Treatment Options for the Twin–Twin Transfusion Syndrome: A Review

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This article reviews the treatment options of the twin–twin transfusion syndrome (TTTS). No single therapy is associated with a uniformly improved outcome for the involved twins and success is primarily related to gestational age and severity at diagnosis. Treatment options for severe cases include digitalization, ligation of the umbilical cord, serial amniocenteses, septostomy, laser occlusion of placental vessels, and selective feticide. These modalities are associated with significant risks of complications, and variable results of fetal morbidity and mortality. Therefore, they should be considered when risks of withholding treatment clearly outweigh those associated with intervention.

Twin–twin transfusion syndrome (TTTS) results from a transplacental inter-twin vascular communication ("third" circulation) that causes blood shunting from the donor to the recipient twin. TTTS has been traditionally diagnosed after birth by finding inter-twin hemoglobin difference > 5 g/dL and birth weight differences > 20%. These criteria have been re-evaluated more than a decade ago to include mainly ultrasonographic signs such as discordant inter-twin abdominal circumference difference > 18–20 mm, twin oligo/polyhydramnios sequence (TOPS), signs of monochorionicity, inter-twin birth weight difference > 15–20%, differences in size of the urinary bladders, documentation of transplacental shunts, and various Doppler signs (Blickstein, 1990; Salim & Shalev, 2001). The syndrome occurs only in monochorionic twins and is associated with high perinatal mortality and morbidity. The older literature cited perinatal mortality rates of 80% to 100% in untreated TTTS before 28 weeks. These prompted clinicians to intervene in hope to augment the potentially ominous outcome.

No single therapy has been associated with a uniformly improved outcome for twins affected by TTTS, as this appears to be primarily related to the gestational age when the syndrome develops. The therapeutic approaches to severely affected cases are summarized in Table 1. It should be stressed from the outset that a recent Cochrane Database System Review concluded that until August 2000 there was no evidence from randomized trials to influence practice (Roberts et al., 2001). However, the clinicians faced with a case of TTTS should be constantly updated with recent advances in the treatment options of TTTS. For this reason, we reviewed the literature related to treatment of TTTS form 1985 to date using the PubMed search engine (National Library of Medicine, accessible at http://www.ncbi.nlm.nih.gov/entrez/). Although we did not use any pre-selection criteria, anecdotal case reports were generally excluded.

Do Nothing

The urge to intervene was based on the extremely poor outcome reported in cases of TTTS prior to the era of sonography. Without a definite diagnosis, treatment options were employed also in presumed cases of TTTS. Consequently, outcome was frequently skewed in favor of intervention when the underlying condition was not in fact the TTTS. The best example is the case of TOPS, which is often associated with growth discordant twins with dichorionic placentas. Recently, Berghella and Kaufmann (2001) evaluated the natural history of TTTS. They found that in older series the overall perinatal survival of TTTS managed without in utero procedures was 30% compared to 63% in recent series.

Another potential problem of comparing results of treatment versus non-treatment emerges from the gestational age at diagnosis and severity of the TTTS when a specific treatment was employed. To overcome this difficulty, one needs to compare outcome between cases of similar severity and gestational age. The first attempt has been recently published by Quintero et al. (2001).

Conservative Management

Digoxin therapy has been advised for congestive heart failure in the recipient (DeLia et al., 1965). Digoxin is passively diffused across the placenta, and therapeutic levels are achieved in the fetus with maternal levels of 0.8–2.6 nmol/L, although it may take up to a week before equilibrium between the maternal and fetal circulations is reached. Roman et al. (1995) successfully treated hydropic recipients by using amniocentesis and digoxin. Arabin et al. (1998) reported that cardiac decompensation and hydrops were reversible following combined surgical (laser) and medical (digoxin) approaches in a case with congestive heart failure

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Table 1

Treatment Modes of Twin-to-Twin Transfusion Syndrome

Mode of treatment
Conservative management with careful monitoring
Monitoring
Ultrasound assessment
Biophysical profile
Doppler blood flow velocimetry
Fetal echocardiography
Cardiotocography
Digoxin
Serial amnioreduction
Septostomy
Fetoscopic laser occlusion of placental vessels
Selective feticide
Cord embolization
Nd: YAG laser technique
Fetoscopic cord ligation
Bipolar coagulation

and hydrops in the recipient. However, digoxin treatment is still controversial because it represents a delicate balance between maternal side effects and the desired beneficial effect in the fetus.

