Stage-based treatment of twin-twin transfusion syndrome

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OBJECTIVE: The purpose of this study was to compare the outcomes of patients with twin-twin transfusion syndrome who were treated with either serial amniocentesis or selective laser photocoagulation of communicating vessels according to disease severity (stage).

STUDY DESIGN: Centers that were experienced in the treatment of twin-twin transfusion syndrome were invited to share stage-based perinatal outcome data. All patients met basic standard sonographic criteria for twin-twin transfusion syndrome (polyhydramnios maximum vertical pocket, ≥ 8 cm; oligohydramnios maximum vertical pocket, ≤ 2 cm). Gestational age at first treatment was <27 weeks of gestation.

RESULTS: Three centers submitted stage-based data, for a total of 173 patients (serial amniocentesis, 78 patients from all 3 centers) and 95 selective laser photocoagulation of communicating vessels (1 center). The distribution of patients by stage was similar in the two groups. Successful pregnancy outcome (at least 1 surviving infant) was correlated inversely with stage in the serial amniocentesis but not in the selective laser photocoagulation of communicating vessels group and was significantly lower in the serial amniocentesis (66.7%) than in the selective laser photocoagulation of communicating vessels group (83.2%). Neurologic morbidity was related directly to stage in the serial amniocentesis group but not in the selective laser photocoagulation of communicating vessels group and was significantly higher in the serial amniocentesis (24.4%) than in the selective laser photocoagulation of communicating vessels (4.2%) group. Intact neurologic survival (at least 1 surviving infant without neurologic morbidity) was significantly lower in the serial amniocentesis group than in the selective laser photocoagulation of communicating vessel group (51.3% vs 78.9%), particularly in stage III and stage IV (23.5% vs 72.7% in stage IV). Patients who were treated with selective laser photocoagulation of communicating vessels were 2.4 times more likely to have at least one survivor than those treated with serial amniocentesis.

CONCLUSION: Our study suggests a relationship between perinatal morbidity and mortality rates and stage in serial amniocentesis but not in selective laser photocoagulation of communicating vessel–treated twin-twin transfusion syndrome patients. These findings could be used to tailor the treatment of twin-twin transfusion syndrome. A clinical trial to confirm these results is being organized by our research groups.

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Key words: Twin-twin transfusion syndrome, amniocentesis, ultrasound, operative fetoscopy

The controversy regarding the optimal treatment of patients with twin-twin transfusion syndrome (TTTS) has been complicated by several factors, which include a lack of standard diagnostic criteria for TTTS, a nonstandardized surgical laser technique, and a failure to include known risk factors in outcome analyses. In addition, dogmatic views about the virtues of serial amniocentesis or laser therapy have hindered actual scientific data to contribute to the understanding of the advantages and limitations of each treatment mode in the treatment of the condition. To address some of these issues, an international registry on serial amniocentesis was organized, and a randomized clinical trial that compared amniocentesis and laser therapy was started by the Eurofetus group (www.eurofetus.org). The international registry showed that patients with early diagnosis, abnormal Doppler studies, or hydrops fared the worst outcome, with survival rates as low as 6%.[1] The randomized clinical trial of amniocentesis versus laser therapy is underway in Europe.

TTTS is not a homogeneous disorder; it occurs at different gestational ages, with normal or abnormal Doppler studies, and with or without hydrops among other variable features. Because outcomes have been associated preliminarily with abnormal Doppler studies and hydrops,[2-4] we believed that the comparison of the

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Table I. Demographic characteristics of the patient population

Characteristic	*Amniocentesis group (n = 78)*	*Laser group (n = 95)*	*P value*
Gestational age at initial therapy (wk)*	21.6 (15.9-26.7)	20.7 (16.7-25.6)	.003
Gestational age at delivery (wk)*	29 (18.4-38)	32 (16.7-40.3)	.005
Interval (wk)*	6.9 (0-19)	10.3 (0-21.4)	<.001
Birth weight of donor (g)†	1219 ± 644	1781 ± 734	<.001
Birth weight of recipient (g)†	1612 ± 724	1940 ± 773	.019

*Data are given as median (range).
†Data are given as mean ± SD.

