Twin-twin transfusion syndrome

Society for Maternal-Fetal Medicine (SMFM), with the assistance of Lynn L. Simpson, BSc, MSc, MD

OBJECTIVE: We sought to review the natural history, pathophysiology, diagnosis, and treatment options for twin-twin transfusion syndrome (TTTS).

METHODS: A systematic review was performed using MEDLINE database, PubMed, EMBASE, and Cochrane Library. The search was restricted to English-language articles published from 1966 through July 2012. Priority was given to articles reporting original research, in particular randomized controlled trials, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Evidence reports and guidelines published by organizations or institutions such as the National Institutes of Health, Agency for Health Research and Quality, American College of Obstetricians and Gynecologists, and Society for Maternal-Fetal Medicine were also reviewed, and additional studies were located by reviewing bibliographies of identified articles. Consistent with US Preventive Task Force guidelines, references were evaluated for quality based on the highest level of evidence, and recommendations were graded accordingly.

RESULTS AND RECOMMENDATIONS: TTTS is a serious condition that can complicate 8-10% of twin pregnancies with monochorionic diamniotic (MCDA) placentation. The diagnosis of TTTS requires 2 criteria: (1) the presence of a MCDA pregnancy; and (2) the presence of oligohydramnios (defined as a maximal vertical pocket of <2 cm) in one sac, and of polyhydramnios (a maximal vertical pocket of >8 cm) in the other sac. The Quintero staging system appears to be a useful tool for describing the severity of TTTS in a standardized fashion. Serial sonographic evaluation should be considered for all twins with MCDA placentation, usually beginning at around 16 weeks and continuing about every 2 weeks until delivery. Screening for congenital heart disease is warranted in all monochorionic twins, in particular those complicated by TTTS. Extensive counseling should be provided to patients with pregnancies complicated by TTTS including natural history of the disease, as well as management options and their risks and benefits. The natural history of stage I TTTS is that more than three-fourths of cases remain stable or regress without invasive intervention, with perinatal survival of about 86%. Therefore, many patients with stage I TTTS may often be managed expectantly. The natural history of advanced (eg, stage ≥III) TTTS is bleak, with a reported perinatal loss rate of 70-100%, particularly when it presents <26 weeks. Fetoscopic laser photocoagulation of placental anastomoses is considered by most experts to be the best available approach for stages II, III, and IV TTTS in continuing pregnancies at <26 weeks, but the metaanalysis data show no significant survival benefit, and the long-term neurologic outcomes in the Eurofetus trial were not different than in nonlaser-treated controls. Even laser-treated TTTS is associated with a perinatal mortality rate of 30-50%, and a 5-20% chance of long-term neurologic handicap. Steroids for fetal maturation should be considered at 24 0/7 to 33 6/7 weeks, particularly in pregnancies complicated by stage ≥III TTTS, and those undergoing invasive interventions.

Key words: amnioreduction, fetoscopy, laser photocoagulation, monochorionic twins, twin-twin transfusion syndrome

Question 1. How is the diagnosis of twin-twin transfusion syndrome made and how is it staged? (Levels II and III)

Twin-twin transfusion syndrome (TTTS) is diagnosed prenatally by ultrasound. The diagnosis requires 2 criteria: (1) the presence of a monochorionic diamniotic (MCDA) pregnancy; and (2) the presence of oligohydramnios (defined as a maximal vertical pocket [MVP] of <2 cm) in one sac, and of polyhydramnios (a MVP of >8 cm) in the other sac (Figure 1).[1] MVP of 2 cm and 8 cm represent the 5th and 95th percentiles for amniotic fluid measurements, respectively, and the presence of both is used to define stage I TTTS.[2] If there is a subjective difference in amniotic fluid in the 2 sacs that fails to meet these criteria, progression to TTTS occurs in <15% of cases.[3] Although growth discordance (usually defined as >20%) and intrauterine growth restriction (IUGR) (estimated fetal weight <10% for gestational age) often complicate TTTS, growth discordance itself or IUGR itself are not diagnostic criteria.[4] The differential diagnosis may include selective IUGR, or possibly an anomaly in 1 twin causing amniotic fluid abnormality.[5] Twin anemia-polycythemia sequence (TAPS) has been recently described in MCDA gestations, and is defined as the presence of anemia in the donor and polycythemia in the recipient, diagnosed antenatally by middle cerebral artery (MCA)–peak systolic velocity (PSV) >1.5 multiples of median in the donor and MCA PSV <1.0 multiples of median in the recipient, in the absence of oligohydramnios-polyhydramnios.[6] Further studies are required to determine the natural history and possible management of TAPS. TTTS can occur in a MCDA twin pair in triplet or higher-order pregnancies.

The most commonly used TTTS staging system was developed by Quintero et al[2] in 1999, and is based on sonographic findings. The TTTS Quintero staging

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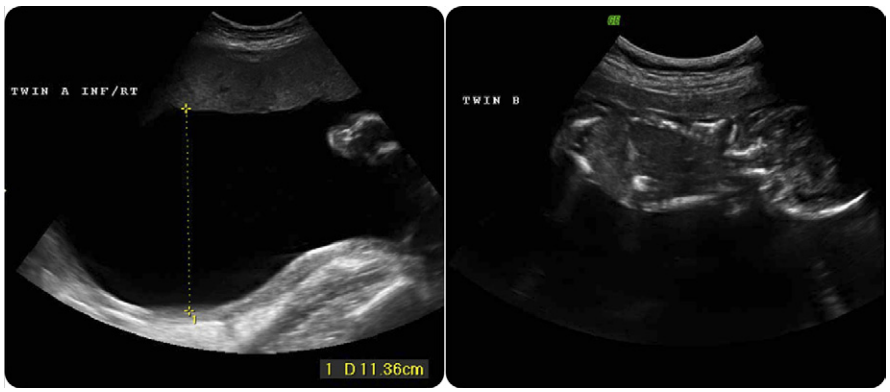
FIGURE 1
Polyhydramnios-oligohydramnios sequence



Monochorionic diamniotic twins with twin-twin transfusion syndrome demonstrating polyhydramnios in recipient's sac (twin A) while donor (twin B) was stuck to anterior uterine wall due to marked oligohydramnios.

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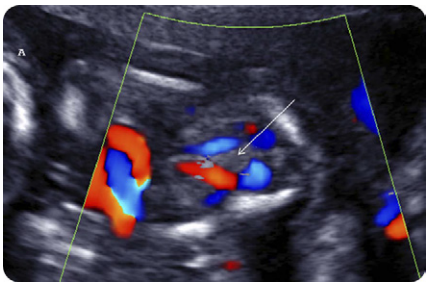
FIGURE 2
Stage II twin-twin transfusion syndrome



Nonvisualization of fetal bladder (*arrow*) between umbilical arteries in donor twin.

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system includes 5 stages, ranging from mild disease with isolated discordant amniotic fluid volume to severe disease with demise of one or both twins (Table 1 and Figures 2 and 3). This system has some prognostic significance and provides a method to compare outcome data using different therapeutic interventions.[2] Although the stages do not correlate perfectly with perinatal survival,[7] it is relatively straightforward to apply, may improve communication between patients and providers, and identifies the subset of cases most likely to benefit from treatment.[8,9]

Since the development of the Quintero staging system, much has been learned about the changes in fetal cardiovascular physiology that accompany disease progression (discussed below). Myocardial performance abnormalities have been described, particularly in recipient twins, including those with only stage I or II TTTS.[10] Several groups of investigators have attempted to use assessment of fetal cardiac function to either modify the Quintero TTTS stage[11] or develop a new scoring system.[12] While this approach has some benefits, the models have not yet been prospectively validated. As a result, a recent expert panel concluded that there were insufficient data to recommend modifying the Quintero staging system or adopting a new system.[8] Thus, despite debate over the merits of the Quintero system, at this time it appears to be a useful tool for the diagnosis of TTTS, as well as for describing its severity, in a standardized fashion.

TABLE 1
Staging of twin-twin transfusion syndrome[2]

Stage	Ultrasound parameter	Categorical criteria
I	MVP of amniotic fluid	MVP <2 cm in donor sac; MVP >8 cm in recipient sac
II	Fetal bladder	Nonvisualization of fetal bladder in donor twin over 60 min of observation (Figure 2)
III	Umbilical artery, ductus venosus, and umbilical vein Doppler waveforms	Absent or reversed umbilical artery diastolic flow, reversed ductus venosus a-wave flow, pulsatile umbilical vein flow (Figure 3)
IV	Fetal hydrops	Hydrops in one or both twins
V	Absent fetal cardiac activity	Fetal demise in one or both twins

MVP, maximal vertical pocket.

