Twin-Twin Transfusion Syndrome: An Update

Daniel W. Skupski
The New York Presbyterian Hospital – Joan and Sanford I. Weill Medical College of Cornell University, New York, NY, USA

Twin-twin transfusion syndrome leads to high rates of perinatal morbidity and mortality due to its poorly understood etiology and difficult diagnosing and treatment. Current therapies are suboptimal and have not been tested through randomized controlled trials. Parent counseling at the time of diagnosis includes informing on poor chance of double survival, relatively high chance of long-term neurologic handicap, the near certainty of prematurity, and the probability of cesarean delivery. Improvement in therapies awaits a better scientific understanding of the etiology of this condition.

Key words: cross transfusion, intrauterine; fetal ultrasound; fetofetal transfusion; intrauterine cross-transfusion; pulmonary stenosis; twin transfusion syndrome

Twin-twin transfusion syndrome occurs in multiple gestations and involves the chronic flow of blood from one twin to its co-twin. The syndrome usually occurs in monochorionic twins, who themselves have a very high rate of complications including severely preterm delivery, fetal growth restriction, fetal death, and twin-twin transfusion syndrome. The end result of twin-twin transfusion syndrome with no treatment is almost always extreme premature delivery (1,2). Even with the treatment, the fetal/neonatal death rate ranges from 40-60% (3-5). Despite much enthusiasm for the particular therapies for this syndrome, salvage rates for these fetuses are less than optimal. This article views the latest advances in our understanding of twin-twin transfusion syndrome and focuses on the limitations of our knowledge.

The good news are recent important progress in our understanding of the pathophysiology in twin-twin transfusion syndrome, advances in means of diagnosis, development of new treatment options, and in increased survival of neonates.

Pathophysiology

Until recently, our knowledge of the pathophysiology of twin-twin transfusion syndrome was limited. However, ultrasound and Doppler studies of the placenta have clarified some of the existing complexities. Today, we know that vascular connections in the placenta between both twins are necessary for twin-twin transfusion syndrome to develop (6). Vascular anastomoses are present in virtually 100% of monochorionic twin pregnancies, whereas twin-twin transfusion syndrome occurs (with rare exception) in 5-10% of monochorionic pregnancies (7-10). The progressive nature of twin-twin transfusion syndrome in utero is thought to be due to one twin (the donor) who slowly pumps blood to the other (the recipient) through the placental vascular anastomoses. The reason for the occurrence of twin-twin transfusion syndrome in only a small proportion of monochorionic twin pregnancies with vascular anastomoses is unknown.

Recent studies have provided clues to the pathophysiology of twin-twin transfusion syndrome. In a research on 10 monochorionic pregnancies diagnosed with twin-twin transfusion syndrome and 10 monochorionic pregnancies without twin-twin transfusion syndrome, Bajoria et al (11) performed immediate post-delivery placental injection studies to characterize the nature of placental vascular anastomoses. Arterio-arterial, veno-venous, and atrio-venous (A-V) anastomoses were described. This study suggested that A-V anastomoses do not occur in the recipient twin, whereas venous anastomoses run in the reverse direction, might be in the etiology of twin-twin transfusion syndrome. However, the sample size in this study was small, and what caused the development of these uncompensated anastomoses remains unknown. There is a differ-
ence of opinion as to whether twin-twin transfusion syndrome can occur in monoamniotic twins; if it does, it is extremely rare. A later study by Bajoria (12) compared these anas to mo ses in monoamniotic and monochorionic pregnancies. A greater number of anastomoses of all types were present in monochorionic pregnancies (12). This finding suggests that the syndrome may develop when there is a relative lack, rather than the presence, of these vascular connections.

Twin-twin transfusion syndrome is a slowly progressive disease. The gestational age of its initial presentation can be as early as 13 weeks, but obstetrical ultrasound usually allows the syndrome to be diagnosed between 17 and 26 weeks. Subsequent complications vary; preterm delivery may occur quickly after the diagnosis or several months later. Progressive oligohydramnios in one sac and polyhydramnios in the other sac is the rule. Death of the fetuses/neonates may be due to preivable delivery, severe growth restriction of the donor, hypoplastic lungs in the donor, or high output cardiac failure in the recipient. These varied findings make studying the efficacy of our interventions very difficult.

Ultrasound Diagnosis

The classic neonatal findings of birth weight difference, hematocrit difference, and plethora in the recipient and pallor in the donor do not apply to the prenatal diagnosis of twin-twin transfusion syndrome (13). Twin-twin transfusion syndrome is a diagnosis made prenatally by ultrasound and great advances have been made in its identification. The hallmarks of the diagnosis are: 1) monochorionic gestation, 2) the combination of polyhydramnios in one sac and oligohydramnios in the other, and 3) the perisent test finding of a small or non-visualized bladder in the donor and a large bladder in the recipient (Table 1) (14).

