Published in final edited form as:
Am J Obstet Gynecol. 2007 October ; 197(4): 396.e1–396.e9. doi:10.1016/j.ajog.2007.07.020.

A prospective randomized multicenter trial of amnioreduction versus selective fetoscopic laser photocoagulation for the treatment of severe twin–twin transfusion syndrome

Timothy M. Crombleholme, MD, **David Shera, ScD**, **Hanmin Lee, MD**, **Mark Johnson, MD**, **Mary D'Alton, MD**, **Flint Porter, MD**, **Jacquelyn Chyu, MD**, **Richard Silver, MD**, **Alfred Abuhamad, MD**, **George Saade, MD**, **Laurence Shields, MD**, **David Kauffman, MD**, **Joanne Stone, MD**, **Craig T. Albanese, MD**, **Ray Bahado-Singh, MD**, **Robert H. Ball, MD**, **Larissa Bilaniuk, MD**, **Beverly Coleman, MD**, **Diana Farmer, MD**, **Vickie Feldstein, MD**, **Michael R. Harrison, MD**, **Holly Hedrick, MD**, **Jeffrey Livingston, MD**, **Robert P. Lorenz, MD**, **David A. Miller, MD**, **Mary E. Norton, MD**, **William J. Polzin, MD**, **Julian N. Robinson, MD**, **Jack Rychik, MD**, **Per L. Sandberg, MD**, **Istvan Seri, MD**, **Erin Simon, MD**, **Lynn L. Simpson, MD**, **Larisa Yedigarova, MD**, **R. Douglas Wilson, MD**, and **Bruce Young, MD**

From the Fetal Care Center of Cincinnati (Cincinnati Children's Hospital Medical Center, Good Samaritan Hospital, University Hospital and the University of Cincinnati College of Medicine), Cincinnati, OH (Drs Crombleholme, Bahado-Singh, Livingston, and Polzin); Children's Hospital of Philadelphia, Philadelphia, PA (Drs Shera, Johnson, Bilaniuk, Hedrick, Rychik, Seri, Simon, and Wilson); University of California–San Francisco, San Francisco, CA (Drs Lee, Albanese, Farmer, Feldstein, Harrison, Norton, and Sandberg); Columbia–Presbyterian Medical Center, New York, NY (Drs D'Alton, Robinson, and Simpson); University of Utah Hospital, Salt Lake City, UT (Drs Porter and Ball); University of Colorado Health Sciences Center, Denver, CO (Dr Chyu); Evanston Northwestern Healthcare, IL (Dr Silver); Eastern Virginia Medical School, Norfolk, VA (Dr Abuhamad); University of Texas Medical Branch, Galveston, TX (Dr Saade); University of Washington Medical Center, Seattle, WA (Dr Shields); Magee–Women's Hospital, Pittsburgh, PA (Dr Kauffman); Mount Sinai Medical Center, New York, NY (Dr Stone); Hospital of the University of Pennsylvania, Philadelphia, PA (Dr Coleman); William Beaumont Hospital, Royal Oak, MI (Dr Lorenz); Queen of Angels–Hollywood Presbyterian Medical Center, Los Angeles, CA (Drs Miller and Yedigarova); and New York University School of Medicine, New York, NY (Dr Young).

Abstract

Objective—To examine the effect of selective fetoscopic laser photocoagulation (SFLP) versus serial amnioreduction (AR) on perinatal mortality in severe twin-twin transfusion syndrome (TTTS).

Study Design—5-year multicenter prospective randomized controlled trial. The primary outcome variable was 30-day postnatal survival of donors and recipients.

Results—There is no statistically significant difference in 30-day postnatal survival between SFLP or AR treatment for donors at 55% (11/20) vs 55% (11/20) (p=1, OR=1, 95%CI=0.242 to 4.14) or

Person Responsible for Correspondence and Reprint Requests: Timothy M. Crombleholme, MD, The Fetal Care Center of Cincinnati, Division of Pediatric General, Thoracic, and Fetal Surgery, Cincinnati Children's Hospital, MLC #2023, 3333 Burnet Avenue Cincinnati, OH 45229, Timothy.Crombleholme@cchmc.org, Phone: 513.636.9608, Fax: 513-363-5959.

Presented at the 27th Annual Clinical Meeting of the Society for Maternal–Fetal Medicine, San Francisco, CA, Feb. 5-10, 2007.

recipients at 30% (6/20) vs 45% (9/20) (p=0.51, OR=1.88, 95%CI=0.44 to 8.64). There is no difference in 30-day survival of one or both twins on a per pregnancy basis between AR at 75% (15/20) and SFLP at 65% (13/20) (p=0.73, OR=1.62, 95%CI=0.34 to 8.09). Overall survival (newborns divided by the number of fetuses treated) is not statistically significant for AR at 60% (24/40) vs SFLP 45% (18/40) (p=0.18, OR=2.01, 95%CI=0.76 to 5.44). There is a statistically significant increase in fetal recipient mortality in the SFLP arm at 70% (14/20) versus the AR arm at 35% (7/20) (p=0.25, OR=5.31, 95%CI=1.19 to 27.6). This is offset by increased recipient neonatal mortality of 30% (6/20) in the AR arm. Echocardiographic abnormality in recipient twin Cardiovascular Profile Score is the most significant predictor of recipient mortality (p=0.055, OR=3.025/point) by logistic regression analysis.

Conclusions—The outcome of the trial does not conclusively determine whether AR or SFLP is a superior treatment modality. TTTS cardiomyopathy appears to be an important factor in recipient survival in TTTS.

Keywords

twin-twin transfusion syndrome; amnioreduction; selective fetoscopic laser photocoagulation

Introduction

Twin-twin transfusion syndrome (TTTS) is the single most common serious complication of monochorionic twin gestations accounting for 10 to 17% of all perinatal mortality[1,2]. The natural history of untreated TTTS is well established with mortality rates up to 90%[1,3,4]. The incidence of this serious complication has been increasing in parallel with the increasing incidence of multiple gestations[5].

Numerous treatment options for TTTS have been reported, including amnioreduction (AR)[6–12], intertwin septostomy[13–16], non-selective fetoscopic laser[17–20] selective fetoscopic laser photocoagulation (SFLP)[21–28], and cord coagulation[29–32], all of which have improved survival rates compared to the untreated natural history of TTTS. It has been controversial which of these treatment options would provide the best outcome in specific cases of TTTS. AR has been associated with an average survival of 50%[33], with large international registries reporting 60 to 65% survival[34,35]. Saade et al. suggested the reason AR works is because it inadvertently creates an intertwin septostomy[36]. This inadvertent septostomy has been suggested to account for the "single amnioreduction paradox" in which TTTS appears to stop in up to 20% of patients after only a single AR[36]. Consistent with this view, a prospective randomized trial comparing AR to septostomy found the same 65% survival in each arm of the study[16]. The problem with septostomy has been the risk of creating a mono-amniotic gestation and the attendant risk of cord entanglement with double fetal demise[37]. Cord coagulation, either by fetoscopic bipolar cautery or radiofrequency ablation, at best can only achieve a 50% survival and is unacceptable to many parents as it necessitates the sacrifice of one fetus.

Fetoscopic laser photocoagulation for TTTS was first described by De Lia et al., as a means of functionally converting a monochorionic placenta to a dichorionic one by occluding vascular connections between the twins normally present in monochorionic placentas[17,18]. While these vascular connections are not the cause of TTTS, they are a necessary prerequisite for the syndrome. This technique as originally described, and still in use in some centers, is non-selective in nature, meaning all vessels found to cross the intertwin membrane were photocoagulated[17,18]. Survival with this approach is reported to be 53 to 56%[17–18], comparable to survival rates observed with AR. An intriguing finding which stimulated interest in this approach was the observation that newborn survivors treated by fetoscopic laser appeared to have a lower incidence of head ultrasound or MRI abnormalities (5–7% vs. 14–25%)[5,17–20].