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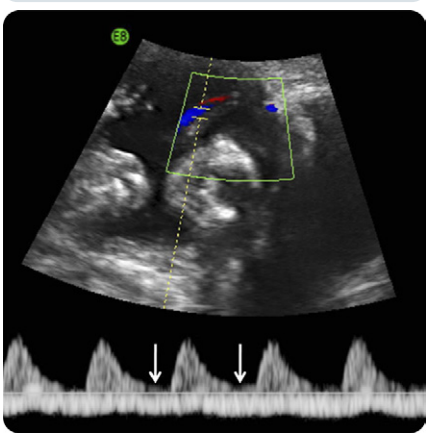
Question 2. How often does TTTS complicate monochorionic twins and what is its natural history? (Levels II and III)

Approximately one-third of twins are monozygotic (MZ), and three-fourths of MZ twins are MCDA. In general, only

FIGURE 3
Stage III twin-twin transfusion syndrome



Absent end-diastolic flow (*arrows*) in umbilical artery of donor twin.

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twin gestations with MCDA placentation are at significant risk for TTTS, which complicates about 8-10% of MCDA pregnancies.[13,14] TTTS is very uncommon in MZ twins with dichorionic or monoamniotic placentation.[15] Although most twins conceived with in vitro fertilization (IVF) are dichorionic, it is important to remember that there is a 2- to 12-fold increase in MZ twinning in embryos conceived with IVF, and TTTS can therefore occur for IVF MCDA pregnancies.[16,17] In current practice, the prevalence of TTTS is approximately 1-3 per 10,000 births.[18]

The presentation of TTTS is highly variable. Because pregnancies with TTTS often receive care at referral centers, data about the stage of TTTS at initial presentation (ie, to nonreferral centers) are lacking in the literature. Fetal therapy centers report that about 11-15% of their cases at referral were Quintero stage I (probably underestimated as some referral centers did not report stage I TTTS cases), 20-40% were stage II, 38-60% were stage III, 6-7% were stage IV, and 2% were stage V.[5,9] Although TTTS may develop at any time in gestation, the majority of cases are diagnosed in the second trimester. Stage I may progress to a nonvisualized fetal bladder in the donor (stage II) (Figure 2), and absent or reversed end-diastolic flow in the umbilical artery of donor or recipient twins may subsequently develop (stage III) (Figure 3), followed by hydrops (stage IV). However, TTTS often does not progress in a predictable manner. Natural history data by stage are limited, especially for stages II-V, as staging was initially proposed in 1999.[2] This is because most natural history data were published before 1999, and therefore was not stratified by stage (Table 2).[19-21] Over three fourths of stage I TTTS cases remain stable or regress without invasive interventions (Table 2).[19-21] The natural history of advanced (eg, stage ≥III) TTTS is bleak, with a reported perinatal loss rate of 70-100%, particularly when it presents <26 weeks.[22,23] It is estimated that TTTS accounts for up to 17% of the total perinatal mortality in twins, and for about half of all perinatal deaths in MCDA twins.[13,24] Without treatment, the loss of at least 1 fetus is common, with demise of the remaining twin occurring in about 10% of cases of twin demise, and neurologic handicap affecting 10-30% of cotwin remaining survivors.[25-27] Overall, single twin survival rates in TTTS vary widely between 15-70%, depending on the gestational age at diagnosis and severity of disease.[22,26] The lack of a predictable natural history, and therefore the uncertain prognosis for TTTS, pose a significant challenge to the clinician caring for MCDA twins.

TABLE 2
Natural history of stage I twin-twin transfusion syndrome[19-21]

Stage	Incidence of progression to higher stage	Incidence of resolution, regression to lower stage, or stability	Overall survival
I	6/39 (15%)	33/39 (85%)	102/118 (86%)

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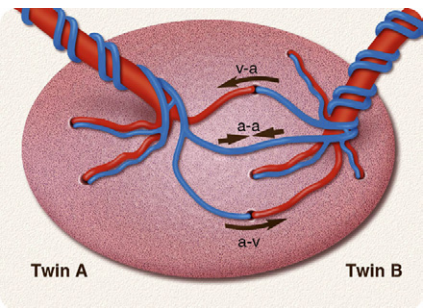
Question 3. What is the underlying pathophysiology of TTTS? (Levels II and III)

The primary etiologic problem underlying TTTS is thought to lie within the architecture of the placenta, as intertwin vascular connections within the placenta are critical for the development of TTTS. Virtually all MCDA placentas have anastomoses that link the circulations of the twins, yet not all MCDA twins develop TTTS. There are 3 main types of anastomoses in monochorionic placentas: venovenous (VV), arterioarterial (AA), and arteriovenous (AV). AV anastomoses are found in 90-95% of MCDA placentas, AA in 85-90%, and VV in 15-20%.[28,29] Both AA and VV anastomoses are direct superficial connections on the surface of the placenta with the potential for bidirectional flow (Figure 4). In AV anastomoses, while the vessels themselves are on the surface of the placenta, the actual anastomotic connections occur in a cotyledon, deep within the placenta (Figure 4). AV anastomoses can result in unidirectional flow from one twin to the other, and if uncompensated, may lead to an imbalance of volume between the twins. Unlike AA and VV, which are direct vessel-to-vessel connections, AV connections are linked through large capillary beds deep within the cotyledon. AV anastomoses are usually multiple and overall balanced in both directions so that TTTS does not occur. While the number of AV anastomoses from donor to recipient may be important, their size as well as placental resistance likely influences the volume of intertwin transfusion that occurs.[30] Placentas in twins affected with TTTS are reportedly more likely to have VV, but less likely to have AA anastomoses.[28] It is thought that these bidirectional anastomoses may compensate for the unidirectional flow through AV connections, thereby preventing the development of TTTS or decreasing its severity when it does occur.[31] Mortality is highest in the absence of AA and lowest when these anastomoses are present (42% vs 15%).[29] However, the presence of AA is not completely protective, as about 25-30% of TTTS cases may also have these anastomoses.[32] The imbalance of blood flow through the placental anastomoses leads to volume depletion in the donor twin, with oliguria

FIGURE 4
Selected anastomoses in monochorionic placentas



Courtesy of Vickie Feldstein, University of California, San Francisco.

a-a, arterioarterial anastomosis; *a-v*, arteriovenous anastomosis; *v-a*, venous-arterial anastomosis.

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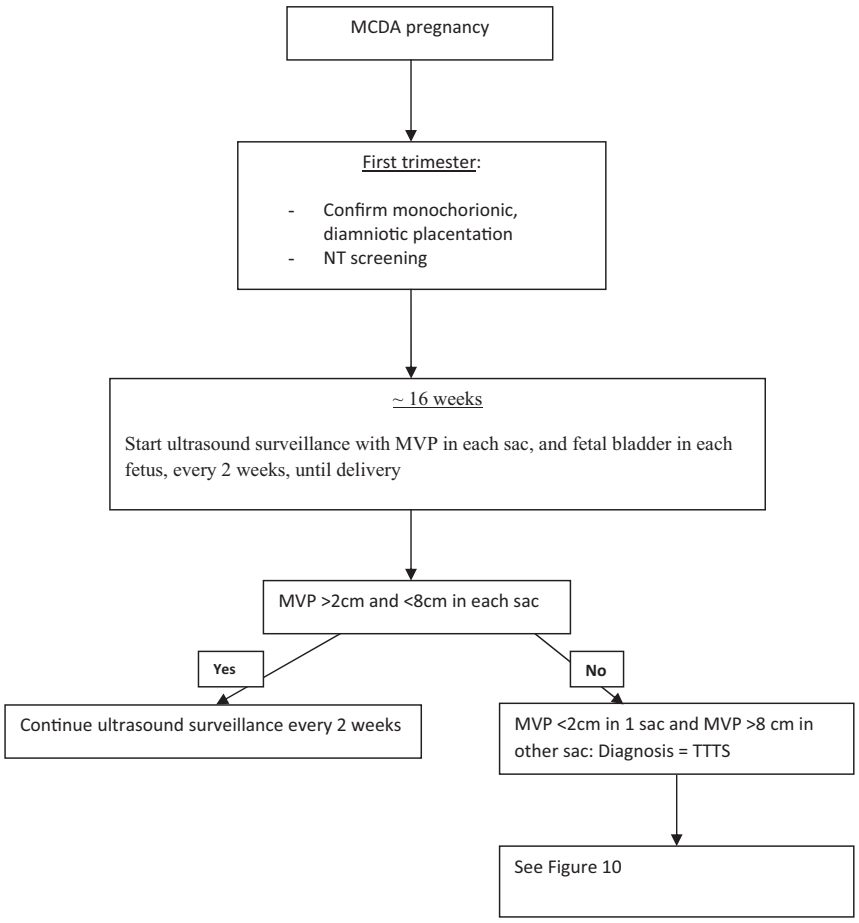
FIGURE 5
Algorithm for screening for TTTS



MCDA, monochorionic diamniotic; *MVP*, maximum vertical pocket; *NT*, nuchal translucency; *TTTS*, twin-twin transfusion syndrome.
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and oligohydramnios, and to volume overload in the recipient twin, with polyuria and polyhydramnios.