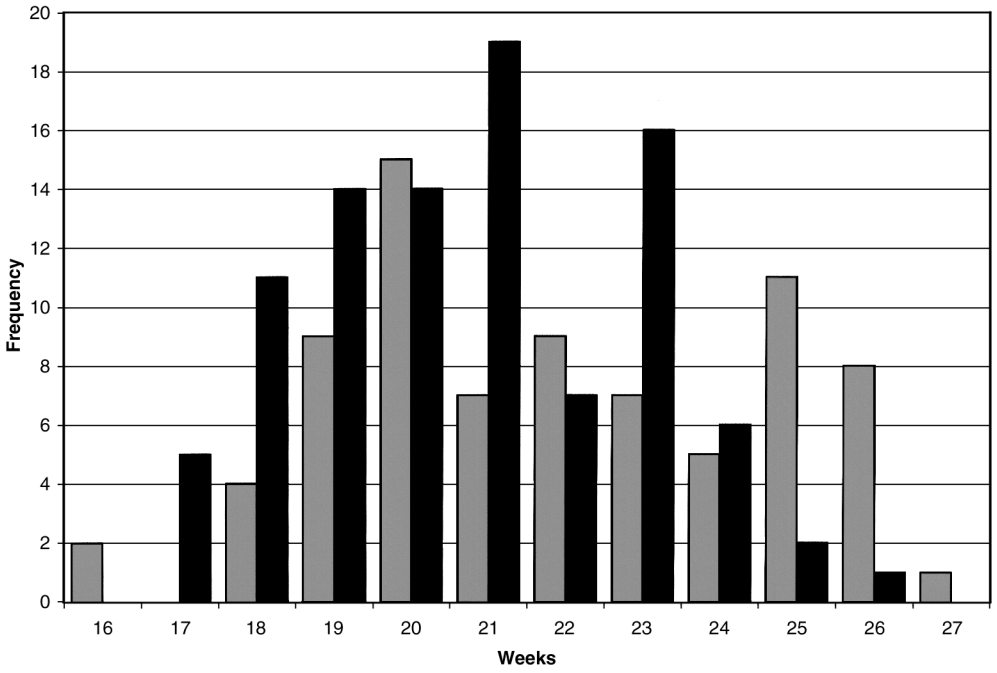

Fig 1. Gestational age at first treatment. Gestational age at first treatment is skewed to right in the amniocentesis group (median, 21.6 weeks of gestation). Gestational age at first treatment is distributed in normal manner in the laser group (mean, 20.7 weeks of gestation). *Gray bars,* Amniocentesis; *black bars,* laser.

different treatments should take into account the various manifestations of the disease. Through empiric observation of patients with TTTS who were followed up serially, Quintero et al[2] proposed a sonographic staging classification of TTTS:

Stage I: The bladder of the donor twin is still visible, and Doppler studies are still normal.
Stage II: The bladder of the donor twin is not visible (during the length of the examination, usually 1 hour), but Doppler studies are not critically abnormal.
Stage III: Doppler studies are critically abnormal in either twin and are characterized as absent or reverse end-diastolic velocity in the umbilical artery, reverse flow in the ductus venosus, or pulsatile umbilical venous flow.
Stage IV: Ascites, pericardial or pleural effusion, scalp edema, or overt hydrops are present.
Stage V: One or both twins are dead.

We proposed that perinatal outcomes of patients with TTTS be assessed on the basis of this staging system.

In addition to developing a staging classification of TTTS, Quintero et al[5,6] also addressed important technical issues regarding the laser surgical technique. First, a selective technique that was capable of identifying deep and superficial vascular anastomoses that allowed differentiation of these vessels from individually perfused areas of the placenta was developed.[5] The technique was called *selective laser photocoagulation of communicating vessels* (SLPCV). Second, surgical techniques for patients with anterior placentas were also developed, which resulted in outcomes that were similar to those of patients with posterior placentas.[6] Finally, treatment of bloody amniotic fluid, laser treatment of vessels that are located in the sac of the donor twin, and complete standardization of the surgical technique were also addressed.[7] With these achievements and developments, we thought it was now appropriate to compare serial amniocentesis and laser