First trimester ultrasound should be performed in all patients at risk for multiple gestation, because chorionicity is best established in the first trimester (15). Patients at risk for multiple gestation include those with a family history of multiple pregnancies, those of Ni ge rian descent (Yoruba tribe), those with uterine size greater than dates in the first trimester, and any patients who underwent the use of assisted reproductive technologies (including ovulation inducing agents, intrauterine insemination, and in vitro fertilization with embryo transfer). Chorionicity can be easily determined in the first trimester with ultrasound by noting the distance between fetuses within the uterus, the thickness of the intervening membrane, and the presence of the lambda sign (see below).

A monochorionic gestation can be identified in the second trimester, its signs consisting of a single placental mass, same sex fetuses, and the lack of the twin peak or lambda sign at the point where the intertwin membrane meets the placental chorionic plate (Fig. 1). Differences in estimated fetal weight or growth discrepancy are not uniformly present in twin-twin transfusion syndrome (16). Normal values for the measurement of amniotic fluid in twin gestations are available (17). Serial ultrasound is necessary for any case in which the diagnosis is entertained but the criteria are not met because 1) twin-twin transfusion syndrome may appear sub sequently, and 2) the distinction between monoamniotic and monochorionic pregnancy needs to be made. A careful search for fetal anomalies should also be undertaken.

The stuck twin syndrome occurs when no amniotic fluid is visualized in the donor’s sac. It may be difficult to distinguish the stuck twin syndrome from a monoa mniotic twin gestation, because the intertwin membrane may be closely wrapped against the donor and cannot be visualized by ultrasound. If, however, one fetus remains restricted to one place against the uterine wall over the course of one or more examinations, and the character of its movements is constricted, it is likely a stuck twin. Careful attention to the relative placements of the placental cord insertions and the course of the umbilical cords may also be helpful in the diagnosis (18).

In addition to the above second trimester diagnostic criteria, ultrasound findings in the first trimester also are associated with the subsequent development of twin-twin transfusion syndrome (19). According to Se bire and co-workers (20), these include the presence of monochorionicity, an increased nuchal translucency measurement >3 mm between 10 and 14 weeks of gestation, poor crown-rump length growth of one fetus, and membrane folding at 10-13 weeks of gestation.

<table>
<thead>
<tr>
<th>Table 1. Twin-twin transfusion syndrome diagnostic criteria</th>
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<tr>
<td>A. Second trimester diagnostic criteria for twin-twin transfusion syndrome</td>
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<tr>
<td>1. Monochorionic gestation</td>
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<tr>
<td>a) Same gender</td>
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<td>b) Single placental mass</td>
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<tr>
<td>c) Thin dividing membrane</td>
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<tr>
<td>d) Lack of lambda or twin peak sign</td>
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<td>2. Abnormal amniotic fluid volume</td>
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<tr>
<td>a) One sac with oligohydramnios, deepest vertical pocket &lt;2.0 cm</td>
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<tr>
<td>b) One sac with polyhydramnios, deepest vertical pocket &gt;8.0 cm</td>
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<td>3. Persistent urinary bladder findings</td>
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<tr>
<td>a) Small or no bladder visualized in twin with oligohydramnios</td>
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<tr>
<td>b) Large bladder visualized in twin with polyhydramnios</td>
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B. Helpful ultrasound findings

1. Estimated fetal weight discordance (>20% of larger twin’s estimated weight)
2. Appearance of a “stuck twin”
3. Hydrops fetalis (presence of one or more of the following in either twin)
   a) Skin edema (>5 mm thickness of scalp skin)
   b) Pericardial effusion
   c) Pleural effusion
   d) Ascites

*Serial scanning may be necessary.*
Treatment Options

Careful antenatal assessment by ultrasound and tocolysis for preterm labor are the cornerstones of conservative management and generally used as adjuncts to other invasive treatments. Frequent antenatal assessment may form the basis of an iatrogenic decision for delivery, and is often associated with prevention of death in utero.

Amnioreduction

Amnioreduction (serial amniotic fluid volume reduction) is currently the most highly regarded treatment and was one of the earliest therapies proposed. Amnioreduction is an amniocentesis with drainage of amniotic fluid from the polyhydramniotic sac to restore a more balanced ratio between the amniotic fluid volumes of the two fetuses. An 18 or 20 gauge needle is used. The amount of fluid drained at a single procedure ranges from 1-7 L, as in one early report (21), and multiple procedures may be necessary if polyhydramnios recurs. Complications occur in about 8% of cases and include chorioamnionitis, preterm labor and delivery, preterm premature rupture of the amniotic mem bran e, and abruptio placentae (21). Later publications (not cited) confirm this, and it appears that these are of the inherent rather than the learning curve variety. A large registry of twin-twin transfusion syndrome patients undergoing amnioreduction has showed that earlier presentation of the disease and a greater number of required procedures are associated with suboptimal outcome (22).

