Twin-to-Twin Transfusion Syndrome: A Literature Review and Case Study

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Abstract

Twin-to-Twin Transfusion Syndrome (TTTS) affects up to 17% of monochorionic twin pregnancies and if left untreated, fatality of one or both twins occurs 80-100% of the time. Four common treatment options are available for patients with TTTS. Each treatment option has pros and cons, and no two cases of TTTS should be treated the same. Studies show laser therapy is the most common treatment option with the highest success rate, but this invasive procedure is not always an option. Most treatments are high risk due to the need for sequential procedures throughout gestation for temporary relief rather than treatment. Laser therapy is the only treatment option available with high success rates that treats TTTS where others simply relieve symptoms.
Introduction

According to Dudenhaussen (2009), multiple gestations occur at different rates varying from country-to-country (p. 45). Compared to singleton pregnancies, the mother’s organisms endure a greater amount of physiological changes during multiple pregnancies. Ultrasound has provided a higher rate at which multiple pregnancies are detected which in turn provides a decreased rate of perinatal mortality. Early diagnosis always plays an important role in managing pregnancies. There are two types of twins including monozygotic and dizygotic. Twin-to-Twin Transfusion Syndrome (TTTS) only occurs in monozygotic twins (Jackson & Mele 2009, p. 226).

Furthermore, monozygotic twins form when an embryo splits into two separate cells. An estimated four out of 1000 twins will be monozygotic. Statistics have shown monozygotic twins face a greater risk of malformations. In 1875, a German obstetrician by the name of Friedrich Schatz first identified TTTS. In 1886, Schatz went on to identify many diagnostic criteria still used in healthcare today. “TTTS, defined as amniotic fluid discordance in the two sacs, occurs in approximately 9-15% of monochorionic twin pregnancies” (Rossi, 2009, p. 53). TTTS is a condition believed to develop due to unequal exchange of blood flow that then leads to imbalanced sharing of nutrients, oxygen, and fluid between twins. Transfusion from one twin to the other is caused by vascular anastomoses or connections of blood vessels within the placenta that result in unequal blood flow.

According to Jackson and Mele (2009), there are three different types of anastomoses believed to cause TTTS including: artery-to-vein, vein-to-vein, and artery-to-artery (p. 227). Generally, identifiers of TTTS consist of monochronicity, amniotic fluid discrepancy, and growth discordance greater than 20%. Commonly, one sac contains polyhydramnios with the
largest vertical pocket measuring greater than 8 cm, and oligohydramnios in the other sac with largest vertical pocket measuring less than 2 cm. Other indicators include inconsistency in abnormal cord Doppler studies, presence of cardiac dysfunction, and abnormalities in umbilical cord size. Each twin attempts to adapt to its environment due to unbalanced blood flow. As an effort to conserve energy, the donor twin urinary output is very marginal, causing low amniotic fluid levels (p. 228).

In addition, Jackson and Mele (2009) define the Quintero staging system and the five stages of TTTS. In stage I, there is polyhydramnios in the recipient and oligohydramnios in the donor, with the bladder of the donor twin remaining visible. Umbilical Doppler studies are not critically abnormal in stage I. Stage II is categorized by continuing polyhydramnios/oligohydramnios, but with no urine visible in the donor’s bladder. The donor is termed stuck because the amniotic sac adheres to the fetus, leaving minimal or no room for movement. Stage III begins when conflicting amniotic fluid levels are complicated by abnormal cord Doppler studies. In stage IV, there is an occurrence of hydrops or fluid gathering in two or more cavities of the donor or recipient. It is important to note that the existence of hydrops is a poor predictive sign. If the syndrome advances to stage V, fetal demise can occur in either fetus (p. 228).

In contrast, research done by Rossi (2009) suggests the Quintero staging system does not associate with the prognosis of TTTS in women who are undergoing selective laser therapy of the placental vessels (SLPCV). Rossi reviewed 400 cases of TTTS treated with SLPCV survival rates ranged from 83%-67% depending on the Quintero stage of TTTS. SLPCV treatment showed an increased number of twins surviving per pregnancy during both mild and advanced stages of Quintero. Therefore, the Rossi staging system was created to assess each twin
separately. This Rossi staging system allows incorporation of symptoms only visible in the individual twin being assessed (p. 54).