There also appear to be additional factors beyond placental morphology, such as complex interactions of the renin-angiotensin system in the twins,[33-35] involved in the development of this disorder.

Question 4. How should monochorionic twin pregnancies be monitored for the development of TTTS? (Levels II and III)

All women with a twin pregnancy should be offered an ultrasound examination at 10-13 weeks of gestation to assess viability, chorionicity, crown-rump length, and nuchal translucency. TTTS usually presents in the second trimester, and is a dynamic condition that can remain stable throughout gestation, occasionally regress spontaneously, progress slowly over a number of weeks, or develop quickly within a period of days with rapid deterioration in the well-being of the twins. There have been no randomized trials of the optimal frequency of ultrasound surveillance of MCDA pregnancies to detect TTTS. Although twin pregnancies are often followed up with sonography every 4 weeks, sonography as often as every 2 weeks has been proposed for monitoring of MCDA twins for the development of TTTS.[36-38] This is in part because, while stage I TTTS has been observed to remain stable or resolve in most cases, when progression does occur it can happen quickly.[39] However, studies that have focused on progression of early-stage TTTS may not be applicable to the question of disease development in apparently unaffected pregnancies.

Given the risk of progression from stage I or II to more advanced stages, and that TTTS usually presents in the second trimester, serial sonographic evaluations about every 2 weeks, beginning usually around 16 weeks of gestation, until delivery, should be considered for all twins with MCDA placentation, until more data are available allowing better risk stratification[37,38] (Figure 5). Sonographic surveillance less often than every 2 weeks has been associated with a higher incidences of late-stage diagnosis of TTTS.[40] This underscores the importance of establishing chorionicity in twin pregnancies as early as possible.[41] These serial sonographic evaluations to screen for TTTS should include at least MVP of each sac, and the presence of the bladder in each fetus. Umbilical artery Doppler flow assessment, especially if there is discordance in fluid or growth, is not unreasonable, but data on the utility of this added screening parameter are limited. There is no evidence that monitoring for TAPS with MCA PSV Doppler at any time, including >26 weeks, improves outcomes, so that this additional screening cannot be recommended at this time.[6]

In addition to monitoring MCDA pregnancies for development of amniotic fluid abnormalities, there are several second- and even first-trimester sonographic findings that have been associated with TTTS. These findings are listed in Table 3.[28,42-49] Before 14 weeks, MCDA twins can be evaluated with nuchal translucency and crown-lump length. Nuchal translucency abnormalities and crown-lump length discrepancy have been associated with an increased risk of TTTS.[28,29,38] If such findings (Table 3) are encountered, it may be reasonable to perform more frequent surveillance (eg, weekly instead of every 2 weeks) for TTTS. Velamentous placental cord insertion (Figure 6) has been found in approximately one third of placentas with TTTS.[28] Intertwin membrane folding (Figure 7) has been associated with development of TTTS in more than a third of cases.[42] The clinical utility of the sonographic findings listed in Table 3 has not been prospectively evaluated, and several require Doppler evaluation not typically performed in otherwise uncomplicated MCDA ges-

tations. Thus, while they are associated with TTTS and may potentially improve TTTS detection, they are not specifically recommended as part of routine surveillance.

In addition to TTTS, MCDA gestations are at risk for discordant twin growth or discordant IUGR. When compared to MCDA twins with concordant growth, velamentous placental cord insertion (22% vs 8%, $P < .001$) and unequal placental sharing (56% vs 19%, $P < .0001$) are seen more commonly in cases with discordant growth.[50] Unequal placental sharing occurs in about 20% of MCDA gestations and can coexist with TTTS, complicating the diagnosis and management of the pregnancy. For example, abnormal umbilical artery waveforms in MCDA twins may represent placental insufficiency, but may also be secondary to the presence of intertwin anastomoses and changes in vascular reactivity typical of TTTS (Figure 3). Overall, the development of abnormal end-diastolic flow in the umbilical artery, especially absent or reversed, has been associated with later deterioration of fetal testing necessitating delivery in MCDA twins,[51,52] but latency between Doppler and other fetal testing changes is increased in these gestations compared to singletons.[53] Frequent, eg, twice weekly, fetal surveillance is suggested for MCDA pregnancies with abnormal umbilical artery Doppler once viability is reached.[52]

TABLE 3
First- and second-trimester sonographic findings associated with twin-twin transfusion syndrome

First-trimester findings
Crown-rump length discordance[43]
Nuchal translucency >95th percentile[42,44] or discordance >20% between twins[45,46]
Reversal or absence of ductus venosus A-wave[47,48]
Second-trimester findings
Abdominal circumference discordance[43]
Membrane folding[28,42]
Velamentous placental cord insertion (donor twin)[28]
Placental echogenicity (donor portion hyperechoic)[49]

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Question 5. Is there a role for fetal echocardiography in TTTS? (Levels II and III)

Screening for congenital heart disease with fetal echocardiography is warranted in all monochorionic twins as the risk of cardiac anomalies is increased 9-fold in MCDA twins and up to 14-fold in cases of TTTS, above the population prevalence of approximately 0.5%.[54] Specifically, the prevalence of congenital cardiac anomalies has been reported to be 2% in otherwise uncomplicated MCDA gestations and 5% in cases of TTTS, particularly among recipient twins.[55] Although many cases are minor septal defects, an increase in right ventricular outflow tract obstruction has also been reported.[55] It is theorized that the abnormal placentation that occurs in monochorionic twins, particularly in cases that develop TTTS, contributes to abnormal fetal heart formation.[54]

The functional cardiac abnormalities that complicate TTTS occur primarily in recipient twins. Volume overload causes increased pulmonary and aortic velocities, cardiomegaly, and atrioventricular valve regurgitation (Figure 8). Over time, recipient twins can develop progressive biventricular hypertrophy and diastolic dysfunction as well as poor right ventricular systolic function that can lead to functional right ventricular outflow tract obstruction and pulmonic stenosis (Figure 9).[54,56] The development of right ventricular outflow obstruction, observed in close to 10% of all recipient twins, is likely multifactorial, a consequence of increased preload, afterload, and circulating factors such as renin, angiotensin, endothelin, and atrial and brain natriuretic peptides.[57-59] The cardiovascular response to TTTS contributes to the poor outcome of recipient twins while recipients with normal cardiac function have improved survival.[60]