Amnioreduction

Polyhydramnios frequently complicates the situation by overdistending the uterus, causing respiratory difficulties in the mother. Moreover, the development of polyhydramnios may cause preterm labor and preterm rupture of membranes leading to premature birth. Hence, amnioreduction has the potential to prevent premature labor and improve fetal outcome, despite contradictory reports that did not find significant prolongation of gestation (Chescheir & Seeds, 1987; Gonsoulin et al., 1990; Schneider et al., 1985) or significantly improved outcomes (Gonsoulin et al., 1990; Saunders et al., 1992). Dennis and Winkler (1997) retrospectively evaluated the efficacy of aggressive amniocentesis and reported a survival rate of 82% in the treated versus 50% in the untreated groups. Newborns in the treated group were delivered at a later gestational age and weighed more than those in the untreated group. Joa et al. (2001) reported a survival rate of 50% when the diagnosis was made before 24 weeks' gestation and 100% if after 24 weeks for an overall rate of 71%. Survival depended on the need for amniodrainage and the rate dropped from 100% if amniodrainage was not required to 56% if required. Hubinont et al. (2000) reported that amnioreduction increases survival rate to a range of 40–87%. Trespidi et al. (1997) reported an overall survival rate of 57%, but in only 39% of the pregnancies did both twins survive without handicap. Absence of end-diastolic flow in the umbilical artery of the donor twin was associated with poor outcome for both fetuses, but the presence of fetal hydrops or ascites did not worsen the prognosis. Elliot et al. (1991) reported a survival rate of 79% in fetuses treated with serial amniocenteses and suggested that the prolongation of pregnancy was influenced by gestational age at diagnosis and at onset of therapy. Decompression by removal of large amounts of fluid causes distinct placental thickening on ultrasound and may improve urine production of the "stuck twin". Saunders et al. (1991) reported a survival rate of 37%, less than half the reported rate by Elliot et al. (1991). Outcome of conservative management was poorer than with interventions. Their data indicated that the greater the disparity in fetal sizes at initial examination the worse the prognosis. It has been suggested that repeated amniocentesis, at least in some cases, may allow the fetal cardiovascular system to overcome the effect of placental anastomosis.

The risks of aggressive amniocentesis include infection, rupture of membranes, and placental abruption due to removal of large volumes of amniotic fluid over a relatively short period of time. Jauniaux et al. (2001) compared 15 severe TTTS cases in which amnioreduction was performed by means of a vacuum bottle system for rapid and radical drainage and 15 cases with similar conditions and matched for gestational age, but drained by standard equipment. Radical amnioreduction resulted in significant increase in placental thickness and in 80% overall survival with at least one survivor in 93%. Bajoria divided TTTS cases into two groups according to the presence or absence of superficial anastomoses (Bjoria, 1998). In the group without arterio-arterial/veno-venous anastomoses, amnioreduction was required more often and perinatal mortality was higher. It appears that the presence of same-vessels anastomoses was associated with increased efficacy of amnioreduction and a more favorable prognosis. Mari et al. reported the results of a multi-center registry of amnioreduction for TTTS (Mari, 1998). The overall survival rate among 175 cases was 66%, with at least one survivor in 75%. One fifth of the survivors had major abnormalities in their neonatal head sonograms. More recently Mari et al. (2000, 2001) updated this registry to show an overall survival of 78%, with 60% alive at the age of 4 weeks. Both fetuses survived to 4 weeks in 48.8%, whereas at least one fetus survived in 70.8%. Bower et al. (1995) reported on changes in the uterine circulation following amnioreduction. The resistance and pulsatility indices decreased after amnioreduction suggesting an improved uteroplacental perfusion and supporting the theory of an impaired donor's placental perfusion due to increased pressure in the recipient's sac. It was also shown that fetal blood gas status was inversely related with amniotic pressure, suggesting that uteroplacental perfusion may be impaired in cases with severe polyhydramnios (Fisk et al., 1994).

Suzuki et al. (1999) studied Doppler waveforms in the middle cerebral artery (MCA) and the umbilical artery (UA) of growth-restricted fetuses with and without TTTS. Pulsatility Index (PI) MCA values in the TTTS group, especially in fetuses who subsequently developed periventricular leukomalacia (PVL), were significantly higher than normal values. This presumable absence of blood flow redistribution is similarly observed in hypoxemic and growth restricted fetuses due to placental insufficiency. The UA PI values in the smaller twin were significantly higher in the TTTS group compared with the non-TTTS group. The values decreased after amnioreduction, suggesting recovery of the fetal circulation (Dickinson et al., 1995).

The increased PI MCA values in some donors were explained by head compression due to polyhydramnion in the co-twin's sac (Hecher et al., 1995) or associated with a reduction in left ventricular output. Both suggest decompensation of fetal cerebral circulation (Weiner et al., 1994).

