Management of Twin–Twin Transfusion Syndrome: Laying the Foundation for Future Interventional Studies

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Twin–twin transfusion syndrome is the most common complication of monochorionic pregnancies affecting between 5 and 15% of such pregnancies and accounts for 15–77% of perinatal mortality in twins. The management of twin–twin transfusion syndrome is complex and various treatment modalities have been tried. This review critically evaluates the different management options available for the syndrome and recommends some guidelines for future interventional studies.

Twin–twin transfusion syndrome (TTTS) is the most common complication of monochorionic pregnancies affecting between 5 and 15% of such pregnancies (Benirsschke & Kim, 1973; Rausen et al., 1965). However, the incidence may have been under-estimated due to different diagnostic criteria of early studies with more recent studies suggesting an incidence as high as 35% of monochorionic pregnancies (Radestad & Thomassen, 1990; Urig et al., 1990). TTTS accounts for 15–77% of perinatal mortality in twins (Steinberg et al., 1990; Weir et al., 1979). The aim of this review is to evaluate the different management options available for TTTS and recommend some guidelines for future interventional studies. To accomplish this, we performed a Medline search using the words "twin to twin transfusion syndrome" and "chorioangiopagus".

Diagnosis and Pathophysiology

The earlier prenatal diagnostic criteria for TTTS were derived from neonatal data using discordant weights of more than 20% and hemoglobin of > 5g/dl (Abraham, 1967; Rausen et al., 1965; Tan et al., 1979). These criteria have been criticized since discordant weights and hemoglobin can be seen in cases of discordant IUGR in the absence of TTTS (Danskin & Neilson, 1989). Recent evidence from fetal blood sampling has shown that discordance in hemoglobin is rarely present in TTTS (Fisk et al., 1990; Saunders et al., 1991). Cheung et al. (1995) have also shown that waiting for 20% weight discordance before diagnosis of TTTS results in a more severe disease. The diagnostic criteria for TTTS currently used by most prenatal diagnostic units include the presence of oligohydramnios-polyhydramnios in same-sex twins, with a single placenta with or without significant weight discordance. Early documentation of chorionicity by first trimester sonographic finding of a thin dividing inter-twin membrane is also of immense importance for diagnosis of TTTS (Sepulveda et al., 1996; Sepulveda et al., 1996).

The differential diagnosis of TTTS includes discordant placental insufficiency, discordant fetal anomaly, discordant chromosomal anomalies and discordant congenital infections. These conditions need to be excluded before diagnosing TTTS.

The TTTS results from imbalance in blood flow through vascular communications in the placenta (chorioangiopagus). The "recipient" twin receives higher blood supply compared with the "donor" twin. These vascular communications exist in all monochorionic but rarely in dichorionic placentas, which explains the observation that TTTS rarely occurs in dichorionic pregnancies. Vascular anastomosis can be artery to artery, vein to vein or artery to vein. It is thought that the artery to vein anastomoses, in particular those deep within the placental cotyledons, are responsible for significant TTTS (Barjoria et al., 1995). Recent evidence has implicated the role of placental derived vasoactive mediators such as endothelin 1; the renin-angiotensin sytem and hypertensive changes in recipient twins affected by TTTS (Bajoria et al., 2002; Mahieu-Caputo et al., 2001). The implications of these findings are that factors other than unbalanced blood transfusion may play a role in the pathophysiology of TTTS.

In the absence of treatment, the possible complications of TTTS include worsening polyhydramnios leading to premature delivery, hydrops secondary to cardiac failure, and intrauterine fetal death of one or both twins.

Staging of Twin–Twin Transfusion Syndrome

Studies reporting the efficacy of various treatments for TTTS are confounded by different inclusion criteria and therefore difficult to compare. Quintero et al. (1999) have proposed a staging system that could be used to standardize entry into future interventional studies. The system includes five stages:

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Stage I Presence of polyhydramnios and oligohydramnios, with the bladder of the donor twin still visible.

Stage II Stage I and lack of visualization of the urinary bladder in the donor twin, and absence of critical abnormal Doppler findings.

Stage III All of the above and critical abnormal Doppler findings of either absent or reversed end diastolic flow in the umbilical artery or reversed ductus venosus flow or pulsatile umbilical venous flow.

Stage IV All of the above and fetal hydrops.

