

Twin-to-Twin Transfusion Syndrome: Diagnosis and Treatment

Bettina Paek* and Laurence E. Shields

Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, University of Washington, WA, USA

Abstract: Almost all monochorionic twin pregnancies have a shared placental circulation. Twenty-five percent of these have an imbalance of blood flow leading to chronic shunting of blood from one twin to the other. Severe Twin-to-Twin Transfusion Syndrome (TTTS) develops in up to half of these pregnancies. Prenatal diagnosis relies on findings of oligo/anhydramnios with a decompressed bladder in the donor twin and polyhydramnios and full bladder in the recipient twin. Progressive decompensation is manifested as increasing polyhydramnios leading to preterm delivery, measurable changes in umbilical artery and ductus venosus Doppler velocimetry, fetal hydrops and eventually demise. Historically outcomes without treatment have been poor with a perinatal survival around 10% to 20% with a rate of neurological damage of 20-40% in survivors. Traditionally, treatment has involved repeated reduction amniocenteses to delay early delivery due to polyhydramnios. Lasering of communicating placental vessels has emerged as a new treatment option. A recent randomized controlled trial in Europe comparing endoscopic laser surgery with serial amnioreduction demonstrated an increased perinatal survival, higher gestational age at delivery and a better neurological outcome at 6 months of age in those fetuses randomized to treatment by laser. Endoscopic laser surgery for TTTS is currently only offered at select centers and its technique is still evolving and is the subject of a large multicenter NIH sponsored randomized trial in the United States. Research investigating the use of therapeutic ultrasound for non-invasive coagulation of communicating placental vessels may provide new treatment options in the future.

INCIDENCE AND DIAGNOSIS OF MONOCHORIONIC TWINS

Classically the incidence of multiple pregnancies has been calculated by Hellin's rule to be 1 in 80^{n-1} , n being the number of fetuses [1]. This yields a frequency of 1 in 80^{2-1} or 1:80 for twins, 1 in 80^{3-1} or 1:6400 for triplets, 1 in 80^{4-1} or 1:512,000 for quadruplets. The widespread use of Assisted Reproductive Technology and a significant increase in maternal age have increased the overall incidence of twins [2]. Twin pregnancies now comprise up to 3% of all pregnancies [3].

Two thirds of twin pregnancies are dizygotic pregnancies, whereas one third are monozygotic [4]. A dizygotic twin pregnancy is the result of two fertilized oocytes that implant in the uterus at the same time and are always genetically different. Their placentation is almost exclusively diamniotic and dichorionic [5]. Monozygotic twins are the result one fertilized oocyte splitting after fertilization; these fetuses are always genetically identical but their chorionicity can vary depending on when the split occurs. If the zygote divides within the first three days after fertilization the resulting pregnancy is dichorionic and diamniotic. This occurs in about 30% of all monozygotic twin pregnancies. If the zygote splits between days three and eight the twins will have separate sacs (diamniotic) but will share a placenta (monochorionic). This occurs in 69% of monozygotic twin pregnancies. If the zygote splits between days nine and twelve the twin will share the placenta and amniotic sac and thus be monochorionic and monoamniotic. This is rare and only occurs in 1% of monozygotic twins. If the zygote splits after day thirteen then conjoined twins result; this occurs only sporadically [1, 6].

Only monochorionic twin pregnancies are thought to be at risk for developing twin-to-twin transfusion syndrome (TTTS). Thus it is quite important to determine chorionicity in a twin pregnancy. This is best accomplished by ultrasound, ideally between six and nine weeks of gestation [7]. Dichorionic pregnancies will show a thick septum between the two sacs. After nine weeks of gestation the insertion of the intertwin membrane onto the placenta will be thickened due to an ingrowth of placental tissue between the two layers of amnion, this is called the lambda sign [8, 9]. This placental tissue that grows in between the amnion and is evident as a thickening of the intertwin membrane towards the insertion into the placenta. After 20 weeks the distinction is much more difficult to make and relies on assessment of differing fetal gender and separate placentas.