In summary, amnioreduction normalizes amniotic fluid volume, prolongs pregnancy, improves placental perfusion and reduces maternal complications. Table 2 shows the reported perinatal survival rates (Bebbington & Wittman, 1989; Brown et al., 1989; Chescheir & Seeds, 1988; Cincotta et al., 1996; DeLia et al., 1999; Dennis & Winkler, 1997; Elliot et al., 1991; Gonsoulin et al., 1990; Hecher et al., 1999; Hecher et al., 2000; Nageotte et al., 1989; Patten et al., 1989; Pinette et al., 1993; Pretorius et al., 1988; Quintero et al., 2000; Quintero et al., 2000; Saunders et al., 1992; Thilaganathan et al., 2000; Trespidi et al., 1997; Urig et al., 1990; Ville et al., 1994; Zikulnig et al., 1999).

Septostomy

Septostomy was suggested for the treatment of TOPS and is performed under ultrasound guidance by intentional disruption of the inter-twin membrane. Saade et al. (1998) used of a spinal needle and observed rapid accumulation of fluid around the "stuck" fetus in all cases following the procedure. When combined with amnioreduction the survival rate was 83.3%. However, the creation of a pseudo-monoamniotic cavity by disruption of the dividing membrane can complicate therapy with cord entanglement associated with high morbidity and mortality rates (Feldman et al., 1998). Hubinont et al. (1996) reported a normalization of amniotic fluid volume in both gestational sacs and improvement in the fetal umbilical artery velocities, followed by a catch-up growth of the donor after septostomy. Pistorius et al. (1999) documented three cases with the improvement in amniotic fluid volumes, one of which was complicated by PROM and preterm birth. The cited fetal/neonatal survival rate of 83% in 12 pregnancies undergoing septostomy (Hubinont et al., 1996) can be contrasted by the report of Suzuki et al. (1999) who described unintentional septostomy with subsequent death both twins in utero. In two recent cases of unintentional septostomy during serial amnioreductions, only two of the four fetuses survived (Cook & O'Shaughnessy, 1997; Feldman et al., 1998). Cord entanglement was seen in both cases and one of the survivors had a severe periventricular leukomalacia.

The effect of septostomy could be explained by equilibration of the amniotic fluid between two sacs that corrects placental circulation, especially in the donor's umbilical vessels and on the placental surface (Zikulnig, 1999). The improved fetal hemodynamic state may increase the donor's urine production. Using a dye dilution method, increased volume of the "stuck" twin's sac after septostomy was seen, but not after amnioreduction (Bruner & Crean, 1999). All these point to the role of two amniotic cavities in the pathogenesis of TTTS (Hubinont et al., 2000).

Fetoscopic Laser Occlusion

Fetoscopy has potential advantages over open fetal surgery, primarily because of decreased procedure-induced preterm labor and fetal loss from preterm delivery (Milner & Crombleholme, 1999; Yang & Adzik, 1998). Initial experimental attempts with lasers during the 1980s led to treatment of women with variable results. Generally, the idea is to interrupt the inter-twin shunt by placental vessel occlusion, using neodymium:yttrium-aluminium-garnet laser light.

DeLia et al. (1995) reported the survival rate of 53% in severe TTTS with 96% normally developing children. This group recently described rates of 82 % for at least one survivor, 69% overall survival, and of 4.3% having significant handicaps (DeLia et al., 1999). Hecher et al. (1999) studied severe mid-pregnancy TTTS treated by either serial amniocenteses or endoscopic laser coagulation. The overall survival rate was not significantly different in both groups (61% vs 51%). The laser-treated group was characterized by higher birth weighs, higher gestational age at delivery,

Table 2

Fetal Survival in Twin Pregnancies with Polyhydramnios Managed Conservatively, by Amniocentesis, or Fetoscopic Laser Occlusion. A – non-Selective Laser Photocoagulation; B — Selective Laser Photocoagulation

Conservative management		Amnioreduction		Fetoscopic laser occlusion	
Author	Survival rate	Author	Survival rate	Author	Survival rate
Pretorius et al. (1988)	1/14	Chescheir et al. (1988)	0/6	De Lia et al. (1999)	93/134
Chescheir et al. (1988)	0/4	Bebbington et al. (1989)	0/6	Hecher et al. (1999)	89/146
Patten et al. (1989)	3/48	Nagoette et al. (1989)	2/4	Zikulnig et al. (1999)	156/242
Brown et al. (1989)	1/8	Gonsoulin et al. (1990)	4/22	Hecher et al. (2000)	172/254
Urig et al. (1990)	0/10	Urig et al. (1990)	6/18	Quintero et al. (2000)	A: 18/36
B: 87/142		Elliot et al. (1991)	27/34	Thilaganathan et al. (2000)	11/20
		Saunders et al. (1992)	14/38	Quintero et al. (2001)	42/121
		Pinette et al. (1993)	21/26		
		Cincotta et al. (1996)	17/28		
		Trespidi et al. (1997)	26/46		
		Dennis et al. (1997)	18/22		