There are treatment options available for twins diagnosed with TTTS, but decisions should be made based on gestational age, severity of the syndrome, as well as patient preference. If left untreated, prognosis of twins diagnosed with TTTS is very poor with high mortality rates of 80-100% or significant risk of neurological damage in survivors (O’Donoghue, Cartwright, Galea, & Fisk, 2007, p. 958).

**Literature Review**

**Treatment Options Available Today**

According to Yamamoto and Ville (2005), there are two steps critical to outlining TTTS. First, the gold standard for diagnosing TTTS is visualization of the polyhydramnios/oligohydramnios on ultrasound regardless of other differences including: estimated hemoglobin levels or fetal weight. Second, randomized studies and literature research has shown laser therapy is more successful than amnioreduction in treating TTTS. It is very important to diagnose TTTS before 26 weeks of gestation (p. 973). This helps improve efforts to increase survival rates and develop new strategies for complications that arise in treated patients. According to Jackson and Mele (2009), there are four common procedures to treat TTTS. These four procedures include amniotic septostomy, umbilical cord occlusion, amnioreduction, and laser therapy (p. 229).

Amnioreduction (AR) was first introduced to help improve comfort of the mother by controlling polyhydramnios, but is also the most common treatment for TTTS (Jackson & Mele, 2009, p. 229) AR utilizes amniocentesis to aspirate two to three liters of amniotic fluid from the recipient’s amniotic sac. The motivation for AR is to restore normal fluid volumes in both twin
sacs as well as prolong pregnancy by decreasing premature membrane rupture and preterm contractions. AR does not repair the condition that causes the transfusion syndrome, so eventually amniotic fluid will re-accumulate and require sequential amnioreductions. The greatest disadvantage of AR is the probable need for multiple amnioreductions which increases risk of injury or infection for either mother and/or fetuses. In a recent trial, 69% of patients that underwent AR required more than one procedure throughout gestation (p. 229).

Jackson and Mele (2009) also mention the deliberate perforation of the intertwin membrane in an effort to allow amniotic fluid volumes to equalize between recipient and donor twins. This is a treatment option for TTTS known as amniotic septostomy. Similar to AR, septostomy does not eliminate the underlying cause of TTTS, but may offer relief of symptoms for some patients. A study performed to test results of septostomy was terminated before completion when results yielded similar rate of survival of at least one twin as AR. A common risk associated with septostomy is the potential for creating a hole in the intertwin membrane which will increase the risk for entanglement of umbilical cords, which could possibly lead to death of one or both twins (p. 229).

According to Jackson and Mele (2009), in 1990 a researcher by the name of De Lia led a group that initiated the use of laser photocoagulation (LPC) as a treatment opportunity for TTTS. LPC is an invasive procedure that inserts a tiny camera using ultrasound guidance into the uterus through a laser beam that will then coagulate the vascular anastomoses intersecting vascular communication between twins. Advances made in this field led to the development of selective photocoagulation. The concept behind selective photocoagulation is to only coagulate the vessels participating in the syndrome instead of all vessels crossing the intertwin membrane. Laser
surgery compared with AR dropped the perinatal death rate nearly 20%. Matched with serial amnioreduction, this study shows improvement in neonatal outcomes (p. 229).

Furthermore, fetoscopic cord coagulation uses ultrasound guidance along with an instrument used to occlude the umbilical cord of one twin are used during this procedure. The goal is to coagulate the vessels in that twin’s cord. It is noted that when this procedure is performed, vessels between the donor and placenta remain intact. Selective reduction is set aside for cases in which severe cardiomyopathy is evident in the recipient twin and there is no chance for survival of that twin. In these cases, if laser therapy is attempted, it likely will result in death of the donor twin due to unequal placental sharing between donor and recipient. Validation of cord coagulation states by sacrificing one twin, TTTS progression will stop and gestation will be sustained maximizing outcome of the donor twin. In such cases, cord coagulation is performed as a last resort (Jackson & Mele, 2009, p. 230).