ETIOLOGY OF TWIN-TO-TWIN TRANSFUSION SYNDROME (TTTS)

Almost all monochorionic twin pregnancies have a shared placental circulation [10]. These anastomoses can occur either as arterial-arterial (AA) or veno-venous (VV) anastomoses that are visible on the fetal surface of the placenta, or they can be "deep" anastomoses [10]. These are formed by a cotyledon that draws its arterial blood supply from one twin and drains into the venous system of the other twin [11]. When examining a placenta, this is seen as an unpaired artery (not accompanied by a vein) arising from the umbilical cord of one twin and terminating at a cotyledon. The draining vein then arises out of the cotyledon and leads to the umbilical vein of the co-twin, similarly unpaired by an accompanying artery. These follow a natural pressure gradient from artery to vein and can shunt large volumes of blood whereas AA or VV anastomoses may be protective in balancing out net blood flow [12]. Recent evidence supports that twin pairs with a smaller number of anastomoses are more likely to develop TTTS because they are more likely to have unbalanced arterio-venous anastomoses and thus a net

*Address correspondence to this author at the Department of Obstetrics and Gynecology, University of Washington, Medical Center, 1959 NE Pacific Street Box 356460, Seattle, WA, USA; Tel: (206) 598-0003; Fax: (206) 616-9479; E-mail: bettina@u.washington.edu

shunting of blood from one twin to the other [12, 13]. Twenty-five percent of monochorionic twin pairs have a net imbalance of blood flow leading to chronic shunting of blood from one twin to the other. Severe TTTS develops in up to half of these pregnancies. The donor twin develops relative hypovolemia causing an activation of the renin-aldosterone system and develops oliguria leading to oligohydramnios. The recipient experiences hypervolemia and consequently an increase in Atrial Natriuretic Peptide leading to polyuria and polyhydramnios.

Often there is unequal sharing of the placental territory by the twins, i.e. one twin has a larger percentage of the placenta than the other which may in part explain some of the growth discrepancy that is frequently seen with the syndrome, but is not part of the definition [13]. In addition the cord insertion of the donor twin is often marginal or even velamentous and maybe more sensitive to pressure occlusion that can occur with polyhydramnios [14].

DIAGNOSIS OF TTTS

Most cases of TTTS are diagnosed by rapidly increasing uterine growth due to polyhydramnios in the recipient twin. Prenatal diagnosis relies on the following ultrasound findings in a monochorionic twin pregnancy: Oligo/anhydramnios and a decompressed bladder in the donor twin and polyhydramnios and full bladder in the recipient twin [15, 16].

Early signs of TTTS include an infolding of the intertwin membrane indicating a sudden shift in fluid and decreasing fluid in one sac. On ultrasound exam this typically appears "Y" shaped. This occurs in 25% of all monochorionic twins. As the syndrome progresses anhydramnios in the donor and dramatic polyhydramnios in the recipient twin are seen [17].

The distinction between anhydramnios in one twin and monoamniotic twins can be difficult since there is no visible inter-twin membrane in either case. However, in anhydramnios the donor twin will be in a stuck position even with maternal position changes (thus leading to the name of "stuck twin syndrome"), whereas in monoamniotic twin pregnancies both twins will usually be fully mobile.

Progressive decompensation of the donor is manifested as a dilated heart, hyperechogenic bowel, and absent end diastolic flow in the umbilical artery. The recipient can develop a dilated dyskinetic heart, tricuspid regurgitation, absent/reversed flow in the ductus venosus indicating fluid overload and eventually hydrops [15]. Both fetuses are at risk for intrauterine fetal demise and persistent cardiac decompensation results in the postnatal death in about 10% of the survivors.

Potential pitfalls in the diagnosis are oligohydramnios in one twin due to other etiologies such as placental insufficiency with IUGR, renal dysplasia or agenesis, or preterm premature rupture of membranes (PPROM) as well as polyhydramnios due to an abnormal karyotype, fetal neurologic or gastrointestinal disorders, or micrognathia.