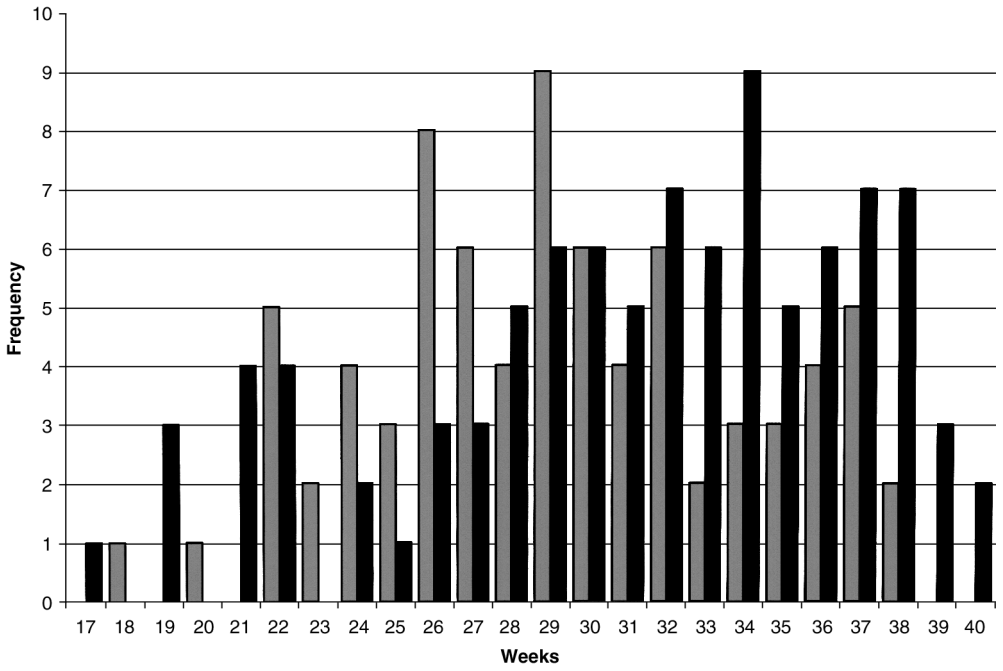

Fig 2. Gestational age at delivery. Gestational age at delivery was distributed in normal manner in the amniocentesis group (mean, 29.2 weeks of gestation). Gestational age at delivery is skewed to right in the laser group (median, 32 weeks of gestation). *Gray bars,* Amniocentesis; *black bars,* laser.

therapy with the use of standard sonographic diagnostic criteria, standard surgical technique, and the inclusion of disease severity (stage) in the analysis. This study compares the outcomes (stratified by stage) of patients with TTTS who were treated with either serial amniocentesis or SLPCV.

Material and methods

An attempt was made to contact all national and international centers that had experience in the treatment of ≥10 patients with TTTS. Standard diagnostic criteria for TTTS were used: polyhydramnios of ≥8 cm maximum vertical pocket (MVP) in the recipient twin, oligohydramnios MVP of ≤2 cm in the donor twin, single placenta, thin dividing membrane, and similar external genitalia. Staging was assigned as described earlier.[2] Gestational age was limited to <27 completed weeks of gestation at the time of first treatment. Serial amniocenteses were performed with sonographic guidance and sterile technique; the aim was to reach a MVP of 6 to 7 cm. Patients were scanned at least weekly, and repeat amniocenteses were performed if the MVP of fluid reached ≥8 cm. SLPCV was performed as previously described, from December 1997 to September of 2000.[5,8] Some of patients who underwent amniocentesis were included in previous series.[1] Some of the patients with SLPCV were also included in previous series.[2,5,6,8] Patients were counseled about all treatment alternatives and gave written informed consent. SLPCV was not available during the study period in Australia. The study was approved by the Institutional Review Board of St Joseph's Hospital in Tampa, Fla.

Table II. Distribution of patients by stage

Stage	*Amniocentesis group (No.)*	*Laser group (No.)*	*Total (No.)*
I	11 (15.3%)	21 (21.6%)	32 (18.9%)
II	23 (29.5%)	35 (36%)	58 (33.5%)
III	27 (34.6%)	28 (30.2%)	55 (31.8%)
IV	17 (21.8%)	11 (11.3%)	28 (16.2%)
Total	78 (45%)	95 (55%)	173 (100%)

$P = .15$.

Pregnancy outcome was defined as neonatal survival of at least one twin. Miscarriage was defined as pregnancy loss before 24 completed weeks of gestation. Neurologic morbidity was defined as microcephaly, periventricular leukomalacia, ventriculomegaly, grade III or IV intraventricular hemorrhage, or cerebral palsy that was diagnosed before 18 months of age by the respective pediatricians in liveborn infants. Intact neurologic outcome was defined as neonatal survival of at least one twin with neither twin having neurologic morbidity.