Fetoscopic Laser Occlusion of Chorioangiopagus Placental Vessels

Fetoscopic laser occlusion of chorioangiopagus placental vessels is a totally different therapy that attempts to treat the problem by interposing the vascular anastomoses within the placenta. Through endoscopic visualization into the polyhydramniotic sac, the vesca lar equator of the placenta is delineated, vascular anastomoses are identified, and laser is directed to photocoagulate these vessels. The recent introduction of the selective use of laser to coagulate deep or A-V anastomoses is an important advance (23) in treatment. Fetoscopic laser occlusion of chorioangiopagus placental vessels is a more invasive procedure than other treatments, with greater maternal morbidity, including the complications of amnioreduction, which is also performed during fetoscopic laser occlusion of chorioangiopagus placental vessels.

Septostomy

Septostomy is the intentional puncture of the intertwin membrane or septum. This allows amniotic fluid to circulate between the two amniotic cavities (24). It was observed that monoamniotic pregnancies did not develop twin-twin transfusion syndrome, and thus intentional puncture of the intertwin membrane was proposed as a therapy for twin-twin transfusion syndrome (25). Unfortunately, however, septostomy is associated with a risk of umbilical cord entanglement (pseudo monoamniotic twins) (26). Use of a 22-gauge needle eliminates the complication of a pseudo monoamnionite (24). The most recent report on this therapy shows a fetal/neonatal survival rate of 83% in 12 pregnancies undergoing septostomy (24). Failures of septostomy appear not to diminish the future prospects for this therapy, because these cases presented with preterm labor (27), and the prognosis for prolongation of gestation is dismal when preterm labor has begun (2).

Other Options

Because of the high mortality rate in twin-twin transfusion syndrome, removal of one twin at hysterotomy has been expected to eliminate the hemodynamic derangements and increase the chance of surviving of the other twin (28). But,
know factors. The efficacy of all treatments provided, or other uncertainties encountered in some treatments, a lack of diagnostic criteria in some instances, the technical difficulties encountered in some treatments, a lack of efficacy of all treatments provided, or other unknown factors.

Historical Controls

Treatments for twin-twin transfusion syndrome have not as yet been subjected to a randomized controlled trial (RCT). In fact, only three controlled trials of any treatment for twin-twin transfusion syndrome have been published, and all three have compared historical controls to those undergoing amnioreduction (2,3,32). A selection bias is present favoring a better outcome for patients in later time periods (the treated patients) of up to 30-40% in those studies which use historical controls (39,40). For example, in the three controlled trials of amnioreduction for twin-twin transfusion syndrome, although the p values range from 0.04 to 0.0000001, the treatment effect is only 30-40% (risk ratio for fetal or neonatal death 0.60-0.66) (41). Simply stated, serial amnioreduction has not been adequately demonstrated to be effective, although it is widely used and highly regarded as a therapy for this condition.

Table 2 clearly documents an increasing survival rate with successive publications for each of the therapies for twin-twin transfusion syndrome, suggesting a different cause for the apparent success—namely, advances in neonatal care. An analysis of the deaths in the three controlled trials above shows that 2/3 were neonatal and only 1/3 fetal, allowing for this possibility. However, as noted in the preceding paragraph, it is difficult to document any truly objective benefit from amnioreduction. The only study addressing this issue suggests a possible benefit of amnioreduction over and above the increased survival due to advances in neonatal care for those twin-twin transfusion syndrome twins delivered ≤7 weeks of gestation (42). In addition, the increased survival in later series of fetoscopic laser occlusion of chorioangiopagus placental vessels clearly may be due to a lack of technical expertise in earlier cases. This, as well as an increase in the diagnosis-to-delivery interval (38), provides some empirical evidence for a benefit from fetoscopic laser occlusion of chorioangiopagus placental vessels. However, despite these advances in therapeutic technique, and prompt results so far in the largest and most recent series, mortality from twin-twin transfusion syndrome remains 40-50% overall.

Pseudo-Twin-Twin Transfusion Syndrome

A spectrum of severity exists for all diseases, including twin-twin transfusion syndrome. The presence of “mild” or “pseudo” twin-twin transfusion syndrome further complicates the evaluation of current treatment trials. It has been suggested that early diagnosis and treatment improves outcomes in twin-twin transfusion syndrome (33), but this may not be true for two reasons. First, during the time period in which advances in neonatal care were rapidly improving the survival for infants born with severe prematurity (42). Second, cases of pseudo-twin-twin transfusion syndrome, i.e., low normal amniotic fluid volume in one sac with high normal amniotic fluid in the other, or growth restriction of one twin and normal growth of the other, often are diagnosed subjectively as twin-twin transfusion syndrome and included in
these treatment trials. Thus, the outcomes for pseudo-twin-twin transfusion syndrome have been shown to be better than in twin-twin transfusion syndrome (43).