Quintero has proposed a staging system to quantify severity of TTTS (see Table 1) [15]. Stage progression has been associated with worsening outcome [18].

Table 1. Staging of TTTS by Ultrasound [15]

Stage of TTTS	Findings
Stage I	Combination of oligohydramnios/polyhydramnios in monochorionic twins
Stage II	Decompressed bladder in donor twin
Stage III	Abnormal Doppler indices (absent end diastolic flow in the umbilical artery, reverse flow in the ductus venosus, pulsatile flow in the umbilical vein)
Stage IV	Hydrops in either twin
Stage V	IUFD

NATURAL HISTORY

Historically outcomes without treatment have been poor with a perinatal survival around 10% to 20% with a rate of neurological damage of 40% in survivors [19]. Progressive polyhydramnios usually leads to preterm labor and premature rupture of membranes [20] resulting in early delivery, which significantly impacts neonatal survival and neurologic outcome. Decompensation of donor or recipient twin will manifest as abnormal Doppler indices, hydrops and intrauterine fetal demise [15]. Fetal demise is associated with a high risk of abnormal neurologic outcome in the surviving twin [21, 22]. Demise of the co twin can lead to run-off of blood volume into the low resistance circulation of the dead twin through placental vascular communications. Neurologic damage is commonly attributed to transient hypovolemic shock in the surviving twin [23].

TREATMENT STRATEGIES

Serial Amnioreduction

Traditionally treatment of severe TTTS has consisted of repeated reduction amniocenteses [24]. These are thought to delay early delivery due to polyhydramnios and preterm labor. Some of the therapeutic effect may also lie in the decrease of intrauterine pressure leading to improvement of venous return to the donor and decompression of compensatory VV anastomoses.

Improvement of TTTS is evident in reaccumulation of fluid around as well as a visible bladder in the donor. Close ultrasound follow up is mandatory to watch for signs of development of polyhydramnios in the recipient sac. Amniocentesis is repeated with recurrence of symptomatic polyhydramnios.

The largest study shows in a group of 223 pregnancies shows an overall survival of 60% with an 8 week interval to delivery after diagnosis of TTTS and a neurologic impairment in survivors of 24% [24]. Other Studies have confirmed these findings [25, 26]. Complications of amnioreduction include preterm premature rupture of membranes (PPROM), preterm delivery, fetal distress, intrauterine demise, abruption and chorioamnionitis (see Table 2). Amnioreduction can be performed at any time in gestation after 15 weeks. After attaining pulmonary maturity, delivery should be considered in cases of severe TTTS.

Table 2. Complications after Laser Therapy vs Amnioreduction in the Eurofoetus Trial [16]

	Laser group n= 69	Amnioreduction group n=68	P value
Number of procedures	1 (except for two women who underwent a second laser procedure)	2.6±1.9	
Intraabdominal leakage of amniotic fluid	2/69 (3%)	0	0.5
Placental abruption	1/69 (1%)	2/68 (3%)	0.62
Pregnancy loss within 7 days of the initial procedure	8/69 (12%)	2/68 (3%)	0.1
PPROM within 7 days of initial procedure	4/69 (6%)	1/68 (1%)	0.37
PPROM within 18 days	6/69 (9%)	6/68 (9%)	0.98
IUFD within 7 days of the initial procedure	16/138 (12%)	9/136 (7%)	0.23

Septostomy

With this procedure a single reduction amniocentesis is performed with intentional puncture of the intertwin membrane. In cases where the amniotic fluid in the recipient sac is not massive amnioreduction may not need to be preformed and fluid volume corrections occurs spontaneously. One multicenter randomized trial [26] comparing septostomy to amnioreduction enrolled 30 patients in each arm. The outcomes in both arms were very similar with an overall survival of 65% in both groups and latency to delivery of 8-10 weeks. The authors concluded that given the similarity of the results, a larger randomized trial would be unlikely to demonstrate a significant difference. Complications are the same as for amnioreduction: rupture of membranes, pre-term labor and delivery although the proponents of the procedure quote a decreased risk since only a single and not repeated procedures are performed. In addition to these risks, there is the theoretical risk of cord entanglement if a significant rift in the intertwin membrane is created.