Statistical analysis. Statistical analysis was conducted with the use of SPSS software (version 9.0 for Windows 95 [Microsoft Corporation, Redmond, Wash]; SPSS Inc, Chicago, Ill). Categoric variables such as survival and stage were analyzed with the use of the χ^2 and Fisher exact tests. Interval variables such as gestational age and estimated fetal weight were analyzed with *t* test for inde-

Table III. Pregnancy outcome (at least one neonatal survivor)

	*Amniocentesis group (n = 78)**		*Laser group (n = 95)†*		
Stage	*None*	*At least 1 live birth*	*None*	*At least 1 live birth*	*P value*
I	0	11 (100%)	3 (14.3%)	18 (85.7%)	.53‡
II	2 (8.7%)	21 (91.3%)	5 (14.3%)	30 (85.7%)	.69‡
III	12 (44.4%)	15 (55.6%)	6 (21.4%)	22 (78.6%)	.069
IV	12 (70.6%)	5 (29.4%)	2 (18.2%)	9 (81.8%)	.007
Total	26 (33.3%)	52 (66.7%)	16 (17.7%)	79 (83.2%)	.012

Numbers in parentheses represent the percentage within each stage by group.
**P* < .001, pregnancy outcome comparison by stage within each group.
†*P* = .87, pregnancy outcome comparison by stage within each group.
‡Fisher exact test.

Table IV. Pregnancy outcome as 0, 1, or 2 survivors

	*Amniocentesis group**			*Laser group†*			
Stage	*0*	*1*	*2*	*0*	*1*	*2*	*P value*
I	0 (0%)	1 (9.1%)	10 (90.9%)	3 (14.3%)	4 (19%)	14 (66.7%)	.273
II	2 (8.7%)	4 (17.4%)	17 (73.9%)	5(14.3%)	13 (37.1%)	17 (48.6%)	.155
III	12 (44.4%)	6 (22.2%)	9 (33.3%)	6 (21.4%)	15 (53.6%)	7 (25%)	.048
IV	12 (70.6%)	3 (17.6%)	2 (11.8%)	2 (18.2%)	4 (36.4%)	5 (45.5%)	.022
Total	26 (33.3%)	14 (17.9%)	38 (48.7%)	16 (16.8%)	36 (38.1%)	43 (44.3%)	.005

Numbers in parentheses represent the percentage within each stage by group.
**P* = .001, perinatal outcome analysis by stage within each group.
†*P* = .167, perinatal outcome analysis by stage within each group.

pendent variables or the Mann-Whitney *U* test, as appropriate. Forced entry logistic regression analysis was also conducted. A probability value of <.05 was considered statistically significant.

Results

A total of 13 centers worldwide were invited to participate, but only 3 centers (Brisbane and Perth, Australia; and Tampa, Fla) submitted data. A total of 173 consecutive patients (78 patients who were treated with serial amniocentesis and 95 patients who were treated with SLPCV) were available for analysis.

Table I shows the demographic characteristics of the patient populations. The median gestational age at the time of first therapy was significantly higher in the amniocentesis group (median, 21.6 weeks; range, 15.9-26.7 weeks) than in the SLPCV group (median, 20.7 weeks; range, 16.7-25.6 weeks; *P* = .003, Mann-Whitney *U* test; Fig 1). The median gestational age at delivery was significantly lower in the amniocentesis group (median, 29 weeks; range, 18.4-38 weeks) than in the SLPCV group (median,32 weeks; range, 16.7-40.3 weeks; *P* = .005, Mann-Whitney *U* test; Fig 2). Correspondingly, the median interval between the first treatment and delivery was significantly shorter in the amniocentesis group (median, 6.9 weeks; range, 0-19 weeks) than in the SLPCV group (median, 10.3 weeks; range, 0-21.4 weeks; *P* < .001). The mean birth weight (±SD) was significantly lower in the amniocentesis group (mean, 1219 ± 644 g, for the donor twin mean; and mean, 1612 ± 724 g, for the recipient twin) than in the SLPCV group (mean, 1781 ± 734 g, for the donor twin, *P* < .001; and mean, 1940 ± 773 g, for the recipient twin, *P* = .019).

There was no significant difference in the distribution of patients by stage (χ^2 test, 5.29; df = 3; *P* = .15; Table II).