Subsequently, Quintero et al., recognizing there is no anatomic relationship between the position of the intertwin membrane and the vascular equator, described a selective technique of fetoscopic laser photocoagulation in which only vessels demonstrated to be communicating between the two twins are treated[21]. This selective fetoscopic laser technique is thought to preserve non-communicating vessels and has been associated with survival rates of 62 to 77% [21–28].

In order to eliminate the up to 20% of patients with TTTS that may respond to a single AR, the so-called single "amnioreduction paradox", and to compare the impact on 30-day neonatal survival in patients at the most severe end of the spectrum of TTTS, we conducted a prospective randomized clinical trial on subjects with TTTS presenting prior to 22 weeks' gestation, stages II, III or IV, who failed to respond to AR, and randomized either to SFLP or serial AR.

Materials and Methods

Study Design

This trial was a 5-year multicenter prospective randomized controlled trial to examine the effect of SFLP compared to serial AR on perinatal mortality in severe twin-twin transfusion syndrome. Patients meeting entry criteria (see Table 1) and consenting to enter the trial were randomized to one of the two treatment arms with equal likelihood.

Primary and Secondary Outcomes

The primary outcome variable to be assessed in this trial comparing AR to SFLP is the 30-day neonatal survival of donors and recipients. In addition, secondary outcome variables to be assessed include the number of pregnancies in each arm with one or more twins surviving; and the overall survival to 30 days (total number of twins surviving to 30 days divided by the total number of fetuses treated).

Demographics

Subjects were pregnant women 18 years or older, diagnosed with TTTS at less than 22 weeks' gestation, and randomized and treated prior to 24 weeks' gestation. The subjects must have had no contraindication to general anesthesia or abdominal surgery, history of preterm labor, or uterine anomalies (see Table 1).

Sample Size Considerations

Subjects were assigned to AR or SFLP with equal probability (1:1 odds). The plan consisted of three interim analyses at accrual of 1/4, 2/4, and 3/4 of the planned sample size. The criteria for stopping were based on the O'Brien-Fleming stopping rules[38]. The primary null hypothesis to be tested was that the survival rates of donor/recipient twins at 30 days after birth and no treatment failure are the same between the two treatment groups. With a two-sided Type I error of 0.025 for each of the two primary outcomes and a power of 0.80, it would take 146 patients to detect an increase from a 50% survival rate with AR to a 75% survival rate with SFLP. These estimates were based on pooled reports of overall survival to delivery from published series of patients treated by AR or SFLP[5,12,17–28].

Study Procedures

Pre Screening Criteria—Prior to randomization, each subject underwent a diagnostic evaluation which included ultrasound to confirm monochorionic diamniotic gestation with like sex twins, single placental mass, and a thin intertwin membrane. In addition, there had to be a "stuck" donor twin defined as a twin with a deepest vertical pocket of ≤ 2 cm and a recipient co-twin with polyhydramnios defined with a deepest vertical pocket of > 8 cm, with or without

Doppler or echocardiographic changes, and presenting prior to 22 weeks' gestation. The empty bladder in the donor twin should not be seen to fill during the ultrasound examination (Quintero stage II) unless there are Doppler velocimetry changes in umbilical artery, umbilical vein, or ductus venosus waveforms (Quintero Stage III). In addition, structural anomalies and CNS abnormalities were specifically excluded. A transvaginal ultrasound was performed after the qualifying AR to exclude foreshortened cervix and length < 2.0 cm excluded the mother from the trial. To ensure uniformity, determination of projected gestational age was based on the method used by the NICHD-sponsored Maternal Fetal Medicine Units Network[39].

A single diagnostic and therapeutic qualifying amniocentesis was performed on the polyhydramniotic sac with sufficient fluid removed to reduce the deepest vertical pocket to < 5 cm. This initial qualifying AR was performed by a participating investigator per a standard protocol. A follow-up ultrasound was performed within one hour of the procedure to detect evidence of inadvertent microseptostomy which, if detected, excluded the patient from eligibility for randomization.

Final Screening—If the follow-up ultrasound obtained 12 to 24 hours after the qualifying amniocentesis visualized a decompressed bladder in the donor twin which is not seen to fill during the examination and a deepest vertical pocket of < 2 cm in the donor sac, the subject was considered a candidate for entry into the trial and offered randomization. If the donor deepest vertical pocket was > 2 cm or the bladder was not decompressed and/or seen to fill during the follow-up ultrasound examination 12 to 24 hours later, the subject was considered a responder and not a candidate for randomization (see Table 1).

Pre-Treatment Studies—Prior to initiation of treatment, baseline studies including ultrasound, fetal echocardiogram, and MRI were obtained and recorded on blinded tapes/films and sent to the Data Coordinating Center (DCC). In the SFLP arm, maternal screening for anesthesia by an anesthesiologist and pre-operative CXR, EKG, and CBC were obtained. An ultrasound and echocardiogram were obtained on each fetus at least weekly. Each of these surveillance tests had a checklist of data to be obtained with the examination.

Randomization Plan—Randomization was centralized via faxed case report forms and stratified by cluster and gestational age group. AR was performed at the local clinic. SFLP subjects were sent to either Cincinnati, CHOP, or UCSF based on geographical location.

Selective Fetoscopic Laser Photocoagulation (SFLP)—Mothers randomized to the SFLP arm of the study underwent the procedure under epidural anesthesia and intravenous sedation for comfort. Although most of the procedures could be performed by a single percutaneous port, some cases with an anterior placenta required a mini-laparotomy to expose the surface of the uterus. A 4 mm incision was made in the skin to allow ultrasound-guided placement of a 3.3 mm 3-port fetoscope that has a lens port as well as two working ports; one for the 600μ laser endostat and the other for the Level I for rapid infusion of physiologic saline, if needed, to clear the amniotic cavity. The chorionic plate of the placenta was mapped three times: 1) trace every vessel that leaves the placental cord insertion of the recipient twin to its termination in a cotyledon or in an anastomosis to a vessel crossing to the donor twin's umbilical cord insertion, 2) intraoperatively mark and record location of all connecting vessels for subsequent photocoagulation, and 3) verify that no connecting vessels were missed. All procedures were digitally recorded and a permanent record of vascular anatomy was made for each procedure. All recorded SFLP procedures were independently externally reviewed to ensure quality control. The vessels were photocoagulated using 60 watts power with the endostat positioned at 1 cm from the surface of the vessel. The amniotic fluid volume was reduced such that the deepest vertical pocket was < 5 cm. Antibiotics were instilled into the amniotic cavity prior to trocar removal.

During a 9-month period, the trial was placed on pause when the principal investigator moved from Philadelphia to Cincinnati. During this pause, the NIH and DSMB requested that we incorporate the use of the new Storz remote head fetoscope into the trial as standard equipment at all 3 laser centers. This required IRB approval at all centers because this device at the time was not FDA approved. Up to that time, all three centers were using the Storz 3-3 mm fetoscope with standard head for camera attachments.

Aggressive Amnioreduction (AR)—Mothers who were randomized to the aggressive serial AR arm of the study underwent ultrasound examination on a Monday, Wednesday, Friday schedule. AR was performed whenever the recipient twin sac deepest vertical pocket was ≥ 8.0 cm. The volume of fluid removed during these procedures was sufficient to reduce the deepest vertical pocket to ≤ 5 cm. The AR procedure was standardized by protocol to require use of a 20-gauge needle and vacuum suction bottle. The patient was assessed for an inadvertent microseptostomy by checking the deepest vertical pocket around the donor within 1 hour of the procedure. All fetuses delivered as clinically indicated.