Laser

Fetoscopic laser coagulation of communicating placental vessels aims to correct the intra-placental vascular imbalance between recipient and donor twins. Laser therapy for TTTS *via* a maternal laparotomy was first reported in 1990 from the University of Utah [27]. In 1992 Nicolaides and his group in London reported percutaneous lasering of all vessels crossing the intertwin membrane [28]. In 2000 Quintero proposed the selective coagulation of the communicating vessels only [29] to maximize the remaining placental bed of the donor twin. The same year Harrison's group from UCSF proposed the selective ablation of an arterio-venous anastomosis from the donor to the twin to retain potentially protective AA and VV anastomoses [30]. Currently the most predominant approach favors the selective coagulation of communicating vessels since this is also thought to protect the surviving twin in case of the demise of its co-twin [16].

At present women presenting with severe TTTS between 15 and 24 to 26 weeks are candidates for laser therapy.

Therapy for TTTS is usually reserved for cases of severe disease, Stage II or higher. Laser therapy for TTTS, typically is a one-time procedure that is performed at specialized centers only. The procedural failure rate, i.e. the inability to complete the procedure ranges from 0 [16] to 14% [31]. Rarely patients undergo a second procedure. Most centers choose a transcutaneous approach with local or regional anesthesia using a 3.3mm cannula with a 2mm fetoscope [16]. Prophylactic tocolytics such as nifedipine and indocin as well as antibiotics are administered perioperatively. An amnioreduction through the cannula is performed after the laser procedure. Follow-up includes weekly ultrasounds.

A recent randomized controlled trial [16] comparing endoscopic laser surgery with serial amnioreduction demonstrated an increased perinatal survival, higher gestational age at delivery and a better neurological outcome at 6 months of age in the laser arm (see Tables 3 and 4).

Complications of laser therapy [16] include miscarriage within 7 days of the procedure (12%), PPROM (9%) and intrauterine demise of one or both fetuses (12% of fetuses) (for details see Table 2). Maternal complications include leaking of amniotic fluid through the puncture site at the uterus causing abdominal pain in 3% and placental abruption in 1%. The major criticism of this study has been that survival rates for the amniocentesis group are lower than seen in previous studies [24, 25]. Additionally, one case of intra-abdominal bleeding requiring transfusion of 7 units of packed red blood cells has been reported [32]. A large multi-center NIH sponsored randomized trial in the United States comparing laser therapy to amniocentesis is currently underway.

POSSIBLE FUTURE THERAPEUTIC APPROACHES

Recently High Intensity Focused Ultrasound (HIFU) has been shown to successfully ablate fetal tissue [33]. Careful interrogation of the placental surface by ultrasound with doppler technology can identify intertwin anastomoses [11, 34]. Conceivably this technique could be used to ablate offending anastomoses early in gestation. This non-invasive approach would likely avoid the risks associated with either amnioreduction and fetoscopic laser ablation.

Table 3. Survival after Laser Therapy vs Amnioreduction in the Eurofoetus Trial [16]

	Laser	Amnio	P value
Number of cases	72	70	
%Surviving children at 6 months	56%	38%	P=0.01
Percent of pregnancies with no surviving children	24%	49%	
Percent of pregnancies with one survivor	40%	26%	
Percent of pregnancies with two survivors	36%	26%	
Percent of Pregnancies with at least one survivor	76%	51%	P=0.002
Gest age at delivery	33.3	29.0	P=0.003

Table 4. Morbidity after Laser Therapy vs Amnioreduction in the Eurofoetus Trial [16]

	Laser	Amnio	P value
No. of fetuses	144	140	
Survival at 6 months	81/144 = 56%	54/140=38%	P=0.01
IVH III to IV	1%	6%	P=0.1
Cystic PVL	6%	14%	P=0.02
Healthy survivor	75/81=93%	44/54=81%	P=0.003
Impaired survivor	7%	19%	

