vascular resistance and/or a failing heart. In the recipient, hypervolemia and high-output cardiac failure may lead to progressive right ventricular dilation and varying degrees of tricuspid regurgitation, resulting in reverse blood flow through the ductus venosus and pulsatile flow in the umbilical vein.

If hydrops is present in either twin (defined as the abnormal accumulation of fluid in 2 or more compartments—pericardial or pleural effusion, ascites, or skin edema), the disease has entered stage IV. Finally, (impending) fetal demise of 1 or both twins is termed stage V.

Despite its numerical progression, the Quintero staging system does not accurately predict the natural history of the disease. (17)(18)(19) Not uncommonly, up- or downstaging occurs at random, from week to week, and the timing of progression varies widely. Nevertheless, this and other staging systems help decide the best course of action. As originally described, the Quintero classification determined who benefited from invasive therapy; in a small pilot study, the outcome of expectant management was excellent in stage I, but rapidly worsened for stage II and higher, leading to the concept, still adhered to by most, that fetal intervention should be offered for stages II, III, and IV. (20)(21)

More recently, these perspectives have been challenged. Some believe that a number of stage I patients (ie, without evident Doppler abnormalities) may still show preclinical signs of cardiovascular strain, and should really be considered an advanced stage. Calculating the myocardial performance (Tei) index may help differentiate between a benign course and an aggressive one. (22) Most recently, the notion that nonprogressive stage I disease affords a favorable prognosis and is best observed has been challenged as well. (1)

TTTS in the less common monochorionic, monoamniotic twin gestation will not result in discordance in amniotic fluid volume, because the twins share a common amniotic cavity, making TTTS more difficult to diagnose. Diagnosis relies instead on discordance in size of the urinary bladders, abnormal Doppler patterns, and perhaps development of hydrops; this situation limits the application of the Quintero criteria. TTTS appears to be less common in monoamniotic twins, because of a high prevalence of compensatory AA anastomoses and shorter intercord distance, though the condition may be underdiagnosed in this subset of patients. (23)

TREATMENT OF TWIN-TO-TWIN TRANSFUSION SYNDROME

If the syndrome is diagnosed after the gestational age of viability, close observation is the best course of action, recognizing that early delivery may be necessary if the condition worsens. This requires weekly ultrasonography examinations and the understanding that premature delivery may be preferable to in utero deterioration. Close collaboration between maternal-fetal medicine specialists and neonatologists is therefore paramount.

When TTTS starts early in the second trimester, the treatment options are limited. In the past, the only viable intervention consisted of limiting the negative effects of polyhydramnios (on the mother and the pregnancy). Serial amnioreduction, sometimes requiring 1 to 2 L of amniotic fluid to be removed from the recipient's sac on a weekly basis, led to better fetal and neonatal outcomes than observation alone. (24) Although this approach reduces the risk of preterm rupture of the membranes and premature delivery due to polyhydramnios, normalizing recipient amniotic fluid volume fails to halt the syndrome or offer long-term protection to either twin and has its own associated risk of membrane rupture and unplanned delivery. Inter-twin

TABLE 1. **Ultrasonographic Staging Criteria for Twin-to-Twin Transfusion Syndrome**

Stage I	Oligohydramnios (<2 cm maximal vertical pocket)/Polyhydramnios (>8 cm*) Donor bladder visible
Stage II	Oligohydramnios/Polyhydramnios (as in stage I) Donor bladder not visible
Stage III	Oligohydramnios/Polyhydramnios (as in stage I)
	Critically abnormal Doppler findings: absent or reversed end-diastolic umbilical artery flow in donor and/or pulsatile umbilical vein flow in recipient and/or reversed flow in the ductus venosus (recipient)
Stage IV	Oligohydramnios/Polyhydramnios (as in stage I)
	Hydrops in either twin (≥2 of the following: ascites, pericardial effusion, pleural effusion, scalp or subcutaneous edema)
Stage V	Oligohydramnios/Polyhydramnios (as in stage I)
	Single or dual fetal demise

Based on the study of Quintero et al (16).
**Some centers use >10 cm after 20 weeks' gestational age.*

septostomy was once considered as a treatment for TTTS to restore amniotic fluid dynamics without the need for repeated amnioreduction. However, the possibility of inadvertently creating a large septostomy resulting in an essentially monoamniotic sac with the attendant risk of cord entanglement limited its usefulness.

Today, the gold-standard therapy for advanced or progressive TTTS is FLOC. (21)(25) This procedure uses laser energy to photocoagulate the placental anastomoses between the twins, thereby interrupting the hemodynamic imbalance that defines the syndrome and 'dichorionizing' an initially monochorionic placenta (Fig 1). Although the goal is to halt the syndrome and improve the hemodynamic function of both fetuses, it also protects 1 twin against vascular steal in case of co-twin death.