Table III gives a comparison of the pregnancy outcomes (at least 1 survivor) in the two groups by stage. Overall, patients who underwent amniocentesis were less likely to have a successful pregnancy outcome than patients with SLPCV (66.7% vs 83.2%, respectively; χ^2 test, 6.33; degrees of freedom [df] = 1; *P* = .012). An inverse relationship between survival and stage was noted in the amniocentesis group (χ^2 test, 23.9; df = 3; *P* < .001), but not in the SLPCV group (χ^2 test, 0.69; df = 3; *P* = .87). An analysis by stage showed that stage IV patients were more likely to survive if they were treated with SLPCV than with amniocentesis (81.8% vs 29.4%, respectively; χ^2 test, 7.33; df = 1; *P* = .007).

Table IV shows the pregnancy outcomes as 0, 1, or 2 survivors in both groups by stage. The overall distribution of 0, 1, and 2 survivors was significantly different between the two groups (χ^2 test, 10.8; df = 2; *P* = .005). There were more dual losses (33.3% vs 16.8%) and fewer single survivors in the serial amniocentesis group than in the SLPCV group (17.9% vs 38.1%, respectively). The distribution of 0, 1, or 2 survivors was related significantly to stage in the amniocentesis group (*P* = .001) but not in the SLPCV group (*P* = .167). Table

Table V. Perinatal outcome per total number of fetuses

	*Amniocentesis (n = 156)**		*Laser (n = 190)†*		
Stage	*Dead*	*Alive*	*Dead*	*Alive*	*P value*
I	1 (4.5%)	21 (95.5%)	10 (23.8%)	32 (76.2%)	.08‡
II	8 (17.4%)	38 (82.6%)	23 (32.9%)	47 (67.1%)	.06
III	30 (55.6%)	24 (44.4%)	27 (48.2%)	29 (51.8%)	.4
IV	27 (79.4%)	7 (20.6%)	8 (36.4%)	14 (63.6%)	.001
Total	66 (42.3%)	90 (57.7%)	68 (35.8%)	122 (64.2%)	.21

Numbers in parentheses represent the percentage by stage within each group.
**P* < .001, perinatal outcome analysis by stage within each group.
†P = .084, perinatal outcome analysis by stage within each group.
‡Fisher exact test.

Table VI. Pregnancy losses

	Amniocentesis (pregnancies [n =78]/fetuses [n = 156])	*Laser (pregnancies [n = 95]/fetuses [n = 190])*	*P value*
Miscarriage/2 fetuses	8/16 (10.3%)	8/16 (8.4%)	.67
Fetal death of donor	5* (–1) (6.4%)	25† (–3) (27.4%)	.001
Fetal death of recipient	7* (–1) (9%)	18† (–2) (18.9%)	.06
Neonatal death of donor	21 (26.9%)	6 (6.3%)	<.001
Neonatal death of recipient	19 (24.4%)	8 (8.4%)	.004
Total fetal losses	66 (42.3%)	68 (35.7%)	

Numbers in parentheses represent the percentage within each group. The total number of losses does not add up correctly in the columns because intrauterine fetal deaths are shown even if patients miscarried.
*One pregnancy in the serial amniocentesis group had intrauterine fetal death of the donor twin, and another pregnancy had intrauterine fetal death of the recipient twin before miscarriage.
†One pregnancy in the SLPCV group had intrauterine fetal death of the donor twin, and 2 pregnancies had intrauterine fetal death of the donor and recipient twin before miscarriage. Therefore, one needs to subtract 2 fetuses from the amniocentesis group and 5 fetuses from the SLPCV group to account for the actual total loss (66 and 68, respectively).

V shows the survival rate by stage per total number of fetuses. Although the overall fetal survival rate was not different between the two groups (57.7% vs 64.2%, for the amniocentesis and SLPCV groups, respectively; $P = .21$), an analysis by stage showed an inverse relationship between fetal survival and stage in the amniocentesis group ($P < .001$) but not in the SLPCV group ($P = .084$), and a lower fetal survival rate for the amniocentesis group in stage IV compared with the SLPCV group (7/34 cases; [20.6%] vs 14/22 cases [63.6%], respectively; $P = .001$).