Definition of Treatment Failure—A failure of therapy was defined as the progression of non-immune hydrops or cardiac failure with imminent fetal demise despite therapy in one of the two treatment arms. A fetus would have to meet at least two of the four following criteria in order to meet the definition of cardiac failure despite therapy: 1) development or progression of severe AV valve (mitral or tricuspid) regurgitation, 2) reversal of diastolic flow in the ductus venosus, 3) reversal of diastolic flow in the umbilical artery of the recipient twin, or 4) development or progression of severe biventricular dysfunction. In the event that a subject from either arm of the study was declared a treatment failure, she was offered the treatment of her choice outside the trial. Being declared a treatment failure was treated statistically as equivalent to a death for the purposes of proving endpoint analysis.

Statistical Considerations

Interim Analysis and Early Trial Closure—The Data Safety and Monitoring Board (DSMB) reviewed the trial for efficacy for the primary outcome at the interim analyses performed after 38 randomized patients were evaluable. Adverse events and the primary outcome of perinatal mortality were the only outcome variables considered when deciding to close the trial.

Primary Analysis—The primary outcome variables, survival of the donor and recipient twins at 30 days after birth, were analyzed using a logistic regression model with treatment (AR, SFLP) as one of a list of predictor covariates. Other covariates included gestational age at diagnosis, Quintero stage (II, III, or IV), marital status, cohort, transportation for SFLP, and an echocardiographic score based on the Cardiovascular Profile Score (CVPS) described by Huhta[42]. Adjustments for pairing and clustering, as is done in studies of paired organs such as eyes and kidneys, were unnecessary because the donor and recipient results were analyzed separately.

The primary null hypothesis to be tested is that there is no difference in success rates between pregnancies randomized to AR or SFLP treatment. The primary alternative hypothesis is that SFLP is superior to serial AR. For power analysis we assumed values of 50% success rate with AR and a 75% success rate with SFLP, a difference considered significant in a clinical sense.

Results

The study was stopped early, after 42 subjects were randomized, at the request of the investigators. Referring physicians were increasingly unwilling to refer eligible subjects for

evaluation to participating centers in which SFLP was only available through randomization in the trial. At the same time that the investigators' meeting was held to decide to stop the trial, the Trial Oversight Committee, charged with evaluating all adverse events and serious adverse events, detected a statistical trend in adverse outcome affecting the recipient twin in one treatment arm. The Trial Oversight Committee was blinded to the treatment received in each arm. A recommendation was made to the DSMB that the trial be stopped to allow biostatistical analysis of this adverse trend. The DSMB concurred with the decision to stop the trial.

Enrollment

196 cases (where each case consisted of three individuals; mother, donor, and recipient) were screened a total of 251 times or an average of 1.28 screens per case (see Figure 1). Patients in early stages of TTTS were often screened on more than one occasion until they either met criteria or were ineligible. Of the 196 cases, 58 (29.6%) were deemed eligible by meeting all inclusion criteria (54 cases) or passing via protocol deviation [4 cases had a visible bladder (stage I) but had Doppler changes upstaging them to stage III]. Twelve patients refused a qualifying AR. Of the 46 patients who consented to an AR, only 4/46 (8.7%) were ineligible because of a positive therapeutic response to the AR. Of the 4, 2 had evidence of amniotic fluid around the donor within 1 hour of the AR, consistent with septostomy. Of the 58 cases eligible, 43 (21.9% of screened, 74.1% of eligible) consented to enrollment. Only 42 cases (21.4% of screened) actually got randomized to a treatment arm. One patient dropped out of each arm leaving 20 in the AR arm and 20 in the SFLP arm. Primary analyses were based on an Intent-to-Treat principle where the case is assigned to the treatment strategy whether or not it actually received the treatment.

There is no statistically significant difference in stage distribution between AR and SFLP arms using the Quintero staging system (see Figure 2). The mean gestational age at delivery is 30 and 4.7/7 weeks for patients treated by SFLP and 30 and 2/7 weeks for AR. These differences are not statistically significant. Excluding loss due to PPROM within 7 days of procedure, the mean gestational age at delivery is 32 and 3.8/7 weeks for patients in the SFLP arm and 31 and 2/7 weeks for patients in the AR arm. These differences are not statistically significant.

Primary Outcome by Treatment

There is no significant difference in the primary outcome of 30-day postnatal survival between SFLP or AR treatment for donors in the AR arm (55%, 11/20) versus the SFLP arm (55%, 11/20) (p=1, OR=1.00, 95%CI=0.24 to 4.14) or recipients in the AR arm (45%, 9/20) versus the SFLP arm (30%, 6/20) (p=0.51, OR=1.88, 95%CI=0.44 to 8.64) (see Figure 3). There is no significant difference in 30-day survival of one or both twins on a per pregnancy basis between AR 75% (15/20) and SFLP 65% (13/20) (p=0.73, OR=1.62, 95%CI=0.34 to 8.09) (see Figure 4). There is no significant difference in overall 30-day survival (newborns divided by fetuses treated) between AR and SFLP at 60% (24/40) vs. 45% (18/40) (p=0.18, OR=2.01, 95%CI=0.76 to 5.44) (see Figure 5). There is a statistically significant increase in fetal mortality among recipient twins treated by SFLP 70% (14/20) versus AR 35% (7/20) (p=0.03, OR=5.31, 95%CI=1.19 to 27.6) (see Figure 6). Within stages III and IV there is a significant difference in 30-day survival for AR of 67% versus SFLP of 12.5% (p,0.03, OR=14.21) (see Figure 7). There are more treatment failures in the AR treatment arm (7) versus the SFLP arm (0) (p=0.0083, OR=Infinity), resulting in no significant overall differences between the treatment arms at 30 days (see Figure 5). In 7 of 7 AR cases meeting criteria for treatment failure, it was due to recipient findings of hydrops (4/7) or development or progression of severe AV valve regurgitation and development or progression of severe biventricular dysfunction despite AR treatment (3/7). Neonatal death occurred in 6 of the 7 recipients in the AR arm meeting criteria for treatment failure and offsetting the increased fetal recipient mortality in the SFLP arm.

Efficacy Adjusted for Covariates

A straightforward logistic regression of recipient success based on treatment, after adjusting for all other covariates of interest [stage, marital status, echocardiographic score, long-distance transportation, gestational age, and cohort (pre/post-pause for equipment changes)], shows a non-significant difference between SFLP and AR in the full model, but with SFLP having a worse outcome which is lost during backward variable selection. For donors there are only negligible differences between treatment arms in the full model which is also lost during backward variable selection.

The most predictive models for recipients used only their echocardiographic score (OR=3.025/point, p=0.0552). The score was based on the 10-point Cardiovascular Prognostic Score (CVPS) described by Huhta[42] using as many parameters as possible with the measures and observations available from ultrasound and echocardiograms. Missing values were replaced with means in computing the score. For donors, the most predictive models were stage (OR=0.446/stage, p=0.1249) and gestational age (OR=1.052/day, p=0.0987). In addition, fitting models including each covariate alone with treatment in the predictor list had similar results.

Additional Approaches

Several alternative analysis approaches were explored because of the small sample size and to further examine the roles of the covariates. The use of alternative analysis methods also helped to show if results are robust to variations in approach. With *conditional* logistic regression, the results show that echocardiographic score is a useful predictor for recipients (OR=2.84, p=0.0576) in the same direction as before. No other covariates or treatment are significant using this approach. We also created new treatment categorizations to more accurately reflect the AR cases which experienced treatment failure and went on to receive other treatments. Similarly, we examined different definitions of outcome such as survival to thirty days ignoring treatment failure. One situation has strong and interesting results: when the outcome is survival to birth, the recipient twins are under a significant disadvantage under SFLP (OR=0.124, p=0.0084) along with a slight negative effect for later gestational age (OR=0.95, p=0.1428). The reason that it does not show up in the primary analysis is that recipient twins under AR tend to make up for the difference with treatment failures instead. Analyses using variations on the intent-to-treat principle such as only including subjects who actually received the assigned treatment or by treatment actually received are comparable.