The randomized Eurofoetus Trial first demonstrated higher survival rates after laser therapy (76% survival of at least 1 twin) than with serial amnioreduction (56% survival). (21) The Eurofoetus Trial also showed the superiority of laser coagulation with respect to short-term neurologic outcome and gestational age at delivery. A 4-week gestational age advantage was noted at delivery (33 vs 29 weeks) in the laser group, which also had a 6% incidence of periventricular leukomalacia in the survivors, compared with 14% in the amnioreduction group. A few centers have therefore advocated for fetoscopic intervention even after the fetuses have reached the gestational age of viability. The Leiden group in particular has been offering intervention well into the third trimester, claiming better neonatal outcomes. (26)

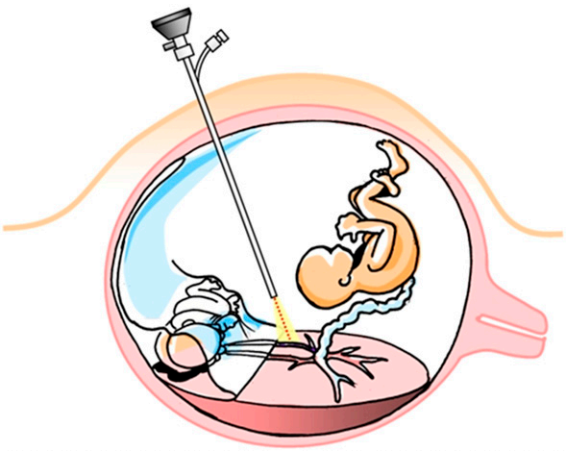

Figure 1. Schematic illustration of fetoscopic surgery for severe twin-to-twin transfusion syndrome. Donor (left) has oligohydramnios and is "stuck" behind the inter-twin membrane. Endoscopic instrument is inserted through the recipient's polyhydramniotic sac. Laser beam (dotted line) aims at placental anastomoses between donor and recipient. (Courtesy of Francois I. Luks, MD [CC BY-SA 3.0 (http://creativecommons.org/licenses/by-sa/3.0)] via Wikimedia Commons.)

Fetoscopic surgery is considered minimally invasive, but is still the most aggressive intervention for TTTS. It is most often performed under local or regional anesthesia, though some offer general anesthesia as well. (27) It involves the insertion of a 3- to 4-mm diameter cannula into the uterus through the maternal abdominal wall, allowing the introduction of a small telescope and a 400- to 600-μm diameter laser fiber. The telescope is introduced into the recipient's sac under ultrasonographic guidance, the placental surface is visually explored, and the placental equator is identified. Any vessel seen crossing the inter-twin membrane at the equator is evaluated, and twin-twin anastomoses (AV, AA, or VV) are occluded using a diode or neodymium:yttrium aluminium garnet (Nd:YAG) laser (Fig 2). At the end of the procedure, any significant excess amniotic fluid is removed from the recipient's sac. (28) Specific techniques may vary from center to center, but the general principles are the same.

In the initial nonselective approach described by De Lia et al, (29) all vessels crossing the inter-twin membrane were photocoagulated. It was later recognized that this included paired vessels (arterial branch and venous return to the same twin), which were needlessly sacrificed. Selective elimination of shared cotyledons only (artery from 1 twin connecting with a vein to the co-twin) led to improved survival. (30) Further refinements in technique included the sequential approach, whereby donor artery–to–recipient vein anastomoses are coagulated first, based on the untested notion that this will allow back flow of blood from the recipient to the donor, thereby lessening the effect of the syndrome on both fetuses. (31)

The ultimate goal of FLOC is the obliteration of all placental communications. Although the technique is highly successful in halting the syndrome, it has been long recognized that some vascular anastomoses persist in up to 30% of cases. (5)(6) This incomplete coagulation does not necessarily result in persistence of the syndrome (as the flow imbalance may have been sufficiently dampened to allow the twins to recover). However, the theoretical risk of recurrence, damage to a surviving twin should the co-twin die, or even reverse TTTS (whereby the donor becomes recipient and vice versa) led to the development of the Solomon technique. (32) Named after King Solomon's legendary ruling, it consists of physically dividing the placental equator (rather than just the individual vessels) in a scorched-earth fashion, effectively separating the 2 fetoplacental circulations. A randomized, controlled study suggested that the Solomon technique significantly reduced the incidence of twin anemia polycythemia sequence (TAPS) and recurrent TTTS, though it increased the