Table VI shows pregnancy losses per number of fetuses in terms of miscarriage and fetal or neonatal death. There was no difference in the frequency of pregnancy losses before 24 weeks of gestation (10.3% vs 8.4%, for the amniocentesis and SLPCV groups, respectively). Donor fetuses were more likely to die in utero in the SLPCV group than in the amniocentesis group (27.4% vs 6.4%, respectively; χ^2 test, 11.8; df = 1; $P < .001$). However, donor fetuses were more likely to die in the newborn period in the amniocentesis group than in the SLPCV group (26.9% vs 6.3%, respectively; χ^2 test, 13.8; df = 1; $P < .001$). There was no difference in the incidence of fetal death of recipient twins (9% vs 18.9%, amniocentesis and SLPCV groups, respectively). However, recipient twins were more likely to die in the newborn period in the amniocentesis group than in the SLPCV group (24.4% vs 8.4%; χ^2 test, 8.26; df = 1; $P = .004$). The overall survival rate of donor twins (45/78 cases [57.6%] vs 59/95 cases [61.1%]) and recipient twins (45/78 cases [57.6%] vs 64/95 cases [67.3%]) was not different significantly between the amniocentesis and SLPCV groups, respectively.

Patients who were treated with amniocentesis were less likely to be delivered after 32 weeks of gestation than were patients who were treated with SLPCV (28.2% vs 50.5%; χ^2 test, 8.85; df = 1; $P = .003$; Table VII). An analysis by stage showed an inverse relationship between the frequency of delivery at >32 weeks of gestation and stage in the amniocentesis group ($P < .001$), but not in the SLPCV group. Thus, 7.4% vs 32.1% of stage III patients (χ^2 test, 5.25; df = 1; $P = .022$) and 0% vs 45.5% of stage IV patients ($P = .005$, Fisher exact test) were delivered beyond 32 weeks of gestation in the amniocentesis group versus the SLPCV group, respectively.

Table VIII gives the incidence of neurologic morbidity in the two groups by stage. One patient in the amniocentesis group and none of the patients in the laser group was lost to follow-up. Overall, the incidence of neurologic morbidity in one or both fetuses per total number of pregnancies was 24.4% (19/78 pregnancies) in the am-

Table VII. Delivery at >32 weeks of gestation

Stage	*Amniocentesis group (n = 78)*	*Laser group (n = 95)*	*P value*
I	10/11 (90.9%)	13/21 (61.9%)	.115*
II	10/23 (43.5%)	21/35 (60%)	.217
III	2/27(7.4%)	9/28 (32.1%)	.022
IV	0/17 (0%)	5/11 (45.5%)	.005*
Total	22/78 (28.2%)	48 (50.5%)	.003
P value†	<.001	.1	

Numbers in parentheses represent the percentage by stage within each group.
*Fisher exact test.
†Analysis for delivery at >32 weeks of gestation by stage within each group.

Table VIII. Neurologic morbidity (at least one fetus) per pregnancy*

	Amniocentesis group (n = 78)	*Laser group (n = 95)*	*P value*
By pregnancy			
Stage I	0/11	0/21	—
Stage II	3/23 (13%)	1/35 (2.9%)	.29†
Stage III	13/27 (48.1%)	2/28 (7.1%)	.001
Stage IV	3/17 (17.6%)	1/11 (9.1%)	1†
Total	19/78 (24.4%)	4/95 (4.2%)	<.001
P value‡	.003	.5	
By live-born donor and recipient by group			
Donor	12/66 (18.2%)	3/65 (4.7%)	.014
Recipient	11/64 (17.2%)	1/71 (1.4%)	.001
P value§	NS	NS	

Numbers in parentheses represent the percentage within each group. *NS,* Not significant.
*Four patients in the amniocentesis group had neurologic morbidity of both fetuses: 1 patient in stage II, 2 patients in stage III, and 1 patient in stage IV. Therefore, the total number of fetuses with neurologic morbidity in the amniocentesis group is 23 (19 + 4). No patient in the laser group had neurologic morbidity of both fetuses.
†Fisher exact test.
‡Neurologic morbidity analysis by stage within each group.