**What the Statistics Show**

O’Donoghue et al. (2007) determined there is now reasonable evidence based on observational studies and randomized trial that laser therapy proves superior to conservative management and amnioreduction in cases of severe TTTS (Quintero stages III-IV). Recently, Eurofetus randomized trial published before 26 weeks gestation, laser photocoagulation (LPC) allows neonatal survival of at least one twin and intact survival of six months in 76% of cases, compared to 56% of cases treated by amnioreduction (p. 959). Furthermore, re-analysis of allies in a stage-adjusted series suggested laser therapy resulted in a higher perinatal death rate than amnioreduction during Quintero stages I-II. Current evidence is not provided to determine optimal treatment for early stage I of TTTS due to the small number of cases treated at this stage to date.
Research has shown, “initial case series and cohort studies on amnioreduction, endoscopic laser, and microseptostomy as treatment for TTTS, regardless of Quintero staging, suggest that neonatal outcomes are improved with all three techniques, compared with the baseline morbidity and mortality risks seen in cohorts with no therapy” (Stamilio, Fraser, & Moore 2010, p.10). Survival of neonates is 37-60% with amnioreduction in most cases and as high as 82% at best. Neurologic damage for serial amnioreduction ranges from 17-33%. As for endoscopic laser therapy, neonatal survival rate ranged from 55-73% with neural damage from 4-18%. Septostomy treatment is linked to over 80% survival rate, with no records reported in early data.

Van Mieghem et al. (2011) conducted an observational study that was performed at University Hospital Leuven (Belgium) and Hospital Clinic (Spain) between January 2007 and January 2009. During this time period, 45 participants with moderately discordant amniotic fluid levels were seen in Belgium. The only patients included in the final analysis were monochorionic diamniotic twin pregnancies with moderate fluid discordance. Diagnosis of monochorionicity was based on first semester ultrasound criteria, which was also confirmed by examination of the placenta after birth. Following the diagnosis of moderately discordant amniotic fluid, ultrasound exams were performed to begin with at a 2-3 day interval for a week. In the event that fluid levels were stable, further ultrasound exams were planned at one week intervals until delivery. In cases that fluid remained stable or regressed and TTTS did not occur, delivery was scheduled for 35-37 weeks gestation. However, when TTTS criteria were met, intervention prenatally was offered. During the same time period, 52 patients with moderately discordant amniotic fluid levels were seen in Barcelona. A finalized diagnosis of TTTS was evident in 11 cases. In this population, the best analyst of TTTS was fluid discordance severity for gestational age (p. 16).
Side Effects of Treatment

According to Cruz-Martinez et al. (2011), for severe TTTS, LPC is the first-line of treatment. It is associated with survival rates ranging from 75-85%, however, any invasive fetal procedure has risks and laser treatment is accompanied by increased risk of preterm premature rupture of membranes (PPROM). This rupture of membranes may occur as frequently as 28% of cases and is also linked with preterm delivery 30% of the time before 32 weeks (p. 459). Clinical studies show septostomy can be a complication of laser therapy. It is a side effect of the donor’s collapsed membrane at uterine insertion, or may be caused by the need to coagulate placental anastomoses through the intertwin membrane.

Also, it is very important for this study to assess the development of pseudoamniotic band syndrome (PABS) and determine whether or not it is associated with laser therapy treatment. A study was conducted from June 2006 continuing through December 2009 at Hospital Clinic in Spain and University Hospitals in Belgium. Participants for this study included 414 patients that were monochorionic diamniotic twin pregnancies with confirmed TTTS and had to meet Eurofetus criteria in order to qualify for surgery. Following laser ablation, the laser center searched every 24 hours for the first three days and 72 hours thereafter for any signs of septostomy via ultrasound exams. In all 414 pregnancies fulfilling criteria for surgery, laser coagulation was successful. Overall, 73% of both twins survived, and success rate for survival of at least one twin was 92%. Septostomy occurred postoperatively within a week in 30 cases, and eight cases were diagnosed postnatally with PABS all as limb constrictions. This study suggests septostomy increases the risk of PABS, which supports the belief that it should not be an option for monochorionic twins that are already complicated by TTTS (Cruz-Martinez et al. 2011, p. 461)
Yamamoto and Ville (2005) suggest cases of TTTS treated by LCP are susceptible to complications later such as intrauterine growth restriction (IUGR). It is possible for IUGR to occur due to insufficient placental flow after laser therapy because of necrosis of placental cotyledons that have been devascularized. Any evidence of LPC leaving restricted placental vasculature IUGR is a risk for one or both twins, and eventually if restriction remains, fetal demise may occur (978).