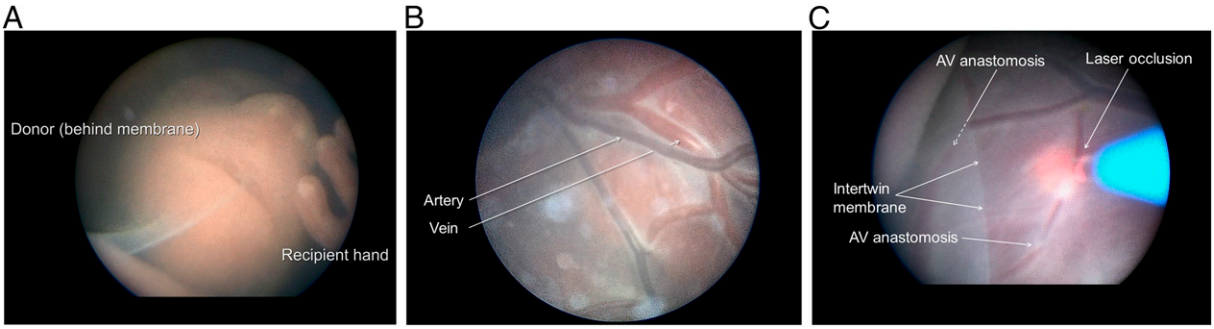

Figure 2. Fetoscopic views in twin-to-twin transfusion syndrome. A. View of donor fetus through the inter-twin membrane. Note membrane folds tightly draped over donor's neck. Fingers of recipient twin visible on the other side of the membrane. B. Placental vascular anatomy. Paired arteries and veins from 1 twin. Typically, arteries lie on top of their corresponding vein. Note deoxygenated (dark) blood in arteries and bright red, oxygenated blood in veins. C. Twin-twin anastomoses. Note 2 unpaired vessels crossing the inter-twin membrane. Laser occlusion on the recipient's side of the membrane. AV=artery-to-vein.

incidence of preterm premature rupture of membranes (PPROM). (32)

POSTOPERATIVE RESULTS

Following the 30- to 60-minute procedure, the patient remains in the hospital for 1 to 2 days, and will require 1 to 2 weeks of convalescence, but bedrest is not usually necessary. Tocolysis varies by center and can be tailored to the patient, but is often required for the first few days. In the United States, nifedipine has mostly replaced magnesium sulfate because it is better tolerated.

Ultrasonography follow-up is recommended twice a week for the first 14 days, and can usually be decreased to once a week thereafter. (33) The ultimate goal of therapy is delivery near term and intact dual survival. The procedure itself is highly successful in halting or altering the course of TTTS. Signs of this hemodynamic alteration can be detected as early as 2 to 5 days postoperatively: visualization of the donor bladder, resolution of Doppler anomalies in the recipient or donor umbilical vessels, and improved cardiac contractility and (tricuspid) valvular function in the recipient. However, FLOC does not directly improve the fetuses' cardiovascular status, and advanced fetal stress may still result in postoperative fetal demise. The donor has an approximately 10% survival disadvantage relative to the recipient, but both twins are at risk for early postoperative death. (11) Unfortunately, predictive models are imperfect, and there is no reliable method to determine impending death of either twin. (34) Of note, FLOC effectively separates the fetal circulations, and postoperative demise of 1 twin does not have the potentially disastrous consequence for the co-twin that untreated TTTS carries. (12)

Overall results of FLOC for severe TTTS are reasonably good, particularly when compared with the dismal outcome if left untreated. Since the first randomized trial in 2004, (21) numerous (mostly nonrandomized) studies have shown survival rates ranging from 70% to 90%. A recent meta-analysis of all available series showed an average survival for at least 1 twin of 81% (and overall survival of 67%). (35) There are several reasons for the mixed survival results. As mentioned, some fetuses are already too sick to be able to recover after FLOC. The placental share of some donors is so small that placental vascular resistance is exceedingly high; in those circumstances, the AV anastomoses to the recipient, although detrimental in the long run, offer a "pop-off" release by decreasing the afterload. Following FLOC, the sudden rise in placental vascular resistance can worsen the donor's cardiac function, leading to hydrops. Although this can be a temporary phenomenon, it can prove fatal if the donor was already critically ill.

Similarly, advanced disease in the recipient may preclude recovery after FLOC. In addition to the (right) ventricular strain caused by hypervolemia, recent evidence has shown that in a fraction of recipients, cardiac dysfunction can be exacerbated by FLOC. The etiology can be attributed to either underlying (and preexisting) pulmonary stenosis or inappropriate vasoactive stimulation (through the donor) that may have created an exaggerated cardiovascular response to hypervolemia, rendering the recipient more fragile.