Finally, one question that cannot be adequately addressed by the analyses above is the influence the status of the co-twin has on the outcome. A time-to-event, proportional hazards (a.k.a. Cox) model was fit to the data with time-varying covariates, one of them being the status of the co-twin. The hypothesis is that the demise of the co-twin might reduce the competition and improve the chances of success. As it turns out, however, treatment failure or death of the co-twin means a poorer prognosis for the twin (Hazard Ratio = 32.6 for recipients and 12.88 for donors, p = 0.0001 and 0.0003, respectively). This result argues against the removal of competition and rather towards a sharing of predicament. In other words, if the co-twin is in trouble, both are in trouble.

Safety Analyses

In this study, adverse events and serious adverse events were common and often closely related to the primary outcome which is death and/or treatment failure. Every adverse event whether serious or not, related or not, anticipated or not, was reported to the Trial Oversight Committee and the IRBs. Due to the broad definition of adverse events these were frequent in both arms of the study. There were no maternal deaths and no serious maternal adverse events related to

the operative procedure, even in the 7 cases in which a minilaparotomy was used to expose the surface of the uterus.

No patient in the study had a chorioamniotic separation as a result of the qualifying AR. In one case there was uterine bleeding occurring during an SFLP procedure (4.7%) which did not require maternal transfusion but did compromise visualization and necessitated the procedure being stopped. There was a single case of spinal headache (2.3%) resulting from placement of an epidural catheter which responded to blood patch. Maternal hospitalization at any time during the remainder of the pregnancy required for preterm labor, short cervix, preterm premature rupture of membranes (PPROM), or to monitor for fetal growth occurred in 9.5% of cases in both the AR and SFLP arms of the study. The specific incidence of PPROM occurring prior to 28 weeks' gestation was 0% in the AR arm and 4.8% in the SFLP arm. The incidence of preterm labor requiring tocolysis was 4.8% in the AR arm and 0 in the SFLP arm. The incidence of delivery prior to 28 weeks' gestation was 4.8% (n=1) in the AR arm and 9.5% (n=2) in the SFLP arm. These differences are not statistically significant.

Comments

The results of this trial show no statistically significant difference in overall neonatal survival to 30 days of life or neonatal survival of one or both twins in the same pregnancy in cases of severe TTTS treated by either AR or SFLP. Despite these overall results, there is a statistically significantly worse fetal survival observed among recipient twins in pregnancies treated by SFLP compared to those treated by AR. This apparent conundrum can be accounted for by recipient fetal losses in the SFLP arm being offset by an increase in treatment failures among recipient subjects in the AR arm. These results suggest that, in these highly selected cases of severe TTTS, neither treatment is superior to the other. Once TTTS reaches this severity, the mortality among recipients will be considerable, but the losses may occur at different times depending on treatment. The impact of TTTS severity on fetal survival is further supported by the significantly worse fetal survival among recipient twins in stages III and IV compared to stage II. One of the strongest predictors of recipient demise is echocardiographic evidence of TTTS cardiomyopathy. The losses of fetal recipients treated by SFLP usually occur within 24 hours of the procedure. In contrast, the recipients treated by AR are not lost following the procedure, but there is progressive TTTS cardiomyopathy as reflected by more recipients in the AR arm meeting criteria to be declared treatment failures. In every case, it was due to findings in the recipient twin which met criteria for treatment failure. Taken together these data suggest a disproportionate impact of TTTS cardiomyopathy on recipient survival in advanced stages of TTTS no matter what treatment they receive.

The Quintero staging system was found to be an independent predictor of outcome among recipient twins with worse survival in recipients in stages III and IV compared to stage II. This was found to be the case despite the Quintero staging system being heavily weighted toward the impact of TTTS on the donor. Stage II is based on absence of visualization of urine in the bladder in the donor. In stage III, the most commonly observed abnormality in critical Doppler waveforms is absent end diastolic flow in the umbilical artery of the donor twin. Other critical Doppler changes which occur in the recipient twin in TTTS such as the loss or reversal of the a wave in the ductus venosus, pulsatile umbilical vein, and absent or reversed diastolic flow in the recipient twin's umbilical artery are late changes only observed in more advanced cases of TTTS. Similarly hydrops, required for stage IV, is usually seen in the recipient twin which was the case in each of our stage IV subjects. TTTS cardiomyopathy, which specifically affects the recipient twin, appears to be one of the most important contributing factors in recipient mortality in advanced cases of TTTS. The results of this trial suggest that in advanced cases of TTTS, the recipient survival may be compromised no matter what treatment the patient receives. Consistent with these findings in the trial, Shah et al. recently reported the use of the

cardiovascular prognostic score (CVPS) as an indicator of the severity of TTTS cardiomyopathy demonstrating a negative impact on recipient survival[41].

Despite differences in patient selection (22 vs 26 weeks' gestation) and response to qualifying AR versus primary therapy, the NIH-sponsored trial has comparable overall survival of one or both twins to those reported in the Eurofoetus trial[20]. The survival with AR is significantly better in the NIH trial (60%) than in the Eurofoetus trial (41%) and consistent with single institution series[6–12], a prospective randomized trial[15,16], and registries (60–65%)[34,35]. This may be due to the standardized aggressive protocol used for serial AR in the NIH trial. Conversely, the survival in the NIH trial for SFLP-treated TTTS is significantly less than reported previously using this technique both in single institution series as well as in the Eurofoetus trial[19–28]. One possible explanation for the poorer survival observed in the SFLP arm could be a lack of proficiency of the surgeons performing the SFLP in the three laser centers in the trial. However, every SFLP procedure was recorded and independently reviewed by fetal surgeons not participating in the trial with significant experience with the SFLP technique. This review independently confirmed the adequacy of the procedures. Minor differences in technique were identified among the laser centers in which one center frequently used a mini-laparotomy to access the uterus while the other two centers used an entirely percutaneous approach. The placental mapping and the SFLP technique used were the same in all three centers. The results in these centers with SFLP, before and after the NIH trial, support the view that problems with technical proficiency do not account for differential fetal survival of recipients observed in this trial[40]. The more likely explanation, as noted above, is the severity of TTTS cardiomyopathy.

The outcome of this trial does not conclusively answer the question of which treatment, AR or SFLP, is the superior treatment modality. The results do suggest, however, that no matter which treatment is employed, survival is likely to be compromised if treatment is initiated later in the disease progression, particularly among recipients. TTTS cardiomyopathy appears to be an important factor in recipient survival in TTTS. The Cincinnati modification of the Quintero staging system to incorporate echocardiographic changes into stage III, as suggested by Harkness et al., may be useful to more appropriately stratify recipient risk[40]. Comparisons between this trial and the Eurofoetus trial must be drawn cautiously given the significant differences in the subjects that were treated in each.

Additional trials in TTTS are needed to define the best treatment for a given case of TTTS. It is unfortunate that the state of community equipoise which resulted in a decline of subjects screened for this trial may also prevent randomized trials in TTTS in the future. An alternative strategy may be rigorously designed and controlled prospective cohort studies. The impact of TTTS on neuroimaging, echocardiographic assessment, and long-term neurodevelopmental outcome of the subjects in this trial awaits analysis of the follow-up assessments of survivors.

Acknowledgments

This work was supported by a grant from the National Institute of Child Health and Human Development R01 HD41149 (T. M. C.). Statistical work was partially supported by NICHD MRDDRC at CHOP, 3P30 HD26979-04S2 (D. S.).