niocentesis group versus 4.2% (4/95 pregnancies) in the SLPCV group (χ^2 test, 15.08; df = 1; $P < .001$). There was a significant relationship between the incidence of neurologic morbidity and stage in the amniocentesis group (χ^2 test, 13.8; df = 3; $P = .003$) but not in the SLPCV group (χ^2 test, 2.32; df = 3; $P = .5$). A comparison of both groups by stage shows a higher incidence of neurologic morbidity in the amniocentesis group than in the SLPCV group in stage III (48.1% vs 7.1%, respectively; $P = .001$). Of the 19 pregnancies in the amniocentesis group that were associated with neurologic morbidity, both fetuses were affected in 4 cases (total number of affected newborn infants, 23). Sixty-six live-born donor twins were born in the amniocentesis group; 65 live-born donor twins were born in the SLPCV group. The incidence of neurologic damage in the live-born donor twins was 18.2% (12/66 cases) in the amniocentesis group versus 4.7% (3/65 cases) in the SLPCV group (χ^2 test, 5.8; df = 1; $P = .014$). Sixty-four live-born recipient twins were born in the amniocentesis group; 71 live-born recipient twins were born in the SLPCV group. The incidence of neurologic damage in live-born recipient twins was 17.2% (11/64 cases) versus 1.4% (1/71 cases) in the amniocentesis and SLPCV groups, respectively (χ^2 test, 10.5; df = 1; $P = .001$; Table VIII). Within treatment groups, the incidence of neurologic morbidity was no different between the donor and the recipient twins. Three of 23 fetuses (13%) with neurologic morbidity in the amniocentesis group were associated with previous death of the cotwin versus one of four fetuses in the SLPCV group. These differences are not statistically significant. Conversely, 3 of 10 patients (33%) in the amniocentesis group with a single fetal death had neurologic morbidity of the cotwin versus only 1 of 38 patients in the SLPCV group. This difference (3/10 patients versus 1/38 patients) is statistically significant ($P = .02$, Fisher exact test).

Table IX. Intact neurologic survival (at least one neonatal survivor per pregnancy, neither twin with neurologic damage)

Stage	*Amniocentesis*	*Laser*	*P value*
I	11/11 (100%)	18/21 (85.7%)	.53*
II	18/23 (78.3.%)	29/35 (82.9%)	.7*
III	7/27 (25.9%)	20/28 (71.4%)	.001
IV	4/17 (23.5%)	8/11 (72.7%)	.019*
Total	40/78 (51.3%)	75/95 (78.9%)	<.001
P value†	<.001	.55	

Parentheses represent the percentage by stage within each group.
*Fisher exact test.
†Analysis of intact neurologic survival by stage within each group.

Table IX shows the distribution of intact neurologic survival by stage in the two groups, which was defined as the live birth of one or two babies without neurologic damage of either twin. Overall intact neurologic survival was significantly lower in the amniocentesis group than in the SLPCV group (51.3% vs 78.9%, respectively; χ^2 test, 14.7; df = 1; $P < .001$). An inverse relationship between intact neurologic survival and stage was present in the amniocentesis group (χ^2 test, 29.3; df = 3; $P < .001$,) but not in the SLPCV group (χ^2 test, 2.1; df = 3; $P = .55$). Comparison of the two groups by stage showed a statistically significant difference in stages III (71.4% vs 25.9%; χ^2 test, 11.38; df = 1; $P = .001$) and stage IV (72.7% vs 23.5%; $P = .019$, Fisher exact test; SLPCV vs amniocentesis, respectively).

Logistic regression analysis was performed to determine the factors that were more likely to be associated with a successful pregnancy outcome (at least 1 survivor). Gestational age at first treatment, group (serial amniocentesis vs SLPCV), stage, and the average amount of amniotic fluid that was removed per session were included in the analysis. Patients who were treated with SLPCV were

2.4 times more likely to have at least one survivor than were patients who were treated with amniocentesis (95% CI, 1.07-5.15). Forced-entry logistic regression showed that increased stage was associated with a decreased likelihood of a successful pregnancy outcome in the amniocentesis group but not in the SLPCV group. The gestational age at first treatment or the average amount of amniotic fluid volume that was removed per session were not predictive of outcome in either group.

Comment

Our data show the importance of using stage in the analysis of outcomes of patients with TTTS who were treated with amniocentesis or SLPCV. The data suggest that outcomes with laser therapy are relatively uniform, independent of stage, whereas amniocentesis outcomes are poorer as the stage of the disease increases. These findings may have important implications in the counseling of patients and in the development of a tailored approach to the treatment of TTTS.