Recurrence of TTTS after FLOC has been described in approximately 5% of cases. (36)(37) It may be caused by incompletely occluded or missed anastomoses, and often requires reintervention. There is even the potential risk of new flow imbalance, whereby the donor becomes recipient and vice versa. The ensuing blood volume discordance (whether inversed or not) can be present without the classic hallmarks of TTTS (absent donor bladder, amniotic fluid discordance, Doppler anomalies). It is then referred to as

TABLE 2. **Antenatal Staging of TAPS (39)**

Stage I	MCA-PSV >1.5 MoM in donor *and* <1.0 MoM in recipient without signs of fetal compromise
Stage II	MCA-PSV donor >1.7 MoM *and* MCA-PSV recipient <0.8 MoM without signs of fetal compromise
Stage III	MCA-PSV donor >1.5 MoM *and* MCA-PSV recipient <1.0 MoM *with* cardiac compromise of the donor (defined as critically abnormal flow)
Stage IV	Hydrops of the donor, preceded by TAPS
Stage V	Single or dual fetal demise, preceded by TAPS

MDA-PSV=middle cerebral artery peak systolic velocity; MoM=multiples of the median; TAPS=twin anemia polycythemia sequence.

TAPS (Table 2). (5)(38) The incidence of iatrogenic TAPS varies between reports, with an average of approximately 5% to 10%. Mild to moderate TAPS (stage I or II) is best observed; advanced stages may require intervention, including repeat FLOC or early delivery, depending on the gestational age. (39)

Prematurity is very common: risk factors include twin gestation (more so in monochorionic than in dichorionic twins), TTTS itself, polyhydramnios, (repeated) amnioreductions, and endoscopic fetal surgery. (40)(41) The risk of PPROM after FLOC (also referred to as iatrogenic, or iPPROM) ranges from 9% to 15% within the first 14 postoperative days, and reaches 19% to 50% by 32 weeks of gestation. Consultation with neonatologists is therefore important to discuss options for postnatal interventions should delivery ensue. Preoperative administration of maternal corticosteroids should be considered for patients whose infants will receive full support in the event of delivery.

NEONATAL OUTCOMES

Delivery and cord clamping effectively halts TTTS, but the syndrome may still affect the newborn and infant twins. The most common immediate problems are related to prematurity and the underlying cardiovascular strain on former donor and recipient. Because of smaller placental share, chronic anemia, and increased work, the donor is usually small for gestational age. (4) This may further complicate the management and worsen the outcome of associated hydrops. The recipient is typically appropriate or large for gestational age, and tends to be polycythemic. Underlying pulmonary stenosis, (42)(43) cardiomyopathy, and manifestations of high-output cardiac failure (hydrops) may have an adverse impact on the outcome. Persistent or hemodynamically significant pulmonic valve abnormalities may require cardiac intervention. Nevertheless, prolonged evidence of (right) cardiac strain in the recipient after FLOC is not necessarily associated with poor outcome, and many of these infants will show gradual improvement in cardiac function over time. Indeed, studies at age 10 years have demonstrated little myocardial dysfunction even in those who had severe dysfunction in utero. (44) Both donor and recipient twins are at risk for hypertension related to the cardiovascular and renal adaptations to TTTS, and therefore, blood pressure should be monitored closely. Elevated blood pressures have been reported in 62% of survivors at 2 years of age in both donors and recipients. (45)

Other TTTS-specific morbidities of the newborn include an increased incidence of renal tubular apoptosis seen in

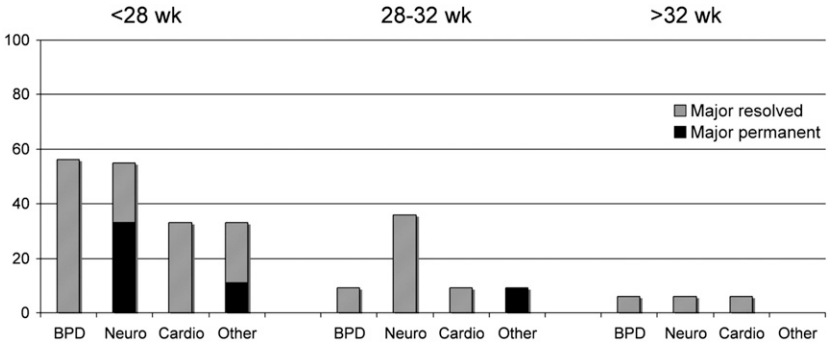

Figure 3. Long-term outcome of twin-to-twin transfusion syndrome. In a case-control study, the degree of prematurity was the only determinant of long-term outcome after twin-to-twin transfusion syndrome that was treated with fetoscopic surgery. The incidence of major sequelae decreased with increasing gestational age (GA) at birth. No permanent sequelae were seen in children born after 32 weeks' GA. Categories at top: GA at birth. BPD=bronchopulmonary dysplasia. (Reprinted with permission from Kowitt et al, 2012 [48].)