**Long-Term Outcome of Treatment**

Li et al. (2011) conducted a study to specifically investigate long-term neurodevelopmental outcome in TTTS cases treated conventionally. In this hospital, laser therapy was not available, so cases that underwent laser therapy will not be included. Between January 1996 and December 2004, 21 pregnancies diagnosed with TTTS were observed at Kyushu University Hospital. Mean gestational age at delivery was 28 weeks. 13 pregnancies were treated with amnioreduction. In the 8 pregnancies not treated with amnioreduction, 1 pregnancy was complicated by PPROM, 2 pregnancies presented with mild TTTS (stage I), and 1 pregnancy chose early delivery. Intrauterine fetal demise affected 5 of the fetuses; all of these were not treated with amnioreduction. Neurological follow up was available for 20 of the remaining survivors. Average age at follow-up was 6.3 years ranging from 2-12 years old. 6 children showed neurodevelopmental impairment, but the remaining 70% had normal neurological development. Out of all 20 cases, 20% of neurodevelopmental impairment was considered severe, which may include but is not limited to: cerebral palsy, mental retardation, epilepsy, and ventricular dilation. Results of this study show “whether TTTS is treated with laser surgery or managed conservatively, the incidence of major neurodevelopmental impairment is high” (Li et al. 2011, p.5). Risks of invasive procedures are definitely something patients need to
keep in mind when choosing their treatment options. It is important to weigh pros and cons of each treatment options in order to determine which will have the best outcome for each individual case.

Case Study

A 28 year old Caucasian female successfully conceived triplets using In Vitro Fertilization (IVF). As defined, IVF is the process of fertilization by hand combining egg and sperm in a laboratory petri dish. When IVF is successful, the process is combined with a procedure known as embryo transfer, where the embryo is physically placed in the uterus. In this case, IVF was used to implant 2 eggs inside the woman’s uterus, but 1 egg split into two embryos. At a routine ultrasound examination at 20 weeks gestation, the twins were diagnosed with TTTS and the stuck twin was identified by low amniotic fluid levels and was pressed against the uterine wall. (See Figure 1) The couple decided laser surgery was the best option for their babies, so they went straight to Los Angeles to have the surgery done. After surgery, doctors in Los Angeles placed the woman on bed rest to prevent preterm labor. Two weeks postop, the stuck twin showed improved fluid levels in its placental sac as well as growing at a rate similar to the recipient twin. (See Figure 2) However, the woman was noncompliant with her orders to remain on bed rest, so the outcome for these babies was not what it could have been. She went into labor at 23 weeks, and the babies were delivered. The twins were shockingly the same size at birth which was a huge rebound for TTTS in a very short three weeks. Outcome for these babies could have been better, and there is a very good chance this woman could have carried these babies to term had she been compliant with doctor’s orders.
Discussion

Of the research that has been conducted to date, 4 treatment options are available to TTTS cases that occur within the limitations of current technology and current data analysis. Many sources agree that although risks will always be associated with invasive procedures, laser therapy has proven to have the lowest mortality rates and highest success rates of saving one or both twins. According to Papanna et al. (2009), coagulation of the communicating vessels via laser tools is now the standard treatment for severe TTTS cases. All other procedures put the fetuses at a higher risk due to the need for multiple procedures that only provide temporary relief.

In conclusion, “TTTS is associated with significant perinatal morbidity and death when untreated, and the results of this limited collection of randomized studies suggest that fetoscopic laser coagulation of anastomoses is the most effective intervention for TTTS, regardless of the disease stage” (Stamilio, Fraser, & Moore 2010, p.11). There is a very limited amount of data available from trials showing treatment for mild TTTS. Current evidence shown today, though it may be limited in qualitative and quantitative data, shows fetal intervention most commonly with laser photocoagulation or amnioreduction can save lives or prevent disability for a large portion of fetuses affected by TTTS.
Figures

Figure 1. Ultrasound view of TTTS at 20 weeks clearly shows the stuck/donor twin against the wall of its sac where very low, abnormal fluid levels are shown. Low fluid levels and a baby “stuck” against the uterine wall is a tell-tale sign of TTTS.

Figure 2. This transverse ultrasound image taken at twenty weeks specifically shows the donor twin “A” next to the recipient twin “B”. This image was obtained solely to show the size difference in the twins’ craniums.
References