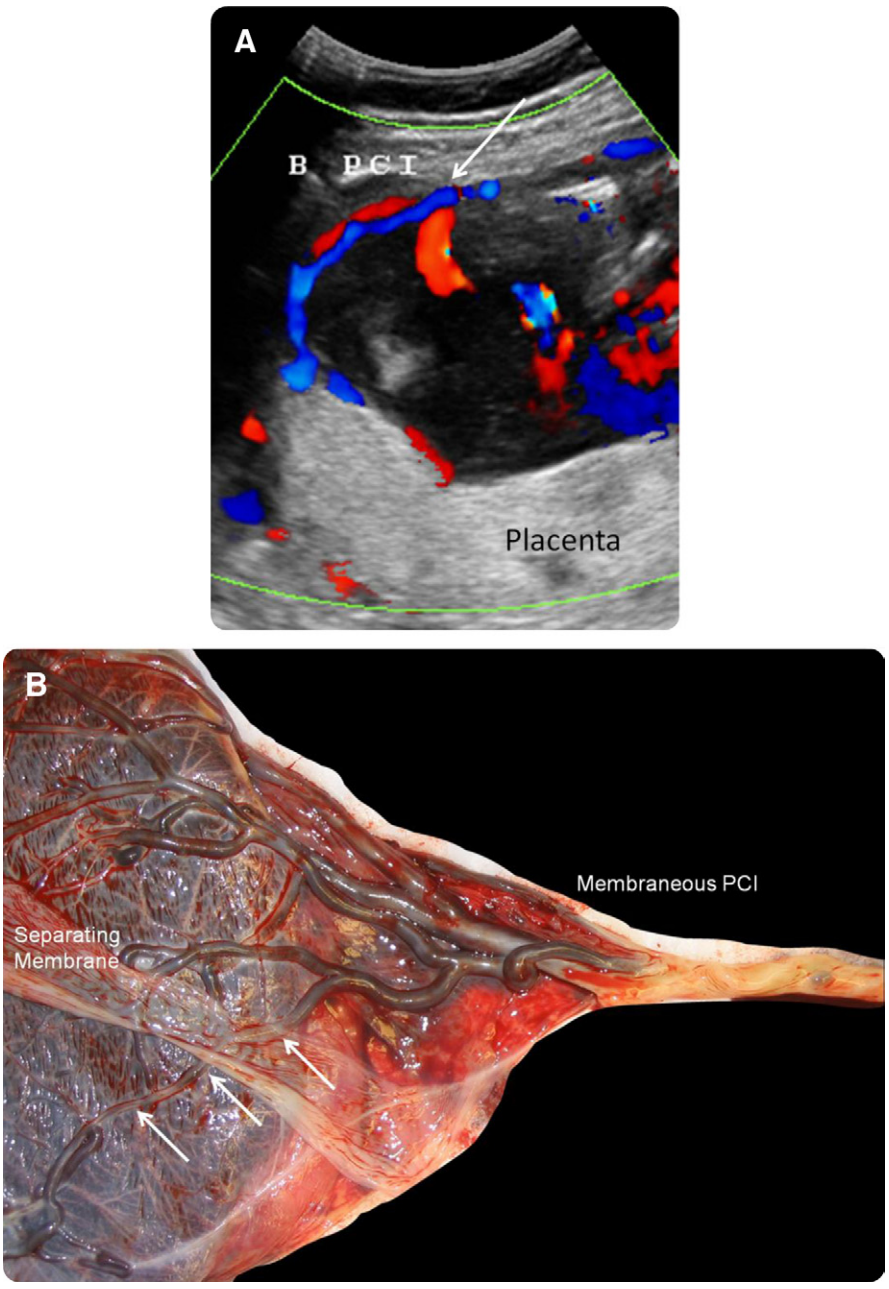
A functional assessment of the fetal heart may be useful in identifying cases that would benefit from therapy and in evaluating the response to treatment. The myocardial performance index or Tei index, an index of global ventricular performance by Doppler velocimetry, is a measure of both systolic and diastolic function,[61] and has been used to monitor fetuses with TTTS.[62] Donor twins with TTTS tend to have normal cardiac function, whereas recipient twins may develop ventricular hypertrophy (61%), atrioventricular valve regurgitation (21%), and abnormal right ventricular (50%) or left ventricular (58%) function.[11,58] Overall, two thirds of recipient twins show diastolic dysfunction, as indicated by a prolonged ventricular isovolumetric relaxation time, which is associated with an increased risk of fetal death.[58]

Although fetal cardiac findings are not officially part of the TTTS staging system, many centers routinely perform fetal echocardiography in cases of TTTS and have observed worsening cardiac function in advanced stages.[11] However, cardiac dysfunction can also be detected in up to 10% of apparently early-stage TTTS.[11] It has been theorized that the early diagnosis of recipient twin cardiomyopathy may identify those MCDA gestations that would benefit from early intervention. In summary, scoring systems that include cardiac dysfunction have been developed, but their usefulness to predict outcome in TTTS remains controversial.[63,64] Further evaluation of functional fetal echocardiography as a tool for decision-making about intervention and management in TTTS is needed.

Question 6. What management options are available for TTTS? (Levels I, II, and III)

The management options described for TTTS include expectant management,

FIGURE 6
Abnormal placental cord insertion



A, Velamentous or membranous placental cord insertion (PCI) (*arrow*) of monochorionic diamniotic twin detected by color Doppler. **B**, Velamentous PCI confirmed on examination of placenta with identification of anastomosis (*arrows*) passing beneath separating membrane and joining circulations of twins.

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amnioreduction, intentional septostomy of the intervening membrane, fetoscopic laser photocoagulation of placental anastomoses, and selective reduction. The interventions that have been evaluated in randomized controlled trials (RCTs) include intentional septostomy of the intervening membrane to equalize the fluid in both sacs, amnioreduction of the excess fluid in the recipient's sac, and laser ablation of placental anastomoses. There have been 3 randomized trials designed to evaluate some of the different treatment modalities for TTTS, all of which were terminated prior to recruitment of the planned subject number after interim analyses, as discussed below.[65-67] Despite the limitations and early termination of these clinical trials, they represent the best available data upon which to judge the various treatments for TTTS. Consultation with a maternal-fetal medicine specialist is recommended, particularly if the patient is at a gestational age at which laser therapy is potentially an option. In evaluating the data, considerations include the stage of TTTS, the details of the intervention, and the perinatal outcome. The most important outcomes reported are overall perinatal mortality, survival of at least 1 twin, and, if available, long-term outcomes of the babies, including neurologic outcome. Extensive counseling should be provided to patients with pregnancies complicated by TTTS, including natural history of the disease, as well as management options and their risks and benefits.

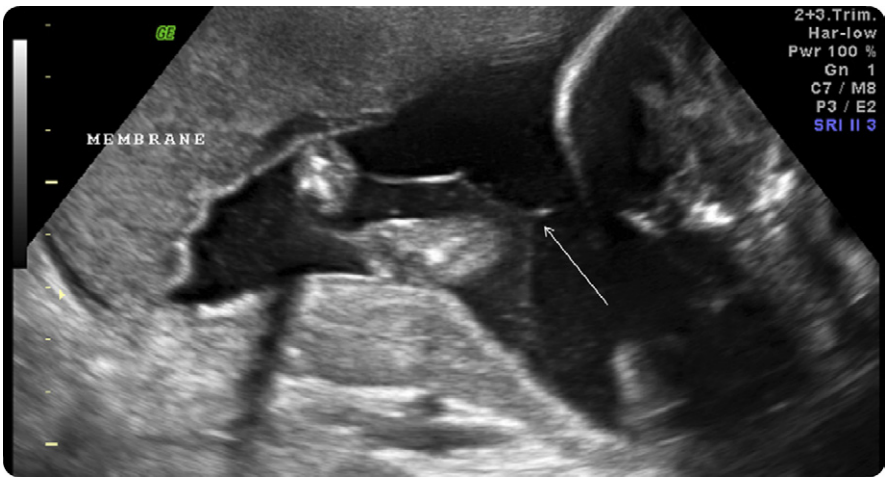
Expectant management involves no intervention. This natural history of TTTS, also called conservative management, has limited outcome data according to stage, particularly for advanced disease (Table 2). It is important that the limitations in the available data are discussed with the patient with TTTS, and compared with available outcome data for interventions.

Amnioreduction involves the removal of amniotic fluid from the polyhydramniotic sac of the recipient. It is usually done only when the MVP is >8 cm, with an aim to correct it to a MVP of <8 cm, often to <5 cm or <6 cm.[65-67] Usually an 18-[65] or 20[67]-gauge needle is used. Some practitioners use aspiration with syringes, while some use vacuum containers.[66] Amnioreduction can be performed either as a 1-time procedure, as at times this can resolve stage I or II TTTS, or serially, eg, every time the MVP is >8 cm. It can be performed any time >14 weeks. Amnioreduction is hypothesized to reduce the intraamniotic and placental intravascular pressures, potentially facilitating placental blood flow,

and/or to possibly reduce the incidence of preterm labor and birth related to polyhydramnios. Amnioreduction may be used also >26 weeks, particularly in cases with maternal respiratory distress or preterm contractions from polyhydramnios.[68] Amnioreduction has been associated with average survival rates of 50%, with large registries reporting 60-65% overall survival.[69,70] However, serial amnioreduction is often necessary, and repeated procedures increase the likelihood of complications such as preterm premature rupture of the membranes, preterm labor, abruption, infection, and fetal death.[71] Another consideration is that any invasive procedure prior to fetoscopy may decrease the feasibility and success of laser due to bleeding, chorioamnion separation, inadvertent septostomy, or membrane rupture.