former donors (46), and isolated thromboembolic phenomena, almost always in the recipient, and believed to be a result of sluggish blood flow and polycythemia. Although rare, these complications can be severe. Limb necrosis has been well documented, as has intestinal atresia. (13)

Several studies have examined the long-term outcome of infants and children after severe TTTS, with or without fetal intervention. (47) Despite the sporadic occurrence of TTTS-specific complications, the overall impression is that the outcome of infants who suffered TTTS in utero is mostly related to the degree of prematurity. (48)(49) Thus, the incidence of mild and severe neurologic abnormalities, (50) lung disease, and complications is similar to that of unaffected twins of similar gestational age at birth (Fig 3). (48) A meta-analysis of studies evaluating neurodevelopmental outcome among twins treated with FLOC showed a rate of neurologic morbidity of 6% at birth and 11% at follow-up from 6 to 48 months of age with no difference between donor and recipient twins. (51) Cerebral palsy was the most frequent neurologic complication, accounting for 40% of abnormal outcomes. These rates are very similar to baseline rates for monochorionic, diamniotic twins in general, (52) suggesting that much of the risk is attributable to monochorionicity and/or prematurity rather than TTTS or its treatment. Regardless, close neurodevelopmental follow-up is important for these patients, with implementation of services as appropriate to maximize positive outcomes.

American Board of Pediatrics Neonatal—Perinatal Content Specifications

- Know the potential fetal complications of multiple gestation such as cord problems, twin-twin transfusion, "stuck twin," conjoined twins, etc.
- Know the implications and treatment options for the surviving fetus when its twin dies in utero.

References

1. Emery SP, Hasley SK, Catov JM, et al; North American Fetal Therapy Network. North American Fetal Therapy Network: intervention vs expectant management for stage I twin-twin transfusion syndrome. *Am J Obstet Gynecol*. 2016;215(3):346.e1–346.e7
2. Chmait RH, Quintero RA. Operative fetoscopy in complicated monochorionic twins: current status and future direction. *Curr Opin Obstet Gynecol*. 2008;20(2):169–174
3. Hecher K, Diehl W, Zikulnig L, Vetter M, Hackelöer BJ. Endoscopic laser coagulation of placental anastomoses in 200 pregnancies with severe mid-trimester twin-to-twin transfusion syndrome. *Eur J Obstet Gynecol Reprod Biol*. 2000;92(1):135–139
4. Chmait RH, Korst LM, Bornick PW, Allen MH, Quintero RA. Fetal growth after laser therapy for twin-twin transfusion syndrome. *Am J Obstet Gynecol*. 2008;199(1):47.e1–47.e6
5. Slaghekke F, Kist WJ, Oepkes D, et al. TAPS and TOPS: two distinct forms of feto-fetal transfusion in monochorionic twins. *Z Geburtshilfe Neonatol*. 2009;213(6):248–254
6. De Paepe ME, Friedman RM, Poch M, Hansen K, Carr SR, Luks FI. Placental findings after laser ablation of communicating vessels in twin-to-twin transfusion syndrome. *Pediatr Dev Pathol*. 2004;7(2):159–165
7. Hack KE, van Gemert MJ, Lopriore E, et al. Placental characteristics of monoamniotic twin pregnancies in relation to perinatal outcome. *Placenta*. 2009;30(1):62–65
8. van den Wijngaard JP, Umur A, Ross MG, van Gemert MJ. Twin-twin transfusion syndrome: mathematical modelling. *Prenat Diagn*. 2008;28(4):280–291
9. De Paepe ME, Shapiro S, Hanley LC, Chu S, Luks FI. Correlation between cord insertion type and superficial choriovasculature in diamniotic-monochorionic twin placentas. *Placenta*. 2011;32(11):901–905
10. Bajoria R, Ward S, Chatterjee R. Brain natriuretic peptide and endothelin-1 in the pathogenesis of polyhydramnios-oligohydramnios in monochorionic twins. *Am J Obstet Gynecol*. 2003;189(1):189–194
11. Muratore CS, Carr SR, Lewi L, et al. Survival after laser surgery for twin-to-twin transfusion syndrome: when are they out of the woods? *J Pediatr Surg*. 2009;44(1):66–69, discussion 70
12. O'Donoghue K, Rutherford MA, Engineer N, Wimalasundera RC, Cowan FM, Fisk NM. Transfusional fetal complications after single intrauterine death in monochorionic multiple pregnancy are reduced but not prevented by vascular occlusion. *BJOG*. 2009;116(6):804–812
13. Carr SR, Luks F, Tracy T, Plevyak M. Antenatal necrotic injury in severe twin-to-twin transfusion syndrome: a case and review. *Fetal Diagn Ther*. 2004;19(4):370–372
14. Lopriore E, Lewi L, Oepkes D, et al. In utero acquired limb ischemia in monochorionic twins with and without twin-to-twin transfusion syndrome. *Prenat Diagn*. 2008;28(9):800–804
15. Shah AD, Border WL, Crombleholme TM, Michelfelder EC. Initial fetal cardiovascular profile score predicts recipient twin outcome in twin-twin transfusion syndrome. *J Am Soc Echocardiogr*. 2008;21(10):1105–1108
16. Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin-twin transfusion syndrome. *J Perinatol*. 1999;19(8 Pt 1):550–555
17. O'Donoghue K, Cartwright E, Galea P, Fisk NM. Stage I twin-twin transfusion syndrome: rates of progression and regression in relation to outcome. *Ultrasound Obstet Gynecol*. 2007;30(7):958–964
18. Luks FI, Carr SR, Plevyak M, et al. Limited prognostic value of a staging system for twin-to-twin transfusion syndrome. *Fetal Diagn Ther*. 2004;19(3):301–304
19. Dickinson JE, Evans SF. The progression of disease stage in twin-twin transfusion syndrome. *J Matern Fetal Neonatal Med*. 2004;16(2):95–101
20. Quintero RA, Dickinson JE, Morales WJ, et al. Stage-based treatment of twin-twin transfusion syndrome. *Am J Obstet Gynecol*. 2003;188(5):1333–1340