Table 5. A Brief Comparison of Serial Amnioreduction and Laser Therapy

Serial Amniocentesis	Laser fetoscopy
Can be performed in most hospitals	Only available in specialized centers
Low maternal risk	Higher maternal risk
Repeated procedures required	Mostly one time procedure
Overall lower perinatal survival	Overall higher perinatal survival
More neurologic impairment in survivors	Less neurologic impairment in survivors

CONCLUSIONS

One third of all twin pregnancies are monochorionic and are therefore at risk for developing TTTS. The diagnosis of a monochorionic pregnancy is ideally made early in pregnancy and discussion of the chorionicity should be made as part of any fetal assessment in twin pregnancies.

Ten to 25% of monochorionic pregnancies will develop TTTS and half of those cases will be severe enough to require intervention. Discussion of treatment options of early onset severe TTTS should include termination of pregnancy, amnioreduction, septostomy and laser therapy. Without treatment the prognosis is poor in terms of mortality and morbidity related to prematurity and death of a co-twin. The survival and neurologic outcome seems to be improved with laser when compared to standard treatment with

amniocenteses. Patients with early onset TTTS (before 24 to 26 weeks) are candidates for laser intervention, which is only performed at several specialized centers around the world.

REFERENCES

- [1] Benirschke K, Kim CK. Multiple pregnancy. 1. N Engl J Med 1973; 288: 1276-84.
- [2] Luke B. The changing pattern of multiple births in the United States: maternal and infant characteristics, 1973 and 1990. Obstet Gynecol 1994; 84: 101-6.
- [3] Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Munson ML. Births: Final Data for 2002. Natl Vital Stat Rep 2003; 52: 1-113.
- [4] Cameron AH, Edwards JH, Derom R, Thiery M, Boelaert R. The value of twin surveys in the study of malformations. Eur J Obstet Gynecol Reprod Biol 1983; 14: 347-56.
- [5] Souter VL, Kapur RP, Nyholt DR, *et al.* A report of dizygous monochorionic twins. N Engl J Med 2003; 349: 154-8.