Septostomy involves intentionally puncturing with a needle the amniotic membranes between the 2 MCDA sacs, theoretically allowing equilibration of amniotic fluid volume in the 2 sacs.[66] In the 1 randomized trial in which it was evaluated, the intertwin membrane was purposefully perforated under ultrasound guidance with a single puncture using a 22-gauge needle.[66] This was usually introduced through the donor's twin gestational sac into the recipient twin's amniotic cavity. If reaccumulation of amniotic fluid in the donor twin sac was not seen in about 48 hours, a repeat septostomy was undertaken.[66] Intentional septostomy is mentioned only to note that it has generally been abandoned as a treatment for TTTS. It is believed to offer no significant therapeutic advantage, and may lead to disruption of the membrane and a functional monoamniotic situation. A randomized trial of amnioreduction vs septostomy ended after an interim analysis found that the rate of survival of at least 1 twin was similar between the 2 groups, and that recruitment had been slower than anticipated[66] (Table 4). In all, 97% of the enrolled pregnancies had stages I-III TTTS, and results were not otherwise reported by stage. In 40% of the septostomy cases, additional procedures were needed. No data on neurologic outcome are available.[66]

FIGURE 7
Membrane folding



Membrane folding (*arrow*) suggestive of discordant amniotic fluid volume in monochorionic diamniotic twin gestation.

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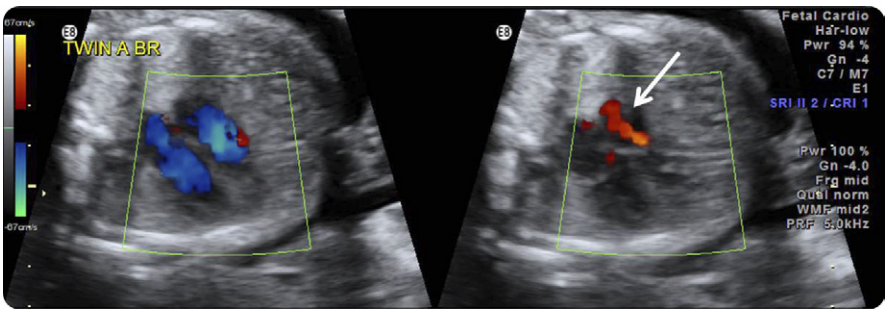
Laser involves photocoagulating the vascular anastomoses crossing from one side of the placenta to the other. This is usually performed by placing a sheath and passing an endoscope under ultrasound guidance. Ultrasound is also used to map the vasculature to determine the placental angioarchitecture. The primary theoretical advantage of laser coagulation is that it is designed to interrupt the placental anastomoses that give rise to TTTS. The goal of laser ablation is to functionally separate the placenta into 2 regions, each supplying one of the twins. This unlinking of the circulations of the twins is often referred to as "dichorionization" of the monochorionic placenta. Adequate visualization of the vascular equator that separates the cotyledons of one twin from the other is critical for laser photocoagulation. Selective coagulation of AV as well as AA and VV anastomoses is preferred over nonselective ablation of all vessels crossing the separating membrane as it appears to lead to fewer procedure-related fetal

FIGURE 8
Cardiac dysfunction in recipient twin



Color flow imaging demonstrating forward flow across atrioventricular valves in diastole and severe tricuspid regurgitation (*arrow*) during systole in recipient twin.

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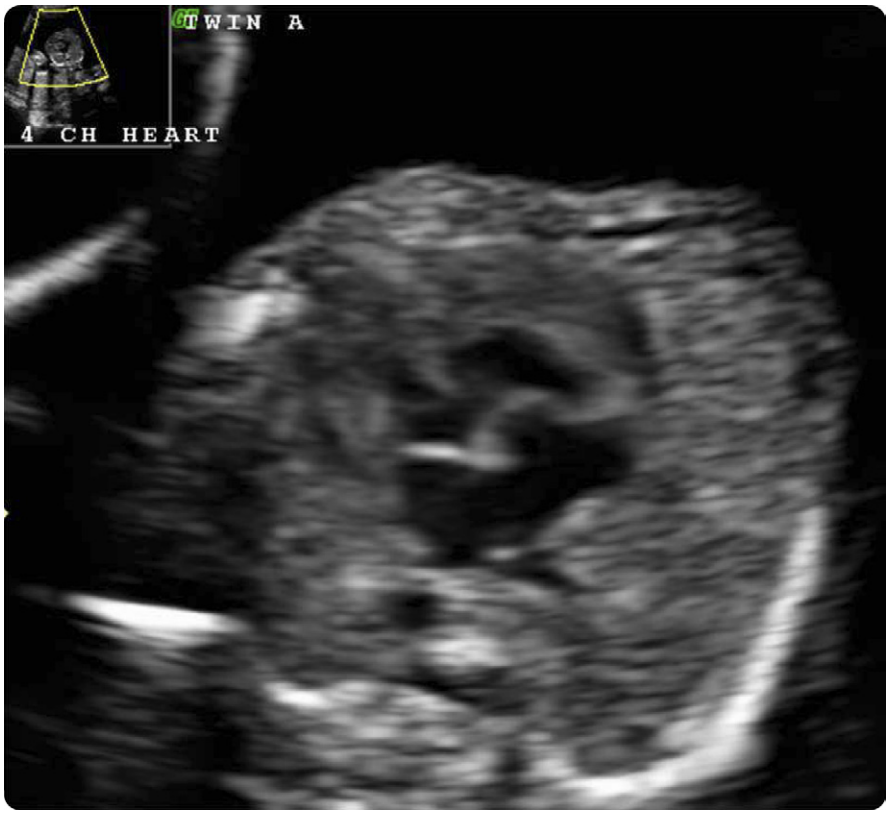
FIGURE 9
Recipient twin cardiomyopathy



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SMFM. Twin-twin transfusion syndrome. Am J Obstet Gynecol 2013.

losses.[72] Sequential coagulation of the donor artery to recipient vein followed by recipient artery to donor vein may theoretically allow some return of fluid from the recipient to the donor prior to severing other connections.[73,74] Criteria for laser have included MCDA pregnancies between about 15-26 weeks with the recipient twin having MVP ≥8.0 cm at ≤20 weeks or ≥10.0 cm at >20 weeks and a distended fetal bladder, and donor twin having MVP ≤2.0 cm in 1 trial,[65] and MCDA pregnancies at <24 weeks with the recipient twin having MVP >8 cm, and donor twin having MVP ≤2 cm and nonvisualized fetal bladder in the other.[67] There is insufficient evidence to recommend management in MCDA pairs with TTTS in higher-order multiple gestations, but laser has been proposed as feasible and effective.[75]

Selective reduction involves purposefully interrupting umbilical cord blood flow of 1 twin, causing the death of this twin, with the purpose of improving the outcome of the other surviving twin. Usually the cord occlusion is performed with radiofrequency ablation or cord coagulation, but other procedures have been employed.[76] Obviously this option can be associated with a maximum of 50% overall survival, so, if ever considered, it is usually reserved for stages III or IV TTTS only.

TABLE 4
Randomized trial of septostomy vs amnioreduction[57]

Variable	Septostomy n = 35	Amnioreduction n = 36	*P* value
Mean gestational age at delivery, wk	30.7	29.5	.24
Survival of at least 1 twin at 28 d of age	80% (28/35)	78% (28/36)	.82
All perinatal deaths up to 28 d of age	30% (21/70)	36% (26/72)	.40

SMFM. Twin-twin transfusion syndrome. Am J Obstet Gynecol 2013.

Question 7. What are the management recommendations according to stage? (Levels I, II, and III)

Stage I

There is no randomized trial specifically including stage I TTTS patients managed without interventions, ie, expectantly or conservatively managed. Patients with stage I TTTS are often managed expectantly, as over three-fourths of cases remain stable or regress spontaneously (Figure 10).[19-21] Because stage I TTTS progresses to more advanced TTTS in 10-30% of cases, interventions have been evaluated.

Stages I and II TTTS have been shown to regress following amnioreduction in up to 20-30% of cases, a rate that is not significantly different than with expectant management, especially for stage I.[20,66]

Laser has been studied for stage I TTTS in only 6 patients in the Eurofetus trial,[65] and no patients in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) RCT.[67] Only limited data exist from nonrandomized studies.[8,9,20,39] In a metaanalysis of stage I TTTS treated with laser photocoagulation, survival of both twins occurred in 45 of 60 twin pairs (75%), with an 83% overall survival, rates that are similar to other management strategies including expectant management, therefore providing no added benefit.[9] In a review of the literature including only stage I TTTS, the overall survival rates were 86% after expectant management, 77% after amnioreduction, and 86% after laser therapy, leading the investigators to suggest that conservative management in stage I TTTS is a reasonable option.[20] The progression to higher stage was only 15% for stage I after expectant management, and

survival was similar if laser was employed as first- or second-choice therapy in this review.[20] Further studies are needed to determine the optimal management of stage I TTTS.