21. Senat MV, Deprest J, Boulvain M, Paupe A, Winer N, Ville Y. Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. *N Engl J Med*. 2004;351(2):136–144
22. Rychik J, Tian Z, Bebbington M, et al. The twin-twin transfusion syndrome: spectrum of cardiovascular abnormality and development of a cardiovascular score to assess severity of disease. *Am J Obstet Gynecol*. 2007;197(4):392.e1–392.e8
23. Paepe ME. Examination of the twin placenta. *Semin Perinatol*. 2015;39(1):27–35
24. Mari G, Roberts A, Detti L, et al. Perinatal morbidity and mortality rates in severe twin-twin transfusion syndrome: results of the International Amnioreduction Registry. *Am J Obstet Gynecol*. 2001;185(3):708–715
25. Khalek N, Johnson MP, Bebbington MW. Fetoscopic laser therapy for twin-to-twin transfusion syndrome. *Semin Pediatr Surg*. 2013;22 (1):18–23
26. Middeldorp JM, Lopriore E, Sueters M, et al. Twin-to-twin transfusion syndrome after 26 weeks of gestation: is there a role for fetoscopic laser surgery? *BJOG*. 2007;114(6):694–698
27. Duron VD, Watson-Smith D, Benzuly SE, et al. Maternal and fetal safety of fluid-restrictive general anesthesia for endoscopic fetal surgery in monochorionic twin gestations. *J Clin Anesth*. 2014;26 (3):184–190
28. Lombardo ML, Watson-Smith DJ, Muratore CS, Carr SR, O'Brien BM, Luks FI. Laser ablation of placental vessels in twin-to-twin transfusion syndrome: a paradigm for endoscopic fetal surgery. *J Laparoendosc Adv Surg Tech A*. 2011;21(9):869–872
29. De Lia JE, Kuhlmann RS, Harstad TW, Cruikshank DP. Fetoscopic laser ablation of placental vessels in severe previable twin-twin transfusion syndrome. *Am J Obstet Gynecol*. 1995;172(4 pt 1):1202–1208, discussion 1208–1211
30. Quintero RA, Morales WJ, Mendoza G, et al. Selective photocoagulation of placental vessels in twin-twin transfusion syndrome: evolution of a surgical technique. *Obstet Gynecol Surv*. 1998;53(12 suppl):S97–S103
31. Quintero RA, Ishii K, Chmait RH, Bornick PW, Allen MH, Kontopoulos EV. Sequential selective laser photocoagulation of communicating vessels in twin-twin transfusion syndrome. *J Matern Fetal Neonatal Med*. 2007;20(10):763–768
32. Slaghekke F, Oepkes D. Solomon technique versus selective coagulation for twin-twin transfusion syndrome. *Twin Res Hum Genet*. 2016;19(3):217–221
33. Emery SP, Bahtiyar MO, Dashe JS, et al. The North American Fetal Therapy Network Consensus Statement: prenatal management of uncomplicated monochorionic gestations. *Obstet Gynecol*. 2015;125 (5):1236–1243
34. Skupski DW, Luks FI, Walker M, et al. Preoperative predictors of death in twin-to-twin transfusion syndrome treated with laser ablation of placental anastomoses. *Am J Obstet Gynecol*. 2010;203:388.e1–e11
35. Ahmed S, Luks FI, O'Brien BM, Muratore CS, Carr SR. Influence of experience, case load, and stage distribution on outcome of endoscopic laser surgery for TTTS: a review. *Prenat Diagn*. 2010;30 (4):314–319
36. Middeldorp JM, Sueters M, Lopriore E, et al. Fetoscopic laser surgery in 100 pregnancies with severe twin-to-twin transfusion syndrome in the Netherlands. *Fetal Diagn Ther*. 2007;22(3):190–194
37. Ville Y. Technical and ethical issues in fetal therapy. *Semin Fetal Neonatal Med*. 2007;12(6):425