In reality pseudo-twin-twin transfusion syndrome does not meet objective diagnostic criteria but has the subjective ultrasound appearance of twin-twin transfusion syndrome, characterized by differences in amniotic fluid volumes, estimated fetal weights, thickness of the umbilical cords, and possibly the presence of a velamentous placental cord in sertion. To date, pseudo-twin-twin transfusion syndrome can not be distin guished from other (non-twin-twin transfusion syndrome) fetal problems that appear similarly by ultrasound, such as growth restriction of one twin with a normal co-twin, or two normal twins with the combination of low normal amniotic fluid volume in one sac and high normal amniotic fluid volume in the other. Under these circumstances, cases of pseudo-twin-twin transfusion syndrome should not be included in treatment trials. The natural history of pseudo-twin-twin transfusion syndrome is unknown and invasive treatment may not be necessary (43). Clearly, adherence to strict and objective diagnostic criteria is important (Table 1). Ad herence to this clinical precept gives the added advantage that efficacious therapies should show a benefit in treatment trials with fewer numbers of patients, because a small change in a high mortality rate is easier to demonstrate.

In addition, pseudo-twin-twin transfusion syndrome may represent those cases in which the fetuses are compensated or in balance. Treatment in this circumstance exposes these pregnancies to the morbidities associated with any treatment, including a risk of 8% with the use of serial amnio- reduction (21), and a 10-20% risk of preterm prema ture rup ture of the mem branes with fetoscopic lacer occlusion of chorioangiopagus placental vessels (23). Fetoscopic lacer occlusion of chorioangiopagus placental vessels (23) can also lead to maternal hemorrhage, ab ruptio placen tae, and serious maternal fluid and electrolyte disturbances.

Serial ultrasound must be performed on a weekly basis (or more frequently) whenever twin-twin transfusion syndrome is suspected but the diagnostic criteria are not met. Since twin-twin transfusion syndrome is a slowly progressive disease, the diagnosis made as early as possible will allow a timely in tervention. Since prolonged pregnancy is unlikely after preterm labor has begun (2), treatment must be initiated as early as possible once diagnostic criteria have been met. With the use of treatment, prolongation of the diagnosis-to-delivery interval is possible, thus providing the benef it of greater gestational age at birth (38).

**Neurologic Outcome**

Neurologic injury is common in survivors of twin-twin transfusion syndrome (44). Antenatal neurologic injury in survivors of twin-twin transfusion syndrome occurs at a higher rate compared with other monochorionic pregnancies (45). The reason is presently unclear. Following one fetal death, acute hemorrhage of the surviving fetus into the di lated vas cu lar sys tem of the dead fetus may result in hypotension and cerebral ischemia (46). However, antenatally acquired neurologic injury also has been reported in cases where both twins have survived (44). Vas cu lar sludging due to an extremely high hemoglobin concentration in the recipient may be operative (44). The same may be said for anemia and hypoxemia in the donor (47). The high incidence of antenatally acquired central nervous system injury in survivors of twin-twin transfusion syndrome, as high as 18% (36), argues for cranial imaging studies in the immediate neonatal period (<48 h after birth) and careful neurodevelopmental follow-up (44). When the initial diagnosis of twin-twin transfusion syndrome is made, the parents must be informed on a possibility of neurologic injury. All monochorionic twin survivors should be referred to pediatricians with a special interest in neurology and development.

**Etiology**

Despite the recent insights, the cause of twin-twin transfusion syndrome is still uncertain. If uncompensated A-V anastomoses are the sole cause, then it still remains to be explained why these develop in only a small proportion of monochorionic twins. It is likely that this begins during placental angiogenesis in the first trimester. Determining a cause (other than that, this is a random event) will require a study of the first trimester placental microenvironment. Today, this is possible only clinically (and to a limited extent) with the use of color and power Doppler ultrasound (48,49), though the presently available technology may not allow firm conclusions.

**Randomized Controlled Trials**

Randomized controlled trials of treatment for twin-twin transfusion syndrome have not been completed, despite the initiation of four such trials, three of which are still under way. Low rates of recruitment of subjects have limited the ability to determine the best currently available therapy.

**Summary**

Although much work remains to be done, the good news about twin-twin transfusion syndrome includes the continuing increase in survival for this devastating syndrome. Importantly, we are in need of RCTs to determine which of the currently available therapies is superior. Also, study of the monochorionic placenta, a somewhat neglected area of research, needs to be expanded.

**References**


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Correspondence to:
Daniel W. Skupski
The New York Hospital Medical Center of Queens
56-45 Main Street, #4 South
Flushing, NY 11355, USA
dwskupski@med.cornell.edu