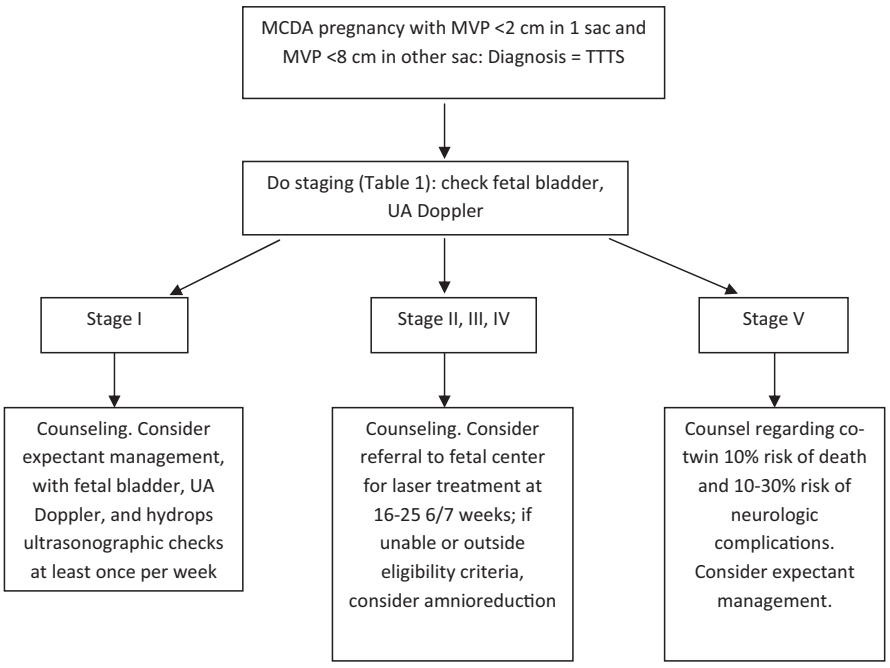
Stages II, III, and IV

Currently, fetoscopic laser photocoagulation of placental anastomoses is considered by most experts to be the best available approach for stages II, III, and IV TTTS in continuing pregnancies at <26 weeks (Figure 10), but metaanalysis data show no survival benefit, and the long-term neurologic outcomes in Eurofetus were not different than in nonlaser-treated controls. There is no randomized trial specifically including a group of TTTS patients with stages II, III, and IV, managed without interventions, ie, expectantly. Data on natural history for stage ≥II are not available (Table 2).

Two randomized trials have evaluated the effectiveness of laser therapy in pregnancies complicated by TTTS. In the first, called the Eurofetus trial, inclusion criteria were MCDA pregnancies between 15 and 25 6/7 weeks with the recipient twin having MVP ≥8.0 cm at ≤20 weeks or ≥10.0 cm at >20 weeks and a distended fetal bladder, and donor twin having MVP ≤2.0 cm. A total of 142 women were randomized from 3 centers in Europe (90% in France) to either selective laser photocoagulation or serial amnioreduction. The trial was stopped after an interim analysis demonstrated laser to be superior to amnioreduction with improved perinatal survival and fewer short-term neurologic abnormalities. Over 90% of the patients randomized had either stage II or III TTTS (6 with stage I; only 2 with stage IV). The laser group also did have an initial amnioreduction at laser surgery. Eleven women (16%) vs no women (0%) had voluntary termination of pregnancy after being randomized to amnioreduction and laser, respectively. Selected results are shown in Table 5.[65,77]

In the second trial, sponsored by the NICHD, inclusion criteria were MCDA pregnancies at <24 weeks with the recipient twin having MVP >8 cm, and donor twin having MVP ≤2 cm and nonvisualized empty fetal bladder. Stage I TTTS was therefore not included. A single diagnostic and therapeutic qualifying amnioreduction was performed on all pregnancies. This trial was also terminated early due to poor recruitment as well as increased neonatal mortality of recipient twins treated with laser therapy.[67] Ninety percent of the patients randomized had either stage II or III TTTS. Three US centers participated (Children's Hospital of Philadelphia; University of California, San Francisco; and Cincinnati Children's Hospital Medical Center). The laser group also had an initial amnioreduction at laser surgery. Selected results are shown in Table 6.[67] In-

FIGURE 10
Algorithm for management of TTTS



MCDA, monochorionic diamniotic; *MVP*, maximum vertical pocket; *TTTS*, twin-twin transfusion syndrome; *UA*, umbilical artery.
SMFM. Twin-twin transfusion syndrome. Am J Obstet Gynecol 2013.

TABLE 5
Randomized trial of laser photocoagulation vs amnioreduction (Eurofetus)[65,77]

Variable	Laser, n = 72 pregnancies/ n = 144 twins	Amnioreduction, n = 70 pregnancies/ n = 140 twins[a]	*P* value
Median gestational age at delivery, wk	33.3	29.0[a]	.004
Survival of at least 1 twin at 6 mo of age	76% (55/72)	56% (36/70)[a]	.009
All perinatal deaths up to 6 mo of age	44% (63/144)	61% (86/140)[a]	.01
Cystic periventricular leukomalacia at 6 mo	6% (8/144)	14% (20/140)	.02
Alive and free of neurologic complications at 6 mo	52% (75/144)	31% (44/140)	.003
Normal neurologic development at 6 y[b]	82% (60/73)	70% (33/47)	.12

[a] Of women in amnioreduction group, 11 (16%) had voluntary termination of pregnancy between 21-25 wk; [b] Includes only children delivered in France and still alive at 6 mo of age.
SMFM. Twin-twin transfusion syndrome. Am J Obstet Gynecol 2013.

TABLE 6
Randomized trial of laser photocoagulation vs amnioreduction (NICHD-sponsored)[67]

Variable	Laser, n = 20 pregnancies/ n = 40 twins	Amnioreduction, n = 20 pregnancies/ n = 40 twin	*P* value
Mean gestational age at delivery, wk	30.5	30.2	NS
Survival of at least 1 twin at 30 d of age	65% (13/20)	75% (15/20)	.73
All perinatal deaths up to 30 d of age	55% (22/40)	40% (16/40)	.18
Recipient twin fetal mortality	70% (14/20)	35% (7/20)	.03

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; *NS,* nonsignificant.

SMFM. Twin-twin transfusion syndrome. Am J Obstet Gynecol 2013.

fant outcome is available for this trial only up to 30 days of age. While the survival of at least 1 twin was comparable to the Eurofetus trial for the laser groups (65% in NICHD vs 76% Eurofetus), this outcome in the amnioreduction groups was better in the NICHD (75%) compared to the Eurofetus study (56%). The better NICHD amnioreduction results may be due to the standardized aggressive protocol used (performed every time the MVP was >8 cm). In contrast, the less favorable NICHD laser results may have been due to the severity of TTTS cardiomyopathy, especially in the recipients; the fact that there were more stage IV TTTS cases in NICHD (n = 4) than in Eurofetus (n = 2); and that the upper gestational age for inclusion was also different in NICHD (<24 weeks) vs Eurofetus (<26 weeks).[65,67] Recipient twin mortality was significantly higher in the laser (70%) than the amnioreduction (35%) group (Table 6).[67] In a meta-analysis of these 2 trials, overall death was not significantly different between laser and amnioreduction (risk ratio, 0.81; 95% confidence interval, 0.65–1.01).[71] These data on laser apply mostly to stage II and III TTTS, given the very limited number of stage I or IV TTTS included in the 2 trials.[65,67]

In summary, laser therapy has been associated with some perinatal benefits in 1 European trial, which had some limitations, while no benefits were seen in another smaller US trial.