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higher proportion of pregnancies with at least one survivor, lower number of cases with spontaneous intrauterine fetal death of both fetuses, and lower incidence of abnormal brain ultrasonography. The higher survival rate among recipients may be explained by unequal placental sharing that limits survival of donors. Recently they confirmed the initial results in a large population of severe second trimester TTTS and the improved outcome after laser therapy as compared to serial amnioreductions (Hecher et al., 2000). Selective coagulation of placental vessels, rather than coagulation of all vessels that cross the inter-twin membrane, reduces the rate of intrauterine death of donors after fetoscopic surgery. These findings indicate that laser coagulation offers a more effective alternative to serial amnioreductions in TTTS. The recent overall survival rate of 68% and 81% for at least one survivor were obtained by coagulation of arterio-venous anastomoses only (Hecher et al., 2000). Other vessels crossing the inter-twin membrane were left patent. It has been shown that photocoagulation of all vessels crossing the inter-twin membrane increases the likelihood of injury or death of the donor twin (Quintero et al., 2000). Quintero et al. (2000, 2001) developed a selective technique that photocoagulates only those vessels involved in blood shunting. The terminal end of the artery from one of the fetuses, which does not have a corresponding vein to the same fetus, identifies the arterio-venous anastomosis. However, there was no significant difference in total survival rates between selective and non-selective laser coagulation group (61% vs 50%). Thilaganathan et al. (2000) proposed coagulation along the vascular equator delineated by a sonogram. This technique was associated with a shorter operating time, less damage to the normal placental surface vasculature, and with survival rates similar to previous studies. A combined surgical approach including endoscopic coagulation of placental vessels and repeated intrauterine transfusions was also tried (Van Peborgh et al., 1998).

In the last decade a new method of laser-induced interstitial thermotherapy (LITT) was introduced, and seems useful in patients with an anterior wall placenta. The instruments are thinner and the energy required for LITT is much lower than for fetoscopic treatment. The laser fiber inserted via a puncture needle is directed to the vessel under ultrasound guidance. Blood vessels connecting the two umbilical cords can be determined prior to the treatment using an ultrasound color technique (Sohn et al., 1996).

Selective Feticide

Selective feticide has been suggested as an alternative therapy for TTTS and was based on the observed gradual resolution in polyhydramnios following fetal demise. This type of therapy is indicated in cases of acardiac twin, severe discordant anomalies, and severe TTTS where one twin has an extremely poor prognosis. Because the commonly used intracardiac or intrathoracic injection of potassium chloride is not suitable in monochorionic pregnancies, there was a need for a cord occlusion technique. All techniques are associated with a variable but significant risk of complications and should only be considered when the risks of not treating clearly outweigh those associated with intervention.

Cord embolization. Cord embolization with coils or sclerosants has a high failure rate and is not recommended any more (Challis et al., 1999; Denbow et al., 1999). There is a high risk of intrauterine death of both fetuses, probably due to incomplete vascular obliteration or migration of the thrombogenic products to the co-twin (Denbow et al., 1999; Mahone et al., 1993).

Nd: YAG laser technique. The advantages of fetoscopic cord coagulation over other approaches include complete extravascular interruption of the blood flow within the cord. Cord coagulation prior to spontaneous death of a co-twin may avoid the neurological and other complications in the survivor twin (Quintero et al., 1996). An overall fetal survival rate of 71% was reported after successful photocoagulation (Challis et al., 1999). Preterm contractions do not seem to be a clinical problem but preterm rupture of membranes complicates about 30–40% of the cases, the majority occurring before 32 weeks (Deprest et al., 1998). A failure rate of 10% was reported (Challis et al., 1999). Unfortunately, laser coagulation of the cord is less successful after 20–22 weeks of gestation, due to a large diameter of cord vessels or the presence of hydropic perivascular tissue that absorbs the laser energy (Hecher et al., 1996). Challis et al. (1999) created a clinical algorithm, whereby Nd:YAG laser prior to 21 weeks is used. In unsuccessful cases and beyond 21 weeks, bipolar cord coagulation or even fetoscopic cord ligation are recommended. The procedure may also be difficult to perform when amniotic fluid is heavily stained. If laser coagulation of the cord is unsuccessful, particularly in later gestation, coagulation of all of the chorionic vessels around the cord root may be attempted (Challis et al., 1999). This method may lead to acute feto-fetal transfusion if the fetus dies before all vessels have been occluded.