38. Lopriore E, Slaghekke F, Oepkes D, Middeldorp JM, Vandenbussche FP, Walther FJ. Hematological characteristics in neonates with twin anemia-polycythemia sequence (TAPS). *Prenat Diagn*. 2010;30(3):251–255
39. Tollenaar LS, Slaghekke F, Middeldorp JM, et al. Twin anemia polycythemia sequence: current views on pathogenesis, diagnostic criteria, perinatal management, and outcome. *Twin Res Hum Genet*. 2016;19(3):222–233
40. Maggio L, Carr SR, Watson-Smith D, et al. Iatrogenic preterm premature rupture of membranes after fetoscopic laser ablative surgery. *Fetal Diagn Ther*. 2015;38(1):29–34
41. Petersen SG, Gibbons KS, Luks FI, et al. The impact of entry technique and access diameter on prelabour rupture of membranes following primary fetoscopic laser treatment for twin-twin transfusion syndrome. *Fetal Diagn Ther*. 2016;40(2):100–109
42. Lopriore E, Bökenkamp R, Rijlaarsdam M, Sueters M, Vandenbussche FP, Walther FJ. Congenital heart disease in twin-to-twin transfusion syndrome treated with fetoscopic laser surgery. *Congenit Heart Dis*. 2007;2(1):38–43
43. Moon-Grady AJ, Rand L, Gallardo S, et al. Diastolic cardiac pathology and clinical twin-twin transfusion syndrome in monochorionic/diamniotic twins. *Am J Obstet Gynecol*. 2011;205:279.e1–e11
44. Herberg U, Bolay J, Graeve P, Hecher K, Bartmann P, Breuer J. Intertwin cardiac status at 10-year follow-up after intrauterine laser coagulation therapy of severe twin-twin transfusion syndrome: comparison of donor, recipient and normal values. *Arch Dis Child Fetal Neonatal Ed*. 2014;99(5):F380–F385
45. Pruetz JD, Schrager SM, Wang TV, et al. Blood pressure evaluation in children treated with laser surgery for twin-twin transfusion syndrome at 2-year follow-up. *Am J Obstet Gynecol*. 2015;213:417.e1–e7
46. De Paepe ME, Stopa E, Huang C, Hansen K, Luks FI. Renal tubular apoptosis in twin-to-twin transfusion syndrome. *Pediatr Dev Pathol*. 2003;6(3):215–225
47. Lopriore E, Middeldorp JM, Sueters M, Oepkes D, Vandenbussche FP, Walther FJ. Long-term neurodevelopmental outcome in twin-to-twin transfusion syndrome treated with fetoscopic laser surgery. *Am J Obstet Gynecol*. 2007;196(3):231.e1–231.e4
48. Kowitt B, Tucker R, Watson-Smith D, et al. Long-term morbidity after fetal endoscopic surgery for severe twin-to-twin transfusion syndrome. *J Pediatr Surg*. 2012;47(1):51–56
49. Lenclen R, Ciarlo G, Paupe A, et al. Neurodevelopmental outcome at 2 years in children born preterm treated by amnioreduction or fetoscopic laser surgery for twin-to-twin transfusion syndrome: comparison with dichorionic twins. *Am J Obstet Gynecol*. 2009;201:291.e1–e5
50. Dickinson JE, Duncombe GJ, Evans SF, French NP, Hagan R. The long term neurologic outcome of children from pregnancies complicated by twin-to-twin transfusion syndrome. *BJOG*. 2005;112 (1):63–68
51. Rossi AC, Vanderbilt D, Chmait RH. Neurodevelopmental outcomes after laser therapy for twin-twin transfusion syndrome: a systematic review and meta-analysis. *Obstet Gynecol*. 2011;118 (5):1145–1150
52. Ortibus E, Lopriore E, Deprest J, et al. The pregnancy and long-term neurodevelopmental outcome of monochorionic diamniotic twin gestations: a multicenter prospective cohort study from the first trimester onward. *Am J Obstet Gynecol*. 2009;200:494.e1–e8