Like all invasive procedures, laser has been associated with complications, including preterm premature rupture of the membranes, preterm delivery, amniotic fluid leakage into the maternal peritoneal cavity, vaginal bleeding and/or abruption, and chorioamnionitis.[78] Fetoscopy equipment is of larger gauge than the spinal needles used for amnioreduction or septostomy and, as a result, the risks of complications are up to 3-fold higher.[65] In the Eurofetus trial, the overall risk for most complications was about 3%.[65] Maternal and perinatal risks can be particularly high in inexperienced hands. Despite these risks, fetoscopic laser photocoagulation appears to be the optimal treatment for stage II-IV TTTS. However, it is important to remember that even with laser therapy, intact survival of both twins with TTTS is only about 50% (Table 7).[74,78-82]

Expectant management and amnioreduction remain 2 options in cases of TTTS stage >I at <26 weeks of gestation, in which the patient does not have the ability to travel to a center that performs fetoscopic laser photocoagulation.

In cases complicated by severe unequal placental sharing with marked discordant growth and IUGR, major malformations affecting 1 twin, or evidence of brain injury either before or subsequent to laser, selective reduction by cord occlusion[76] or by termination of the entire pregnancy may be reasonable management choices for the patient and her family <24 weeks' gestation.

Stage V

In cases of stage V TTTS, ie, death of 1 twin, no intervention has been evaluated in randomized trials to try to ameliorate outcome. As stated above, in cases of death of 1 MCDA twin, the risks to the cotwin included a 10% risk of death and 10-30% risk of neurologic complications (Figure 10).[25-27] It may be that the abnormal neurologic outcome in some survivors of TTTS is more correlated to whether or not there was demise of a cotwin, than the actual modality used to treat the condition.[83] It is well recognized that death of 1 twin of a monochorionic pair can result in periventricular leukomalacia, intraventricular hemorrhage, hydrocephaly, and porencephaly. Prior laser ablation appears to improve neurologic outcomes in the survivor if there is a cotwin demise.[84]

Question 8. After in utero laser for TTTS, what is the expected survival and long-term outcome of the twins? (Levels II and III)

In general, overall survival rates of 50-70% can be expected after fetoscopic laser for the treatment of TTTS.[71] Overall perinatal survival of fetuses with TTTS treated with laser was 56% in the Eurofetus trial at 6 months of age,[65] and 45% in the NICHD trial at 30 days[67] (Tables 5 and 6, respectively). The Eurofetus trial reported an 86% survival rate of at least 1 fetus for combined stage I and II disease treated with laser, decreasing to 66% for combined stage III and IV.[65] In recent nonrandomized large series, summarizing >1000 cases of TTTS (about 86% with stages II and III) treated with laser, the overall perinatal survival was about 65% (Table 7). Given publication bias, these data probably represent the best current possible outcomes with this procedure.

Although the risk of membrane rupture may be as low as 10% in experienced centers, there remains a 10-30% procedure-associated fetal loss with laser.[65,72,80,85] Both double and single fetal demise are common complications in advanced stages of TTTS treated with laser (Table 7). In a multicenter observational study, fetal demise occurred in 24% of donors and in 17% of recipients after laser.[86] Survival of 1 or 2 fetuses after laser may depend on coexisting unequal placental sharing that may not be visible before or even at the time of feto-

scopy. Preoperative IUGR with absent or reversed end-diastolic flow in the umbilical artery has a 20-40% increased risk of postoperative donor demise.[86,87] Recipient twin demise after laser is more common when the recipient has IUGR, reversed a-wave in the ductus venosus, or hydrops.[86] Improved recipient twin survival has been reported with the maternal administration of nifedipine 24-48 hours prior to laser photocoagulation in cases of TTTS cardiomyopathy,[88] but more data are needed to suggest its use in this clinical situation. After successful laser photocoagulation, the cardiac function of recipient twins tends to normalize in about 4 weeks.[89] Pulmonic valve abnormalities, affecting about 20% of recipient twins with advanced TTTS, have also been observed to improve after laser with less than a third of surviving twins having persistent pulmonic valve defects requiring treatment after birth.[90] Overall, 87% of postlaser recipient twins who survived were reported to have normal echocardiograms at a median age just under 2 years.[59]

Although procedure-related fetal loss is a recognized complication of fetoscopic laser photocoagulation, survival with neurologic handicap is also a serious long-term sequela of TTTS, with or without treatment. While the gestational age at delivery is a significant risk factor for adverse neurologic outcome, initial studies suggested that neurologic outcomes may be better for those cases managed with laser photocoagulation, compared to amnioreduction. Infants in the laser group of the Eurofetus trial had a lower incidence of cystic periventricular leukomalacia and were more likely to be free of neurologic complications at 6 months of age compared to those treated with amnioreduction (Table 6).[65] However, 6-year follow-up of 120 children from this trial found that laser therapy conferred no significant benefit in terms of difference in major neurologic handicap among TTTS survivors treated with laser vs amnioreduction.[77] Another recent study also reported no difference in neurodevelopmental outcome at 2 years of age among donors and recipients treated with laser or amnioreduction, although they did observe a trend of increased major neurologic impairment in survivors after

TABLE 7
Perinatal outcomes of twin-twin transfusion syndrome pregnancies treated with fetoscopic laser ablation

Study	n	Stage I	Stage II	Stage III	Stage IV	Median GA at delivery, wk	Pregnancies with 2 survivors	Pregnancies with 1 survivor	Pregnancies with 0 survivors	Neonatal death	Overall perinatal survival
Ville et al,[79] 1998	132	0	78.0% (103/132)	12.1% (16/132)	9.9% (13/132)	Not reported	36% (47/132)	38% (50/132)	27% (35/132)	4.5% (12/264)	54.5% (144/264)
Hecher et al,[80] 2000	200	0	100%[a] (200/200)	Doppler not reported	Hydrops not reported	33.7–34.4	50% (100/200)	30% (61/200)	20% (39/200)	3.8% (15/400)	65.3% (261/400)
Yamamoto et al,[75] 2005	175	9.7% (17/175)	48% (84/175)	37.5% (66/175)	4% (8/175)	Not reported	35% (61/175)	38% (67/175)	27% (47/175)	5.4% (19/350)	54% (189/350)
Huber et al,[81] 2006	200	14.5% (29/200)	40.5% (81/200)	40% (80/200)	5% (10/200)	34.3	59% (119/200)	24% (48/200)	17% (33/200)	4.8% (19/400)	71.5% (286/400)
Quintero et al,[74] 2007	137	16.1% (22/137)	28.5% (39/137)	43.8% (60/137)	11.7% (16/137)	33.7	73.7% (101/137)	16.8% (23/137)	9.5% (13/137)	11.3% (31/274)	82.5% (224/275)
Morris et al,[82] 2010	164	0	4.8% (8/164)	78.7% (129/164)	16.5% (27/164)	33.2	38% (63/164)	46% (76/164)	15% (25/164)	6.4% (21/328)	61.6% (202/328)
Totals	1008	6.7% (68/1008)	51.1% (515/1008)	34.8% (351/1008)	7.3% (74/1008)		48.7% (491/1008)	32.2% (352/1008)	19.1% (192/1008)	5.8% (117/2016)	64.8% (1306/2016)

GA, gestational age.
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[a] All cases met criteria for stage II and classified as such because Doppler and hydrops not reported.

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TABLE 8
Long-term neurologic outcome of laser-treated twin-twin transfusion syndrome survivors

Study	n	Approximate age at assessment, mo	Normal development	Major neurologic abnormalities	Minor neurologic abnormalities
Sutcliffe et al,[93] 2001	66	24	—	9%	—
Banek et al,[83] 2003	89	22	78%	11%	11%
Graef et al,[94] 2006	167	38	86.8%	6.0%	7.2%
Lenclen et al,[91] 2009	88	24	88.6%	4.6%	6.8%
Lopriore et al,[92] 2009	278	24	82%	18%	—

SMFM. Twin-twin transfusion syndrome. Am J Obstet Gynecol 2013.

amnioreduction compared to those treated with laser (9.5% vs 4.6%).[91]

Overall, rates of long-term neurologic sequelae in laser-treated stage I TTTS are reported to be about ≤3%, with rates of about 5-20% in survivors of any stage TTTS (Table 8).[83,91-94] The risk of abnormal neurodevelopment seems to be similar in donor and recipient survivors, and not drastically different between those treated with laser or amnioreduction. Antenatally acquired severe brain lesions, including cystic periventricular leukomalacia and grade-3 or -4 intraventricular hemorrhage, affect 10% of TTTS compared to 2% of MCDA twins without TTTS ($P = .02$); this difference was seen to persist in findings seen on cranial ultrasounds at the time of hospital discharge (14% vs 6%, $P = .04$).[95] Other risk factors for neurodevelopmental impairment in TTTS survivors are advanced gestational age at laser surgery, low birth weight, and severe TTTS.[92] Both ultrasound and magnetic resonance imaging (MRI) can be used to evaluate abnormalities of the fetal brain. In general, fetal MRI to evaluate cortical development and assess for ischemic injury is best in the third trimester. Following single twin demise in a MCDA gestation, neurologic injury, when present in the surviving twin, may be detected by ultrasound in about 1-2 weeks, and by MRI as early as 1-2 days after the demise of the other twin.[96,97] Routine neuroimaging with MRI cannot yet be recommended given the limited data on benefit, although this has been suggested by some authors for TTTS both prior to and after therapeutic interventions, or in cases complicated by single twin demise.[84,85,97,98] Follow-up studies of all survivors of TTTS are critical to determine accurate long-term outcomes and stage-specific rates of neurologic handicap of these complicated MCDA pregnancies.