Stage V Demise of one or both fetuses.

The ideal patients for interventional studies would be stages II–IV.

Management of Twin–Twin Transfusion Syndrome

Several treatment modalities have been proposed and utilized for TTTS including:

- medical management
- serial amnioreduction
- selective and non-selective laser photocoagulation
- inter-twin membrane microseptostomy
- selective feticide and umbilical cord ligation.

In the absence of any intervention, mortality rates as high as 100% have been reported for TTTS (Saunders et al., 1991).

Medical Treatment of TTTS

There have been few case reports of using medical treatment for TTTS. De Lia et al. (1985) reported a successful resolution of hydrops in a recipient twin using digoxin with a successful delivery of the twins at 34 weeks. The suggested mechanism of action is treatment of underlying heart failure. Reports on the use of indomethacin have yielded conflicting results. While Lange et al. (1989) reported successful resolution of polyhydramnios using indomethacin, Jones et al. (1993) have reported an associated fetal death with its use. To our knowledge, no study with a large experience in the use of medical treatment for TTS has been published. Because of this, medical management of TTTS is rarely used and may need further evaluation.

Serial Amnioreduction

Serial amniocentesis was initially performed for the relief of symptoms from the polyhydramnios associated with TTTS. It is still the most commonly employed treatment for TTTS. It has been hypothesized that the decompression caused by amniotic fluid drainage leads to improved circulation to the donor twin (Elliot et al., 1991). These authors demonstrated placental changes suggestive of improved circulation after amnioreduction. Bower et al. (1995), have also demonstrated improved uterine blood flow on Doppler studies following amnioreduction.

Table 1 depicts some of the case series using amnioreduction for the treatment of TTTS. The success rates have varied from 15 to 82%. The wide range may be secondary to the small number of patients in most of the reports. Interpretation of the reports is also limited by their varied gestational age at diagnosis, amount of fluid drained, the number of amniocentesis performed per case and the definition of perinatal survival and the definition / severity of TTTS.

In an attempt to rectify this, Registries for TTTS have been organized. The Australian and New Zealand Registry for TTTS reported their findings in 1999 (Dickinson and Evans). They found a survival rate of 62.5% from 112 cases of TTTS. Mari et al. (2001) reported the findings of the International Twin–Twin Transfusion Syndrome Registry. The registry included 346 twin pairs and following

Table 1

Reports of Serial Amnioreduction for Treatment of TTTS

Reference	No. of patients	Mean No. of amniocentesis	Mean vol. amniotic fluid removed	Mean duration of prolongation of gestation from girst amniocentesis (weeks)	Perinatal survival
Rivett (1933)	5	1.8	1351	5.6	50%
Urig et al. (1990)	5	2.2	NA	1.7	20%
Mahony et al. (1990)	8	3.5	6150	9.7	69%
Schneider et al. (1985)	9	4.6	5725	3.1	44%
Gonsoulin et al. (1990)	13	1.9	1200	3.0	15%
Radestad et al. (1990)	18	2	3700	3.4	53%
Elliott et al. (1991)	17	4	1683	11.6	79%
Saunders et al. (1992)	19	3	2600	7.3	37%
Pinette et al (1993)	13	3.7	NA	11.3	80%
Dennis et al. (1997)	11	5.5	8000	8	82%
Trespidi et al. (1997)	23	NA	NA	NA	57%
Berghella et al. (2001)	19	NA	NA	NA	48%
Total	137				54% (mean)

Note: NA = not available

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amnioreduction, 48% of both fetuses and 71% of at least one fetus survived to 4 weeks after birth. Table 1 also illustrates the differences in amniotic fluid volume removed. The terminology of "aggressive amnioreduction" has been used in some series, but the definition of aggressive versus conservative amnioreduction is yet to be standardized. Operators have been reluctant to remove large amount of amniotic fluids during a single procedure due to the theoretical risk of placental abruption from sudden decompression. However, Saunders et al. (1992) have reported drainage of greater than 6 liters of amniotic fluid at one setting without complications.