NeoReviews Quiz

There are two ways to access the journal CME quizzes:
1. Individual CME quizzes are available via a handy blue CME link in the Table of Contents of any issue.
2. To access all CME articles, click "Journal CME" from Gateway's orange main menu or go directly to: http://www.aappublications.org/content/journal-cme.

1. A woman with twin gestation is undergoing evaluation for 1 twin having oligohydramnios. There is concern for twin-to-twin transfusion syndrome (TTTS). Which of the following statements regarding diagnosis of TTTS is appropriately stated?
    A. In dichorionic twin pregnancies, there is a 30% to 50% chance of TTTS being diagnosed, with higher likelihood when the twins are of opposite sexes.
    B. The presence of a positive "lambda" or "delta" sign is highly suspicious for TTTS.
    C. In most TTTS cases, both twins have oligohydramnios.
    D. TTTS is diagnosed based solely on ultrasonographic criteria.
    E. Fetal blood sampling of TTTS is required for definitive diagnosis of TTTS.
2. A woman with monochorionic, diamniotic twin pregnancy is diagnosed with probable TTTS. Oligohydramnios is noted in 1 twin and polyhydramnios in the other. If TTTS is present, which of the following statements regarding this pregnancy is most likely to be correct?
    A. There is likely to be a balanced net blood flow across communicating placental vessels.
    B. The frequency of artery-to-artery anastomoses is typically higher in pregnancies complicated by TTTS than in non-TTTS pregnancies.
    C. If artery-to-vein anastomoses are present, they are likely to be deep and represent cotyledons shared by both fetuses, with both donor-to-recipient and recipient-to-donor communication coexisting, with the net flow favoring donor-to-recipient.
    D. There is less likelihood of peripheral cord insertion compared with non-TTTS gestations, but if it is present, will most likely be found in the recipient twin.
    E. If there is fetal demise, it will most likely occur first in the recipient twin.
3. A woman with twin gestation undergoes ultrasonographic evaluation. The findings are as follows: both twins are alive with normal heart rate; there is no ascites, skin edema, or pleural effusion in either twin; the donor twin has no end-diastolic umbilical artery flow; the donor bladder is not seen during the entire 30-minute ultrasound evaluation, and the recipient twin appears to have moderate tricuspid regurgitation. Which of the following stages (described by Quintero et al [16]) best characterizes TTTS in this pregnancy at this moment?
    A. Stage I.
    B. Stage II.
    C. Stage III.
    D. Stage IV.
    E. Stage V.
4. A twin pregnancy is diagnosed with TTTS. One twin has oligohydramnios and appears growth restricted. The other twin has polyhydramnios. Treatment with fetoscopic laser occlusion of chorioangiopagous vessels (FLOC) is being considered. Which of the following correctly describes this procedure?
    A. The procedure uses laser energy to photocoagulate the placental anastomoses between the twins, which will interrupt the hemodynamic imbalance that characterizes the syndrome.
    B. An inter-twin septostomy is performed to restore amniotic fluid volume balance.
    C. Serial amnioreduction is performed in the recipient's sac, up to 2 L each week.
    D. Watchful waiting is under way, with laser-guided ablation of artery-to-artery connections only when discordance reaches more than 20%.
    E. A stent is placed across the umbilical vessels to create a new vascular connection from the recipient twin to the donor twin and thereby help to restore fluid balance.

NOTE: Learners can take *NeoReviews* quizzes and claim credit online only at: http://Neoreviews.org.

To successfully complete 2017 *NeoReviews* articles for *AMA PRA Category 1 Credit™*, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

This journal-based CME activity is available through Dec. 31, 2019, however, credit will be recorded in the year in which the learner completes the quiz.

5. Twins are delivered after FLOC for TTTS at 34 weeks' gestational age. Which of the following statements concerning neonatal outcomes in TTTS is correct?

   A. Anemia is likely to be present in the recipient twin, with polycythemia in the donor.
   B. The donor is usually appropriate or large for gestational age.
   C. Prolonged evidence of right cardiac strain in the recipient after FLOC is always associated with a poor outcome, with gradual worsening over time.
   D. Renal tubular apoptosis is most commonly seen in recipient twins.
   E. Both donor and recipient twins are at risk for hypertension and should receive close blood pressure monitoring.

What––and Why––the Neonatologist Should Know About Twin-To-Twin Transfusion Syndrome

Joseph M. Bliss, Stephen R. Carr, Monique E. De Paepe and Francois I. Luks

NeoReviews 2017;18;e22
DOI: 10.1542/neo.18-1-e22

NeoReviews™
AN OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF THE PEDIATRICS

What––and Why––the Neonatologist Should Know About Twin-To-Twin Transfusion Syndrome

Joseph M. Bliss, Stephen R. Carr, Monique E. De Paepe and Francois I. Luks

NeoReviews 2017;18;e22
DOI: 10.1542/neo.18-1-e22