In summary, even with the laser treatment option available, TTTS is still a severe condition in terms of perinatal outcomes. Given the 30-50% chance of overall perinatal death and 5-20% chance of neurologic handicap long-term, twin death or neurologic handicap is the outcome in up to two thirds of laser-treated TTTS.[99]

Question 9. What antenatal monitoring should be suggested for pregnancies complicated by TTTS? (Levels II and III)

There are no randomized trials to evaluate the effectiveness of antenatal monitoring for pregnancies complicated by TTTS. Weekly monitoring of the umbilical artery Doppler flow and MVP of amniotic fluid of each fetus may be considered. The evidence for effectiveness of serial (eg, weekly or twice/wk) nonstress tests, biophysical profiles, and other antenatal testing modalities is insufficient to make a recommendation, but these tests can be considered.

One reason for surveillance, even following laser therapy, is that not all anastomoses are ablated at the time of laser.[73,100] Residual anastomoses, either initially undetected, missed, or revascularized after laser, have been observed in up to a third of cases.[101,102] Placental casting has also demonstrated the presence of deep, atypical AV anastomoses beneath the chorionic plate that would not be visible by fetoscopy.[103] Failure to coagulate all AV anastomoses can lead to persistent, recurrent or reversed TTTS.[103] Persistent or recurrent TTTS has been reported in 14% of cases postlaser and reversed TTTS, with the recipient becoming anemic and the donor polycythemic, in 13% of cases.[104,105] While TAPS can occur spontaneously in a MCDA gestation, it is a known iatrogenic complication of laser.

Screening by transvaginal ultrasound for short cervical length in TTTS cases has also been proposed, as this is associated with preterm birth, a known complication of TTTS.[106] As there are no interventions shown to improve outcome based on short transvaginal ultrasound cervical length in TTTS cases, this screening cannot be recommended at this time.[107]

Question 10. When should patients with TTTS be delivered? (Levels II and III)

MCDA pregnancies complicated by TTTS are at increased risk of several complications, including but not limited to preterm birth, fetal demise, and cerebral injury.[108-110] Because of the increased risk of preterm birth, 1 course of steroids for fetal maturation should be considered at 24 to 33 6/7 weeks, particularly in pregnancies complicated by stage ≥III TTTS, and those undergoing invasive interventions.

There are no clinical trials regarding optimal timing of delivery for TTTS pregnancies. This depends on several

factors, including disease stage and severity, progression, effect of interventions (if any), and results of antenatal testing. Recommendations regarding timing of delivery with TTTS vary, with some endorsing planned preterm delivery as early as 32-34 weeks, and others individualizing care and allowing gestation to progress to 34-37 weeks, particularly in cases of mild disease (eg, stages I and II) with reassuring surveillance.

The median gestational age at delivery in the major trials and case series of laser-treated TTTS has been about 33-34 weeks (Table 7).[65,67,74,80-82] Cases treated with laser generally have more advanced disease, and they may be at risk for early delivery due to both TTTS and procedure-related complications. However, prematurity has been identified as an independent risk factor for neurodevelopmental impairment in the setting of TTTS.[92] Given the spectrum of disease associated with TTTS, many variables factor into decisions about timing of delivery, including disease stage, progression, response to treatment, fetal growth, and results of antenatal surveillance. Delaying delivery until 34-36 weeks may be reasonable even after successful laser ablation.

RECOMMENDATIONS

Levels II and III evidence, level B recommendation

1. The diagnosis of TTTS requires 2 criteria: (1) the presence of a MCDA pregnancy; and (2) the presence of oligohydramnios (defined as a MVP of <2 cm) in one sac, and of polyhydramnios (a MVP of >8 cm) in the other sac.

Levels II and III evidence, level B recommendation

2. The Quintero staging system appears to be a useful tool for describing the severity of TTTS in a standardized fashion.

Levels II and III evidence, level B recommendation

3. Serial sonographic evaluations about every 2 weeks, beginning usually around 16 weeks of gestation, until delivery, should be considered for all twins with MCDA placentation.

Levels II and III evidence, level B recommendation

4. Screening for congenital heart disease is warranted in all monochorionic twins, in particular those complicated by TTTS.

Levels II and III evidence, level B recommendation

5. Extensive counseling should be provided to patients with pregnancies complicated by TTTS including natural history of the disease, as well as management options and their risks and benefits. Over three fourths of stage I TTTS cases remain stable or regress without invasive interventions. The natural history of advanced (eg, stage ≥III) TTTS is bleak, with a reported perinatal loss rate of 70-100%, particularly when it presents <26 weeks. The management options available for TTTS include expectant management, amnioreduction, intentional septostomy of the intervening membrane, fetoscopic laser photocoagulation of placental anastomoses, selective reduction, and pregnancy termination.

Levels II and III evidence, level B recommendation

6. Patients with stage I TTTS may often be managed expectantly, as the natural history perinatal survival rate is about 86%.

Levels I and II evidence, level B recommendation

7. Fetoscopic laser photocoagulation of placental anastomoses is considered by most experts to be the best available approach for stages II, III, and IV TTTS in continuing pregnancies at <26 weeks, but the meta-analysis data show no significant survival benefit, and the long-term neurologic outcomes in the Eurofetus trial were not different than in nonlaser-treated controls. Laser-treated TTTS is still associated with a 30-50% chance of overall perinatal death and a 5-20% chance of long-term neurologic handicap.

Levels I and II evidence, level B recommendation

8. Steroids for fetal maturation should be considered at 24 to 33 6/7 weeks, particularly in pregnancies complicated by stage ≥III TTTS, and those undergoing invasive interventions.

Level III evidence, level C recommendation

9. Optimal timing of delivery for TTTS pregnancies depends on several factors, including disease stage and severity, progression, effect of interventions (if any), and results of antenatal testing. Timing delivery at around 34-36 weeks may be reasonable in selected cases.

Quality of evidence

The quality of evidence for each included article was evaluated according to the categories outlined by the US Preventative Services taskforce:

I	Properly powered and conducted RCT; well-conducted systematic review or metaanalysis of homogeneous RCTs.
II-1	Well-designed controlled trial without randomization.
II-2	Well-designed cohort or case-control analytic study.
II-3	Multiple time series with or without the intervention; dramatic results from uncontrolled experiments.
III	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees.

Recommendations are graded in the following categories:

Level A
The recommendation is based on good and consistent scientific evidence.

Level B
The recommendation is based on limited or inconsistent scientific evidence.

Level C
The recommendation is based on expert opinion or consensus.

This opinion was developed by the Publications Committee of the Society for Maternal-Fetal Medicine with the assistance of Lynn L. Simpson, BSc, MSc,

MD, and was approved by the Executive Committee of the Society on September 20, 2012. Dr Simpson, and each member of the Publications Committee (Vincenzo Berghella, MD [Chair], Sean Blackwell, MD [Vice-Chair], Brenna Anderson, MD, Suneet P. Chauhan, MD, Joshua Copel, MD, Jodi Dashe, MD, Cynthia Gyamfi, MD, Donna Johnson, MD, Sara Little, MD, Kate Menard, MD, Mary Norton, MD, George Saade, MD, Neil Silverman, MD, Hyagriv Simhan, MD, Joanne Stone, MD, Alan Tita, MD, PhD, Michael Varner, MD, Ms Deborah Gardner) have submitted a conflict of interest disclosure delineating personal, professional, and/or business interests that might be perceived as a real or potential conflict of interest in relation to this publication. ■

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The practice of medicine continues to evolve, and individual circumstances will vary. This opinion reflects information available at the time of its submission for publication and is neither designed nor intended to establish an exclusive standard of perinatal care. This publication is not expected to reflect the opinions of all members of the Society for Maternal-Fetal Medicine.