The possible complications of amnioreduction include rupture of membranes, preterm labor, chorioamnionitis, iatrogenic conversion to monoamniotic pregnancy (Cooper et al., 2001; Feldman et al., 1998) and placental abruption. More recently, there have been concerns about the long-term neurological outcome of fetuses treated by amnioreduction. Severe neurological abnormalities of between 18–26% have reportedly been associated with TTTS treated with amnioreduction (De Lia et al., 1990; De Lia et al., 1995; Hecher et al., 1999). The hypothesis is that the neurological abnormalities can be attributed to a decrease in cerebral perfusion and ischemic brain injury. In the report of the International Twin–twin Transfusion Syndrome Registry, abnormal neonatal cranial ultrasound findings were reported in up to 25% of the survivors. It is not clear from the report if these neurological findings are caused by amnioreduction or as an expected consequence of the disease process or of preterm delivery. The incidence of periventricular leucomalacia in this report (Mari et al., 2001) was 5%, which was lower than the 11% reported by the Australian and New Zealand Twin–Twin Transfusion Registry (Dickinson & Evans, 1999). The long-term neurological outcomes of the survivors in the International Registry are not yet available. The incidence of cerebral palsy on long-term follow up in a series involving 33 pregnancies was 4.7% (Mari et al., 2000). Larger studies are therefore needed to confirm any association between TTTS treated by amnioreduction and neurological abnormalities, although information from randomized control trials would be most helpful.

Laser Photocoagulation

In 1990, De Lia et al. performed the first treatment of TTTS using fetoscopic laser to ablate the vascular communications in the placenta. Table 2 lists the studies on the use of laser ablation for TTTS. The survival rates have been consistently between 53 and 69%. Interestingly, these studies report a lower incidence of neurological abnormalities (4–6%) for laser photocoagulation compared with amnioreduction.

The early reports on the use of laser photocoagulation for TTTS involved ablation of all vessels visualized around the inter-twin membrane junction. This has been termed "non-selective" laser ablation. Barjoria et al. (1995) have shown that there are numerous deep anastomosis that may be missed using non-selective laser ablation.

Hecher et al. (1999) recently described a technique of "selective" photocoagulation. This involves photocoagulation of only unmatched (artery not associated with a vein and vice-versa) vessels traced to the donor twin (Quintero et al., 2000). This definition of "selective" photocoagulation is not yet universally accepted (De Lia et al., 2000). The purported advantage of this technique is that it identifies the deep communications thought to be more significant in the pathophysiology of TTTS. Quintero et al. (2000, 2001) have reported survival rates of 80–83% using selective laser compared with 61% in the non-selective laser group.

The disadvantages of fetoscopic laser ablation includes being more invasive than amnioreduction with possible need for general anesthesia, preterm premature rupture of membranes, need for greater operator skill, and case reports of intestinal complications including ileal atresia in the recipient twins following laser treatment (Arul et al., 2001).

Umbilical Cord Ligation

Umbilical cord ligation has been used as a management of complications of monochorionic pregnancies including severe TTTS (Deprest et al., 2000; Nicolini et al., 2001;

Table 2

Reports of Laser Photocoagulation as a Treatment for TTTS

Reference	No. of patient	Selective(S) or Non-selective (NS)	Duration of pregnancy prolongation (weeks)	Perinatal survival
De Lia et al. (1995)	26	NS	11.7	53%
Ville et al. (1995)	45	NS	14	53%
Ville et al. (1998)	132	NS	?	55%
De Lia et al. (1998)	67	NS	9.9	69%
Hecher et al. (1999)	73	NS	12.9	61%
Hecher et al. (2000)	127	S	13	68%
Thilaganathan et al. (2000)	10	S	12.5	55%
Quintero et al. (2000)	18	NS	9.6	50%
	74	S	11.7	61%
Total	572			58% (mean)

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Quintero et al., 1996). The aim of such treatments is to achieve selective feticide of the twin with the most severe complication such as hydrops or severe growth restriction. This is also a new technique with the reports limited to few cases only. It could be associated with severe complications and mortality (Nicolini et al., 2001). Its use is therefore also limited.