- [6] Benirschke K, Kim CK. Multiple pregnancy. 2. N Engl J Med 1973; 288: 1329-36.
- [7] Feldstein VA, Filly RA. Complications of monochorionic twins. Radiol Clin North Am 2003; 41: 709-27.
- [8] Sepulveda W, Sebire NJ, Hughes K, Kalogeropoulos A, Nicolaides KH. Evolution of the lambda or twin-chorionic peak sign in dichorionic twin pregnancies. Obstet Gynecol 1997; 89: 439-41.
- [9] Sepulveda W, Sebire NJ, Hughes K, Odibo A, Nicolaides KH. The lambda sign at 10-14 weeks of gestation as a predictor of chorionicity in twin pregnancies. Ultrasound Obstet Gynecol 1996; 7: 421-3.
- [10] Bermudez C, Becerra CH, Bornick PW, Allen MH, Arroyo J, Quintero RA. Placental types and twin-twin transfusion syndrome. Am J Obstet Gynecol 2002; 187: 489-94.
- [11] Machin GA, Feldstein VA, van Gemert MJ, Keith LG, Hecher K. Doppler sonographic demonstration of arterio-venous anastomosis in monochorionic twin gestation. Ultrasound Obstet Gynecol 2000; 16: 214-7.
- [12] Machin G, Still K, Lalani T. Correlations of placental vascular anatomy and clinical outcomes in 69 monochorionic twin pregnancies. Am J Med Genet 1996; 61: 229-36.
- [13] Machin GA, Keith LG. Can twin-to-twin transfusion syndrome be explained, and how is it treated? Clin Obstet Gynecol 1998; 41: 104-13.
- [14] Machin GA. Velamentous cord insertion in monochorionic twin gestation. An added risk factor. J Reprod Med 1997; 42: 785-9.
- [15] Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin-twin transfusion syndrome. J Perinatol 1999; 19: 550-5.
- [16] 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: 136-44.
- [17] Sebire NJ, D'Ercole C, Carvelho M, Sepulveda W, Nicolaides KH. Inter-twin membrane folding in monochorionic pregnancies. Ultrasound Obstet Gynecol 1998; 11: 324-7.
- [18] Taylor MJ, Govender L, Jolly M, Wee L, Fisk NM. Validation of the Quintero staging system for twin-twin transfusion syndrome. Obstet Gynecol 2002; 100: 1257-65.
- [19] Gonsoulin W, Moise KJ Jr, Kirshon B, Cotton DB, Wheeler JM, Carpenter RJ Jr. Outcome of twin-twin transfusion diagnosed before 28 weeks of gestation. Obstet Gynecol 1990; 75: 214-6.
- [20] Weir PE, Ratten GJ, Beischer NA. Acute polyhydramnios--a complication of monozygous twin pregnancy. Br J Obstet Gynaecol 1979; 86: 849-53.
- [21] Haverkamp F, Lex C, Hanisch C, Fahnenstich H, Zerres K. Neurodevelopmental risks in twin-to-twin transfusion syndrome: preliminary findings. Eur J Paediatr Neurol 2001; 5: 21-7.
- [22] Larroche JC, Droulle P, Delezoide AL, Narcy F, Nessmann C. Brain damage in monozygous twins. Biol Neonate 1990; 57: 261-78.
- [23] Liu S, Benirschke K, Scioscia AL, Mannino FL. Intrauterine death in multiple gestation. Acta Genet Med Gemellol (Roma) 1992; 41: 5-26.
- [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: 708-15.
- [25] Hecher K, Plath H, Bregenzer T, Hansmann M, Hackeloer BJ. Endoscopic laser surgery versus serial amniocenteses in the treatment of severe twin-twin transfusion syndrome. Am J Obstet Gynecol 1999; 180: 717-24.
- [26] Saade G, Moise KJ Jr, Dorman K, *et al.* A Randomized Trial of Septostomy versus Amnioreduction in the Treatment of Twin Oligohydramnios Polyhydramnios Sequence (TOPS). Am J Obstet Gynecol 2003; 187 supplement: S54.
- [27] De Lia JE, Cruikshank DP, Keye WR, Jr. Fetoscopic neodymium: YAG laser occlusion of placental vessels in severe twin-twin transfusion syndrome. Obstet Gynecol 1990; 75: 1046-53.
- [28] Ville Y, Hecher K, Ogg D, Warren R, Nicolaides K. Successful outcome after Nd: YAG laser separation of chorioangiopagus-twins under sonoendoscopic control. Ultrasound Obstet Gynecol 1992; 2: 429-31.
- [29] Quintero RA, Comas C, Bornick PW, Allen MH, Kruger M. Selective versus non-selective laser photocoagulation of placental vessels in twin-to-twin transfusion syndrome. Ultrasound Obstet Gynecol 2000; 16: 230-6.
- [30] Feldstein VA, Machin GA, Albanese CT, *et al.* Twin-twin transfusion syndrome: the 'Select' procedure. Fetal Diagn Ther 2000; 15: 257-61.
- [31] 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: 1202-8; discussion 1208-11.
- [32] Ville Y, Hecher K, Gagnon A, Sebire N, Hyett J, Nicolaides K. Endoscopic laser coagulation in the management of severe twin-to-twin transfusion syndrome. Br J Obstet Gynaecol 1998; 105: 446-53.
- [33] Paek BW, Vaezy S, Fujimoto V, *et al.* Tissue ablation using high-intensity focused ultrasound in the fetal sheep model: potential for fetal treatment. Am J Obstet Gynecol 2003; 189: 702-5.
- [34] Feldstein VA. Understanding twin-twin transfusion syndrome: role of Doppler ultrasound. Ultrasound Q 2002; 18: 247-54.