The authors gratefully acknowledge the expert technical assistance of the following:

Victoria **Shokrollah**, MT, Trial Coordinator, The Children's Hospital of Philadelphia

Roberta **Ballard**, MD, Consultant, The Children's Hospital of Philadelphia

Lori J. **Howell**, RN, MS, Study Coordinator, The Children's Hospital of Philadelphia

Jamie **Koh**, Study Coordinator, The Children's Hospital of Philadelphia

Joy **Macdonald**, RN, Study Coordinator, The Children's Hospital of Philadelphia

Joy N. **Williams**, RN, BSN, Study Coordinator, The Children's Hospital of Philadelphia

Kim **Lyons**, RN, BSN, CCRC, Trial Coordinator, Cincinnati Children's Hospital Medical Center

Jennifer L. **Mason**, RN, BSN, Study Coordinator, Cincinnati Children's Hospital Medical Center

Sabine **Bousleiman**, RN, Study Coordinator, Columbia-Presbyterian Medical Center

Barb **Ross**, Study Coordinator, Eastern Virginia Medical School

Patty **Trail**, Study Coordinator, Eastern Virginia Medical School

Elaine **Haney**, BS, MT, Study Coordinator, Evanston Northwestern Healthcare

Elvira **Kolchinshaky**, RDMS, Study Coordinator, Mount Sinai Medical Center

Robin **Bisgaard**, RN, Study Coordinator, University of California, San Francisco

Jody **Farrell**, RN, Site Coordinator, University of California, San Francisco

Jane **Berg**, Study Coordinator, University of Colorado Health Sciences Center

Jennifer M. **Lee-Rollins**, MS, Study Coordinator, University of Texas Medical Branch

Kristi **Nelson**, RN, Study Coordinator, University of Utah

Lindsey **Hancock-Wolosiewicz**, Study Coordinator, William Beaumont Hospital

With special appreciation to the following groups of individuals (listed alphabetically):

Data Coordinating Center

Tina **Alvarado-Taylor**, Randomization Specialist

Mignon **Davis**, Database Designer

Tracy **DeMeio**, Data Manager

Jeff **Dragone**, Safety Officer

Katherine **Gibbs**, BFA, Database Manager

Julie **Distefano-Pappas**, Data Manager

Kathy **Ma**, Biostatistician

Wendy **Sieferheld**, Biostatistician

Margie **Tartaglione**, Data Manager

Marc **Taylor**, Data Entry, Data

Clare **Weiler**, Clinical Research Director/Monitor

Sanyi **Zhao**, Biostatistician

Data Safety Monitoring Board

Nicholas M. **Fisk**, PhD, Member, Imperial College School of Medicine

John C. **Fletcher**, PhD, 1st Chairman, University of Virginia School of Medicine (deceased)

Kurt **Hecher**, MD, Member, Barmbek Hospital, Hamburg, Germany

James **Goldberg**, MD, 2nd Chairman, Pacific Medical Center, San Francisco, CA

Haywood **Brown**, MD, Duke University

Richard **Martin**, MD, Rainbow Babies and Children's Hospital, Cleveland, OH

Trial Oversight Committee

Vinod **Bhutani**, MD, Chairman, Stanford University School of Medicine

Arnold **Cohen**, MD, Albert Einstein Medical Center

Robert **Levy**, MD, Children's Hospital of Philadelphia

David J. **Margolis**, MD, University of Pennsylvania Medical Center

Kim **Olthoff**, MD, University of Pennsylvania

Donna **Sylvester**, RN, Children's Hospital of Philadelphia

Joseph **Zorc**, MD, Children's Hospital of Philadelphia

Abbreviations

TTTS
: twin-twin transfusion syndrome

AR
: amnioreduction

SFLP
: selective fetoscopic laser photocoagulation

OR
: odds ratio

CI
: confidence interval

PPROM
: preterm premature rupture of membranes

CVPS
: cardiovascular profile score

References

1. Weir PE, Ratten GJ, Beischer NA. Acute polyhydramnios-a complication of monozygous twin pregnancy. Br J Obstet Gynaecol 1979;86:849–53. [PubMed: 389280]
2. Steinberg LH, Hurley VA, Desmedt E, Beischer NA. Acute polyhydramnios in twin pregnancies. Austral NZ J Obstet Gynecol 1990;30:196–200.
3. Cheschier NC, Seeds JW. Polyhydramnios and oligohydramnios in twin gestations. Obstet Gynecol 1988;71:882–4. [PubMed: 3285268]
4. Saunders NJ, Snijders RJ, Nicolaides KH. Twin-twin transfusion syndrome during the 2nd trimester is associated with small intertwin haemoglobin differences. Fetal Diag Ther 1991;6:34–6.
5. Callahan TL, Hall JE, Ettner SL, Christiansen CL, Greene ML, Crowley WF. The economic impact of multiple-gestation pregnancies and the contribution of assisted-reproduction techniques to their incidence. N Engl J Med 1994;331:244–9. [PubMed: 8015572]
6. Moise KJ Jr. Polyhydramnios: problems and treatment. Sem Perinatol 1993;17:197–209.

7. Rodestal A, Thomassen PA. Acute polyhydramnios in twin pregnancy. A retrospective study with special reference to therapeutic amniocentesis. Acta Obstet Gynecol Scand 1990;69:297–300. [PubMed: 2244460]
8. Urig MA, Clewell WH, Elliott JP. Twin-twin transfusion syndrome. Am J Obstet Gynecol 1990;163:1522–6. [PubMed: 2240100]
9. Mahony BS, Petty CN, Nyberg DA, Luthy DA, Hickok DE, Hirsch JH. The "stuck twin" phenomenon: ultrasonographic findings, pregnancy outcome, and management with serial amniocenteses. Am J Obstet Gynecol 1990;163:1513–22. [PubMed: 2240099]
10. Elliott JP, Urig MA, Clewell WH. Aggressive therapeutic amniocentesis for treatment of twin-twin transfusion syndrome. Obstet Gynecol 1991;77:537–40. [PubMed: 2002975]
11. Pinette MG, Pan Y, Pinette SG, Stubblefield PG. Treatment of twin-twin transfusion syndrome. Obstet Gynecol 1993;82:841–6. [PubMed: 8414335]
12. Reisner DP, Mahony BS, Petty CH, Nyberg DA, Porter TF, Zingheim RW, et al. Stuck twin syndrome: outcome in thirty-seven consecutive cases. Am J Obstet Gynecol 1993;169:991–5. [PubMed: 8238162]
13. Saade GR, Olson G, Belfort MA, Moise KJ. Amniotomy: a new approach to the "stuck twin" syndrome. Am J Obstet Gynecol 1995;172:429–34.
14. Saade GR, Belfort MA, Berry DL, Bui TH, Montgomery LD, Johnson A, et al. Amniotic septostomy for the treatment of twin oligohydramnios-polyhydramnios sequence. Fetal Diagn Ther 1998;13:86–93. [PubMed: 9650653]
15. Johnson JR, Rossi KQ, O'Shaughnessy RW. Amnioreduction versus septostomy in twin-twin transfusion syndrome. Am J Obstet Gynecol 2001;185:1044–7. [PubMed: 11717630]
16. Saade G, Moise K, Forman K, et al. A randomized trial of septostomy versus amnioreduction in the treatment of twin oligohydramnios polyhydramnios sequence (TOPS). Am J Obstet Gynecol(Society for Maternal-Fetal Medicine. Oral presentation abstract 3) 2003;187
17. De Lia JE, Cruikshank DP, Kaye WR. Fetoscopic neodymium: YAG laser occlusion of placental vessels in severe twin-twin transfusion syndrome. Obstet Gynecol 1990;75:1046–53. [PubMed: 2342732]
18. De Lia JE, Kuhlmann RS, Harstad TW, Cruikshank DP. Fetoscopic laser ablation of placental vessels in severe twin-twin transfusion syndrome. Am J Obstet Gynecol 1995;172:1202–11. [PubMed: 7726257]
19. Ville Y, Hyett J, Hecher K, Nicolaides KH. Preliminary experience with endoscopic laser surgery for sever twin-twin transfusion syndrome. N Engl J Med 1995;332:224–7. [PubMed: 7808488]
20. 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. [PubMed: 15238624]
21. Quintero RA, Morales WJ, Mendoza G, Allen M, Lalter C, Giannina G, et al. Selective photocoagulation of placental vessels in twin-twin transfusion syndrome: evolution of a surgical technique. Obstet Gynecol Surv 1998;53:597–603.
22. 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. [PubMed: 10076153]
23. Quintero RA, Dickinson JE, Morales WJ, Bornick PW, Bermudez C, Cincotta R, et al. Stage-based treatment of twin-twin transfusion syndrome. Am J Obstet Gynecol 2003;188:1333–40. [PubMed: 12748508]
24. Hecher K, Diehl W, Zikulnig L, Vetter M, Hackeloer BJ. Endoscopic laser coagulation of placental anastomoses in 200 pregnancies with sever mid-trimester twin-to-twin transfusion syndrome. Eur J Obstet Gynecol Reprod Biol 2000;92:135–9. [PubMed: 10986447]
25. Huber A, Wiehl W, Bregenzer T, Hackeloer BJ, Hecher K. Stage-related outcome in twin-twin transfusion syndrome treated by fetoscopic laser coagulation. Obstet Gynecol 2006;108:333–7. [PubMed: 16880303]
26. Quintero RA, Comas C, Bornick PW, Allen MH, Kruger M. Selective vs non-selective laser photocoagulation of placental vessels in twin-twin transfusion syndrome. Ultrasound Obstet Gynecol 2000;16:230–6. [PubMed: 11169288]

27. Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin-twin transfusion syndrome. Am J Perinatol 1999;19:550–5.
28. Crombleholme TM, Livingston J, Polzin W, Gottliebson W, et al. Multimodality and sequential therapy for twin-twin transfusion syndrome (TTTS): a stage and gestational age based approach to the use of amnioreduction (AR), selective fetoscopic laser photocoagulation (SFLP), and radio frequency ablation (RFA). Am Obstet Gynecol 2006;195(Suppl):669.(abstr)
29. Robyr R, Yamamoto M, Ville Y. Selective fetocide in complicated monochorionic twin pregnancies using ultrasound-guided bipolar cord coagulation. Br J Obstet Gynecol. (in press)
30. Crombleholme TM, Robertson F, Marx G, Yarnell R, D'Alton ME. Fetoscopic cord ligation to prevent neurologic injury in monozygous twins. Lancet 1996;348:191. [PubMed: 8684164]
31. Danner C, Shahabi S, Thomas D, et al. Selective fetocide by embolization in twin-twin transfusion syndrome. A report of two cases. J Reprod Med 1997;42:747–50. [PubMed: 9408877]
32. Deprest JA, Van Ballaer PP, Evrard VA, Peers KH, Spitz B, Steegers EA, et al. Experience with fetoscopic cord ligation. Eur J Obstet Gynecol Reprod Biol 1998;81:157–64. [PubMed: 9989860]
33. Moise KJ Jr. Polyhydramnios: problems and treatment. Semin Perinatol 1993;17:197–209. [PubMed: 8378802]
34. Mari G, Roberts A, Detti L, Kovanci E, Stefos T, Bahado-Singh RO, 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. [PubMed: 11568802]
35. Dickinson JE, Evans SF. Obstetric and perinatal outcomes from the Australian and New Zealand twin-twin transfusion syndrome registry. Am J Obstet Gynecol 2000;182:706–12. [PubMed: 10739534]
36. Saade, GR.; Ludomirsky, A.; Fisk, NJ. Feto-fetal transfusion. In: Fisk, NM.; Moise, KJ., Jr, editors. Fetal Therapy and Transplacental. Cambridge UK: Cambridge University Press; 1997. p. 225-51.
37. Cook TL, O'Shaughnessy R. Iatrogenic creation of a monoamniotic twin gestation in severe twin-twin transfusion syndrome. J Ultrasound Med 1997;16:853–5. [PubMed: 9402001]
38. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549–56. [PubMed: 497341]
39. Meis PJ. for the NICHD Maternal-Fetal Medicine Units Network. Ultrasound determination of gestational age alters pregnancy outcome measurements. Paediatric and Perinatal Epidemiology 2001;15:A23.
40. Harkness UF, Crombleholme TM. Twin-twin transfusion syndrome: where do we go from here? Semin Perinatol 2005;29:296–304. [PubMed: 16360488]
41. Shah, AD.; Border, WL.; Crombleholme, TM.; Michelfelder, EC. The relationship between cardiovascular status and recipient twin outcomes in twin-twin transfusion syndrome: Assessment by fetal cardiovascular profile score; Presented at the American Heart Association Annual Meeting; November 12–15 2006; Chicago IL.
42. Huhta J. Right ventricular function in the human fetus. J Perinat Med 2001;29:390–8. [PubMed: 11723840]
43. Fisk NM, Galec P. Twin-twin transfusion syndrome – as good as it gets? N Engl J Med 2004;351:182–4. [PubMed: 15238623]

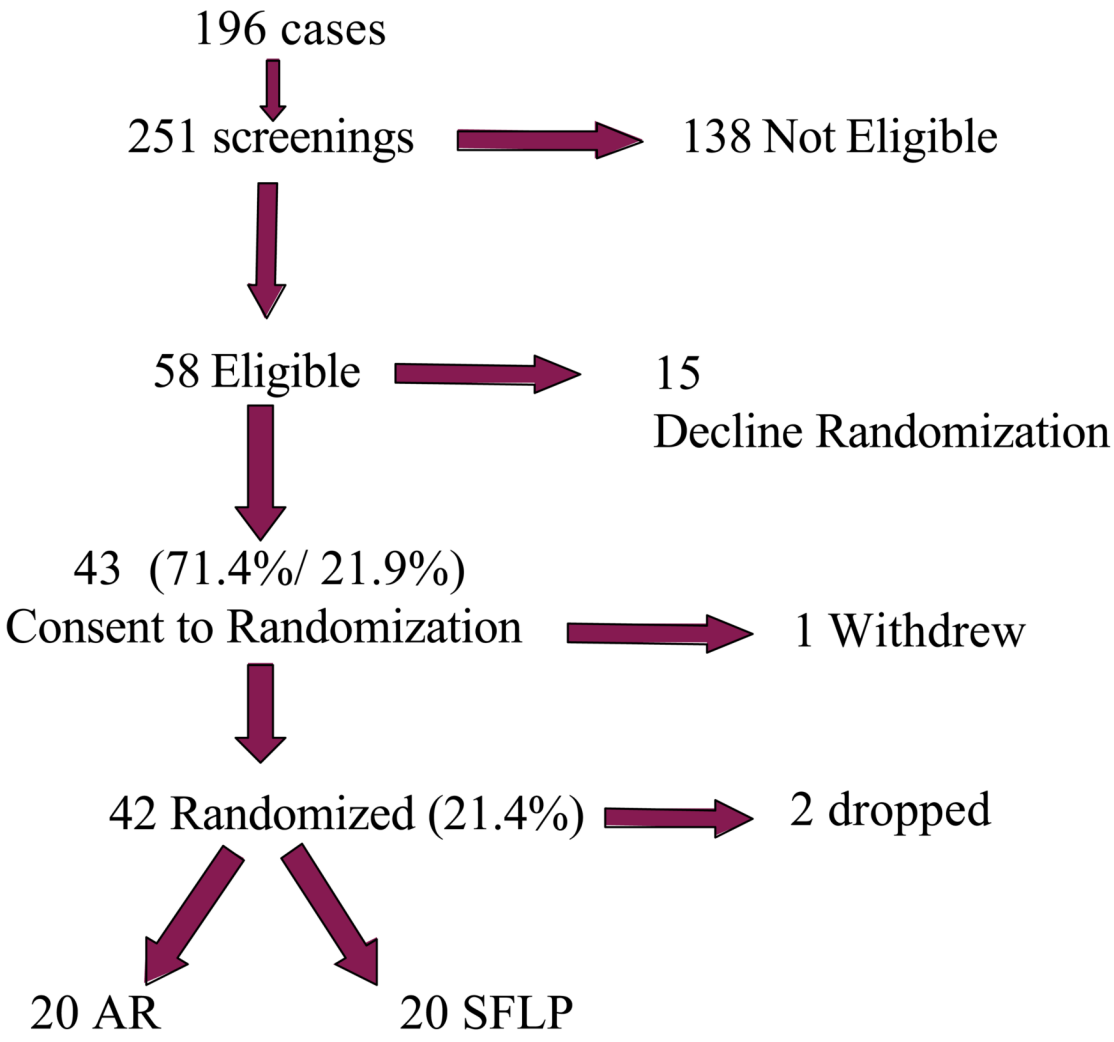

Figure 1.
196 subjects were screened a total of 251 times with 138 subjects not found to be eligible. Of the 58 found to be eligible for the trial, 15 declined randomization. Of the 58 eligible, 43 consented to randomization but 1 withdrew. 21 subjects were randomized to each arm of the study and a single subject dropped out of each arm.