Fetoscopic cord ligation. Fetoscopic surgical ligation of the umbilical cord causes immediate, complete occlusion, of all umbilical cord vessels irrespective of their diameter. Quintero et al. presented the first successful case (Quintero et al., 1996), and Challis et al. (1999) reported a total survival rate of 70%. This procedure requires a higher number of ports and is time-consuming compared to laser coagulation of chorionic plate vessels. It is also associated with a higher rate of complications, especially premature rupture of membranes.

Bipolar coagulation. The key instrument in bipolar cord coagulation under ultrasound guidance is a small caliber bipolar coagulating forceps (2.7–3.0 mm). The procedure has the advantage of obliterating both umbilical vessels simultaneously, resulting in an immediate cessation of blood flow, and preventing agonal interfetal hemorrhage (Deprest et al., 2000). Moreover, it can be performed through a single port by standard instrumentation. The duration of the procedure is significantly reduced and can be performed by those familiar with ultrasound guided invasive procedures. A theoretical advantage is that the electrical current does not travel through the umbilical cord, placenta or fetal body since bipolar current passes only between the two blades of the instrument. The success rate is 100% with overall single survival of 80–93% (Deprest et al.,

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2000; Salim & Shalev, 2001). However, bipolar diathermy is an effective procedure for cord occlusion, although it still has significant morbidity and mortality rates (Nicolini et al., 2002).

Epilogue

Table 3 shows advantages and disadvantages of various treatment options discussed in this paper. TTTS means serious morbidity. However, specific outcome is related to the stage of pregnancy when TTTS occurred and to the severity of the syndrome. The fact that no single therapy emerged as a treatment of choice puts the clinician in difficult position vis-a-vis the patient. In some instances, the primary effect of intervention would be buying time (i.e., increasing gestational age to the point of viability) rather than a true solution to the inter-twin shunt. Obviously, if the case is deteriorating, buying time means delivery of more mature twins who are in a worse condition. Thus, a fair comparison of treatment options by grading the severity of TTTS (Quintero et al., 2001) may not be enough because we are unable to accurately predict which case is going to deteriorate over time. In addition, discordant fetal conditions remote from term poses difficult ethical questions: waiting obviously increases the risk for fetal death and long term morbidity for the ailing twin,

Table 3

Summary of Advantages and Disadvantages of the Various Treatment Options

	Advantages	Disadvantages
Digoxin	Treatment of congestive heart failure in the recipient	Insufficient efficacy in placental edema
	Prevention of sequelae of cardiac failure such as lung hypoplasia, pulmonary stenosis, or endocardial fibroelastosis of the recipient	Maternal and fetal side effects
Amnioreduction	Reducing the risks associated with polyhydramnios	Rupture of membranes
	Improvement of the placental blood flow by reducing the intrauterine pressure	Chorioamnionitis
	Simple	Preterm labor
	Minimally invasive	Placental abruption
	Easy to perform	Secondary amniotic bands
	Inexpensive	
Septostomy	Same as in amnioreduction	Same as in amnioreduction
		Creation of pseudo-monoamniotic twins Secondary amniotic bands
Fetoscopic Laser Coagulation	Treatment of the source of the problem	Requirement of sophisticated instrumentation and well trained operators
	More effective (?) than methods previously described	Technically difficult
	Protective role on the co-twin if one fetus dies (prevention of fetal death and brain damage)	Expensive
	Single procedure	Difficulties in identifying the communicating vessels
	Significant prolongation of pregnancy	Amniotic fluid leakage
		Preterm labor
		Chorioamnionitis
		More invasive
		Higher risk of maternal morbidity
		Incomplete separation of the fetal circulations
		Theoretical risk to the fetal eyes from reflected laser light
Selective Feticide	Prevention of :	Ethical difficulties
	Exsanguination into the circulation of the dying fetus	Negative psychological responses
	Brain and other organ damage,	Incomplete occlusion
	Severe cardiac failure in the “pump” twin	Premature rupture of membranes
	Intrauterine death of normal co-twin	Premature labor

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whereas pregnancy termination by cesarean section exposes both twins to the risk of preterm delivery.

Despite these difficulties, the innovations introduced in recent years for the treatment of TTTS lead to an expected breakthrough in the future.

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