The controversy regarding the optimal treatment of TTTS has centered essentially around serial amniocentesis versus laser therapy. Although the only 2 studies that compared both techniques (with similar diagnostic criteria and a common laser surgeon) have suggested that laser therapy is superior to amniocentesis,[9,10] the debate about the optimal treatment continues. The controversy is fueled by the known marked differences of the two approaches (availability, cost, and the skills needed) but more so by the fact that successful pregnancies can be achieved with either technique. Amniocentesis is available readily and relatively inexpensive, whereas laser therapy is more costly, requires special training, and is only available in a few centers. Our data suggest that the techniques, in fact, do not yield the same results, with different survival rates (66.7% vs 83.2%, at least 1 survivor) and neurologic morbidity rates (24.4% vs 4.2%) for amniocentesis and laser groups, respectively. In addition, the interval between first treatment and delivery, gestational age at delivery, delivery after 32 weeks of gestation, and birth weight and neurologic morbidity after the death of a co-twin are all significantly different to the advantage of patients who are treated with SLPCV.

Despite an overall improved outcome in patients who are treated with laser therapy, we have proposed a closer analysis of these results. In the recently published amniocentesis registry, the risk factors that were identified included gestational age at diagnosis of <22 weeks, absent diastolic flow in the umbilical artery, removal of >1100 mL of amniotic fluid per week, and hydrops.[1] Our data did not show gestational age at first treatment or the amount of amniotic fluid removed as predictive factors for either group. Logistic regression showed stage to be related with a poorer outcome in the serial amniocentesis group, but not in the SLPCV group. Therefore, neither absent diastolic flow in the umbilical artery (stage III) nor hydrops (stage IV) had any influence in the perinatal survival rate in patients who were treated with SLPCV. Stage was also associated directly with a higher incidence of neurologic complications in the amniocentesis group, but not in the SLPCV group. Because results are poorer with advancing stage and possibly with early gestational age at diagnosis in the amniocentesis group[1] but not in the laser group, we believe that the discussion about the optimal treatment option can be narrowed to the classification of patients by stage and possibly by gestational age to develop a tailored therapeutic approach.

The use of standard diagnostic criteria for TTTS (MVP of ≥8 cm in the recipient twin; MVP of ≤2 cm in the donor twin) and the use of staging should also allow a better comparison of treatment outcomes. For example, in the international amniocentesis registry, the diagnosis of TTTS was "left to the discretion of each physician"[1]; 33% of the patients did not meet the criteria for "stuck" twin syndrome. Overdiagnosis of TTTS is well known and has been described.[11] In the >400 patients who were referred to our center in Tampa with the presumptive diagnosis of TTTS, approximately 20% had simple amniotic fluid discordance, which did not meet the standard criteria for TTTS and who therefore were not offered treatment. The inclusion of patients with less strict definitions for TTTS, viable gestational age at entry, or overrepresenation of patients with stage I or II may explain the wide differences in the reported outcomes in the amniocentesis series.[12-14] In comparison, outcomes of the patients who were treated with SLPCV (all of whom are required to meet strict standard sonographic diagnostic criteria and gestational age at entry and for whom stage has no prognostic value) are remarkably similar among experienced centers.[8,10,15]

On the basis of the available data, we currently recommend offering amniocentesis or SLPCV to patients with TTTS, depending on the stage and possibly on gestational age. Patients with stage I or II are likely to do well with serial amniocentesis, particularly if the gestational age at diagnosis is >22 weeks.[1] Stage II disease that manifests at early gestation (<22 weeks) and stage III and stage IV, regardless of gestational age, would probably benefit best from SLPCV rather than serial amniocentesis. We do not recommend the performance of a "test" amniocentesis in any patient, for several reasons. Bloody discoloration of the amniotic cavity is more likely to be present in patients with a previous amniocentesis, regardless of placental location. This complication requires an exchange of the amniotic fluid at the time of the laser surgery, which adds surgical time and potential morbidity to the procedure. Previous amniocentesis may also result in an unintentional perforation of the dividing membrane (unintentional septostomy).[16] This complication may hamper the performance of SLPCV, does not allow

for the monitoring of the amniotic fluid volumes, and actually may result in cord entanglement and fetal death. Previous amniocentesis may also result in membrane detachment, which may preclude altogether the performance of SLPCV.

This cohort series suggests that for advanced stage, SLPCV is preferable to serial amniocentesis in the treatment of TTTS. Although these data are based on the experience of three centers that perform amniocentesis and one center that performs SLPCV, the criteria and techniques used for both groups were those that are used currently in all experienced centers. Thus, the results are likely to be applicable at other institutions. Nonetheless, these findings ideally should be confirmed by stage-based randomized studies that compare amniocentesis and laser therapy. Such a study is being proposed currently by our research groups.

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