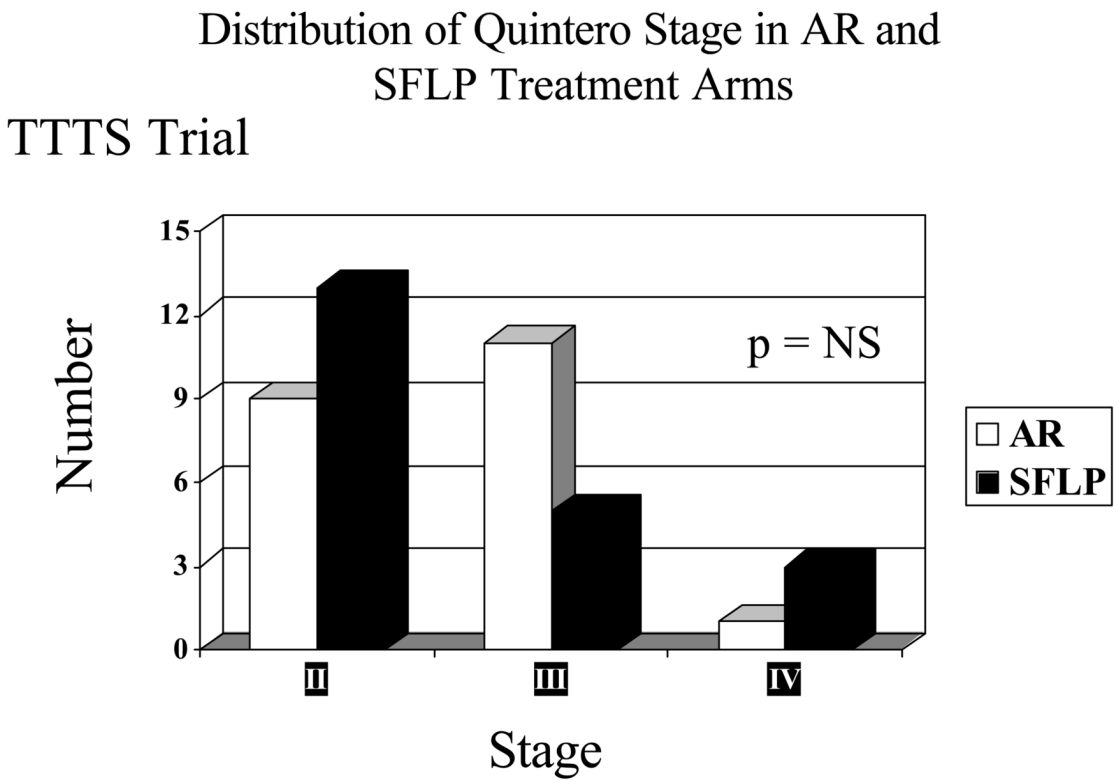

Figure 2.

The distribution by stage using the Quintero staging system is equally distributed among stages II, III, and IV in both the amnioreduction (AR) and selective fetoscopic laser photocoagulation (SFLP) groups. There were no stage I patients in the trial. There is no statistically significant difference in stage distribution between amnioreduction (AR) and selective fetoscopic laser photocoagulation (SFLP).

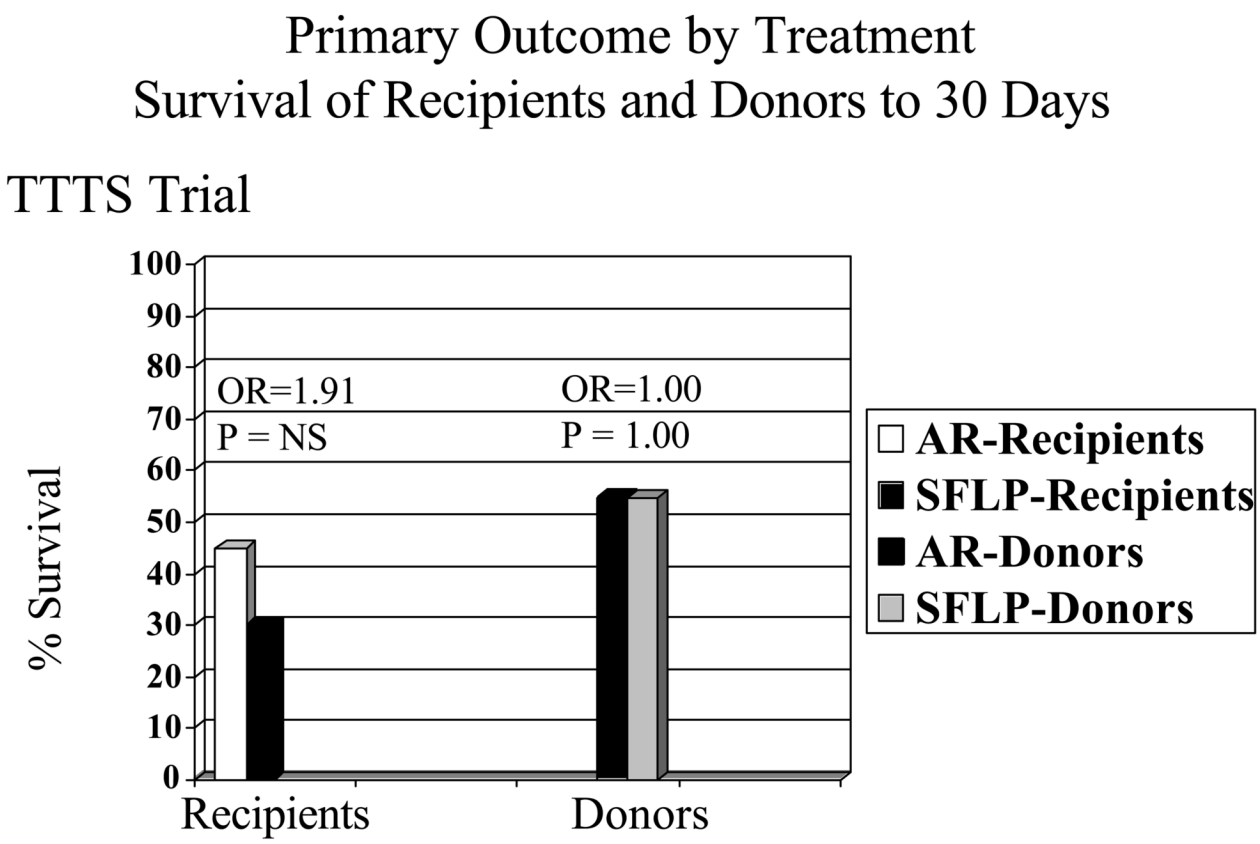

Figure 3.
The survival to 30 days of age when broken down by recipient and donor shows no significant difference in survival between AR) or SFLP groups for either recipients or donors.