Intertwin Membrane Microseptostomy

Intentional amniotomy of the inter-twin membranes was first described by Saade et al. (1995) with the aim of resolving the oligohydramnios in the "stuck" twin. It also reduces the polyhydramnios in the recipient twin, thereby preventing preterm labor. We had previously reported on the risk of cord entanglement from creating an iatrogenic monoamniotic sac (Feldman et al., 1998). In an attempt to prevent this complication, the technique of microseptostomy has been described. The technique involves creating a single amniotomy puncture with a 20 or 22 gauge needle and allowing fluid to drain from the polyhydramnios sac to that of the "stuck" twin (Cook & O'Shaugnessy, 1997; Saade et al., 1998). The survival rate from the procedure was reported in a small series involving 12 patients to be 83% (Saade et al., 1998). Johnson et al. (2001) compared 7 patients treated by microseptostomy with 7 treated by serial amnioreduction. They reported a survival rate for twin pairs of 67%, which was comparable to that of twins treated with amnioreduction. More experience with this technique and data on neurologic outcome is needed before its recommendation as a treatment for TTTS.

Future Interventional Studies of Treatment of TTTS

The difficulty in evaluating the different treatment methods for TTTS is obvious from the above review. Adequate studies comparing the various treatment methods are lacking. The recent review of the Cochrane Database failed to identify any adequate randomized study to influence practice of treatment of TTTS (Roberts et al., 2001). The selection criteria searched for studies of amnioreduction versus laser coagulation, septostomy versus laser coagulation or septostomy versus amnioreduction. In a recent meta-analysis published in this Journal, Skupski et al. (2002) showed no difference in the diagnosis-to-delivery interval or survival rates for any treatment modality for TTTS compared with expectant management. They admitted that a small sample size of the available studies might be responsible for their conclusion. There is therefore an urgent need for randomized studies comparing the various treatment methods. The ideal sample size will be based on an assumption of superiority of one treatment modality over another. For example, a review of Tables 1 and 2 show an overall survival of about 55% for both amnioreduction and laser photocoagulation. If we assume a 25% superiority of amnioreduction over laser (based on the studies of Pinette et al. (1993) and Dennis et al. (1997) with 80–82% survival after amnioreduction) you will require a sample size of 150, seventy-five in each arm (for a significance level of 0.02 and a power of 0.8). We agree with Machin (2002) that randomized trials may not be ethical without a prior therapeutic or diagnostic amniocentesis. Our center is participating in one of such ongoing multi-center study comparing aggressive amnioreduction to selective laser photocoagulation and other similar studies are ongoing. The outcomes of these studies are highly needed. To avoid the difficulties of interpretation seen in previous reports, the following guidelines may be helpful for future studies.

1. Standardization of entry criteria. The diagnosis of TTTS needs to be more consistent. Although not universally accepted, the staging system by Quintero et al. (1999) could be used as an objective means of describing the severity of cases at the time of enrollment.
2. Interventions used need to be well documented and comparable to other studies. The definition of aggressive amniocentesis needs to be standardized possibly using the post-procedure single largest pocket of amniotic fluid, and the amount of amniotic fluid removed at the time of laser coagulation should be documented.
3. The studies should aim to improve our understanding of the pathophysiology of TTTS. This could involve evaluating these pregnancies with fetal echocardiography and Doppler velocimetry (Fesslova et al., 1998; Hecher et al., 1995) and if feasible routine evaluation of the role of placental vaso-active peptides (Bajoria et al., 2002) in the etiology of TTTS.
4. Ascertainment of outcomes should be performed in a multi-disciplinary approach. In previous studies survival have been limited to the perinatal period. Future studies should evaluate survival rates well outside the perinatal period as Mari et al. (2001) have demonstrated a fall in survival rates within the first 4 weeks of life, possibly secondary to complications of TTTS. Likewise, long-term outcomes with special emphasis on neurological and cardiac outcomes need to be documented. This would involve performing postnatal neurological ultrasounds, MRI and neonatal echocardiograms, and long-term neuro-developmental assessment between 1–2 years of age. While some of the previous studies on intervention for TTTS have attempted to document some of the above features, the data have been missing in the majority.
5. Finally, the diagnosis of TTTS needs to be confirmed by postnatal histopathological evaluation. This evaluation will include injection studies to confirm vascular anastomoses, assessment of placental weights, cord insertion, and number of layers in the dividing membranes. Detailed histological evaluation of the placenta to document number and types of anastomoses may increase our knowledge of the pathophysiology of TTTS.

We are aware that some of the above goals may be difficult to achieve, but the potential of producing studies that can guide future management would make the effort worthwhile and commendable. In our ongoing multi-center trial the above principles are incorporated in the protocol and the details will be published in the future.

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