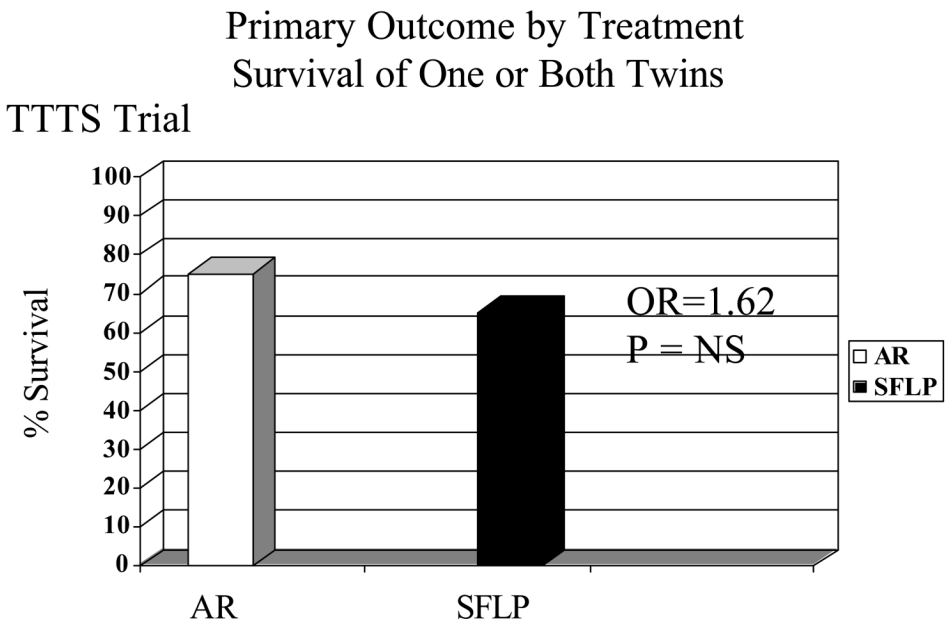

Figure 4.
There is no statistically significant difference in survival of 1 or both twins to 30 days of life.

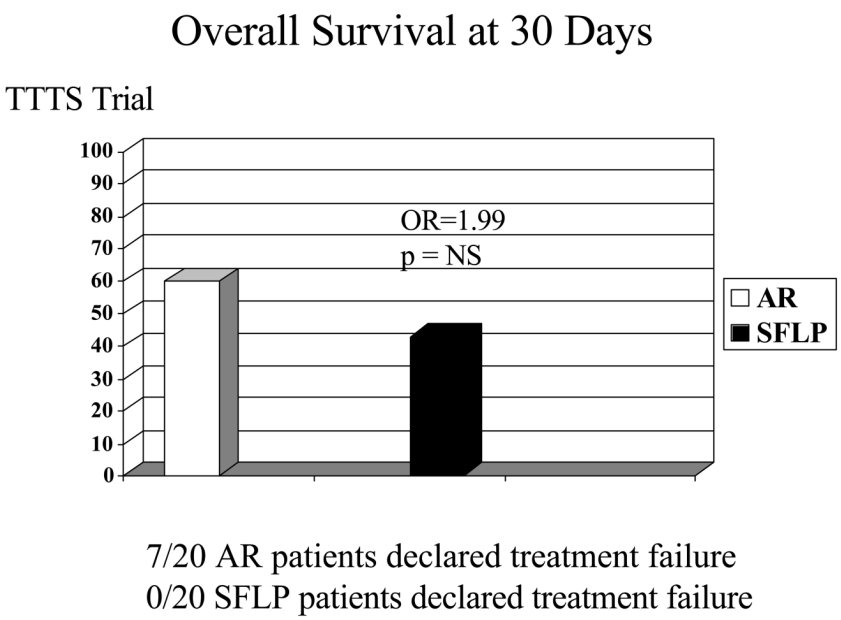

Figure 5.

Despite the differences observed in recipient fetal mortality, there were no statistically significant differences in overall survival to 30 days of age. The reason was that while there were more fetal recipient deaths in the SFLP arm than in the AR arm of the study, more recipients were declared treatment failures in the AR arm (7 of 20), versus the SFLP arm (0 of 20). Neonatal death occurred in 6 of the 7 cases declared treatment failures.

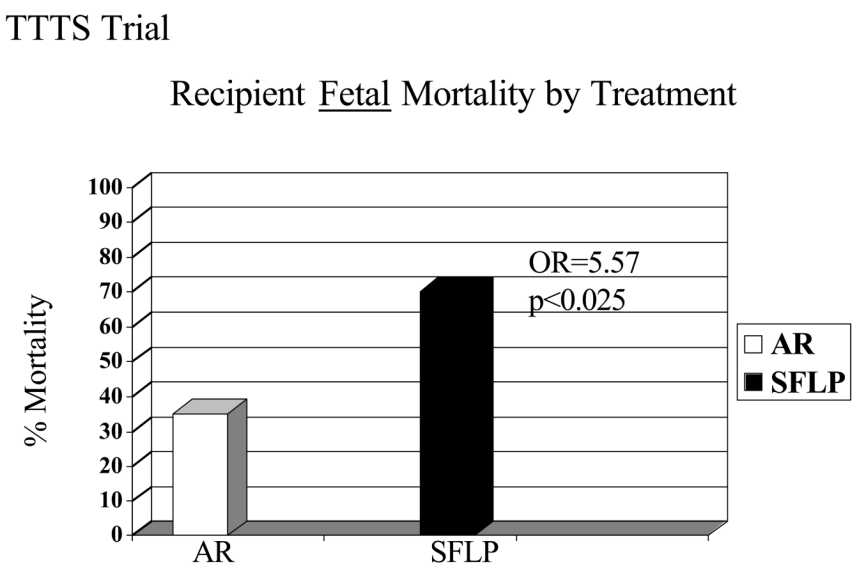

Figure 6.
There is a statistically significantly increased fetal mortality in recipients treated by SFLP (70%) versus those treated by AR (35%, $p < 0.025$, OR=5.31, 95% CI= 1.19 to 27.6)

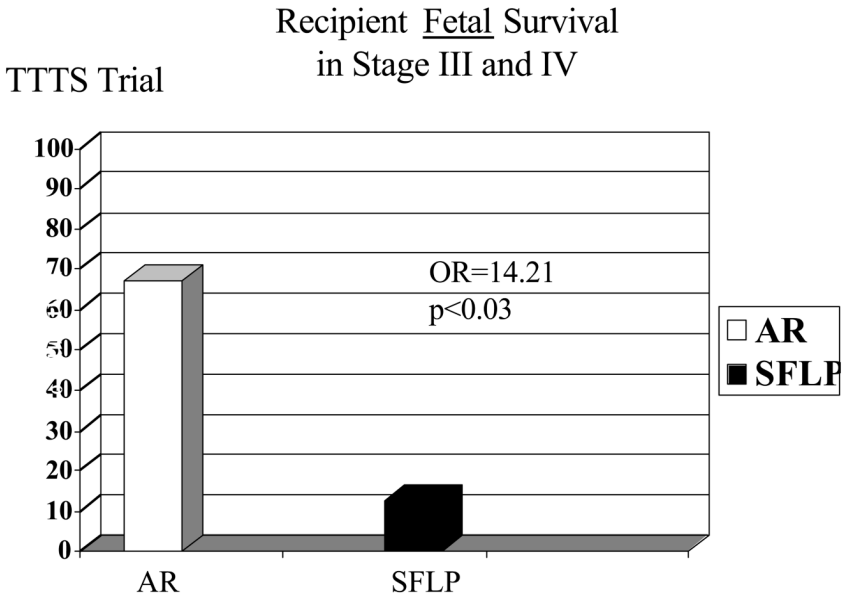

Figure 7.

The difference in fetal recipient survival is more pronounced among recipients in stages III and IV that were treated by AR (63%) versus SFLP (12.5%, $p < 0.03$). Despite these differences in fetal recipient survival, there is no difference in survival at 30 days because 7/20 recipients in the AR arm met criteria for treatment failure (in which 6 of the 7 were neonatal deaths) while 0/20 in the SFLP arm did so.