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# North American Fetal Therapy Network: Timing of and indications for delivery following laser ablation for twin-twin transfusion syndrome

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## Abstract

**Background:** Despite improvements in fetal survival for pregnancies affected by twin-twin transfusion syndrome since the introduction of laser photocoagulation, prematurity remains a major source of neonatal morbidity and mortality.

**Objective:** To investigate the indications and factors influencing the timing of delivery following laser treatment, we collected delivery information regarding twin-twin transfusion syndrome cases in a large multicenter cohort.

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The authors report no conflicts of interest.

**Study Design:** Eleven North American Fetal Therapy Network (NAFTNet) centers conducted a retrospective review of twin-twin transfusion syndrome patients who underwent laser photocoagulation. Clinical, demographic and ultrasound variables including twin-twin transfusion syndrome stage, and gestational age at treatment and delivery were recorded. Primary and secondary maternal and fetal indications for delivery were identified. Univariate analysis was used to select candidate variables with significant correlation with latency and GA at delivery. Multivariable Cox regression with competing risk analysis was utilized to determine the independent associations.

**Results:** A total of 847 pregnancies were analyzed. After laser, the average latency to delivery was 10.11 ± 4.8 weeks and the mean gestational age at delivery was 30.7 ± 4.5 weeks. Primary maternal indications for delivery comprised 79% of cases. The leading indications included spontaneous labor (46.8%), premature rupture of membranes (17.1%), and placental abruption (8.4%). Primary fetal indications accounted for 21% of cases and the most frequent indications included donor non-reassuring status (20.5%), abnormal donor Dopplers (15.1%), and donor growth restriction (14.5%). The most common secondary indications for delivery were premature rupture of membranes, spontaneous labor and donor growth restriction. Multivariate modeling found gestational age at diagnosis, stage, history of prior amnioreduction, cerclage, interwin membrane disruption, procedure complications and chorioamniotic membrane separation as predictors for both gestational age at delivery and latency.

**Conclusion:** Premature delivery after laser therapy for twin-twin transfusion syndrome is primarily due to spontaneous labor, preterm premature rupture of membranes and non-reassuring status of the donor fetus. Placental abruption was found to be a frequent complication resulting in early delivery. Future research should be directed toward the goal of prolonging gestation after laser photocoagulation to further reduce morbidity and mortality associated with twin-twin transfusion syndrome.

### Keywords

fetal therapy; multiple gestation; twin-twin transfusion; TTTS; laser; photocoagulation; spontaneous labor; preterm premature rupture of membranes; donor twin; recipient twin

## Introduction

Prematurity remains the main limitation to fetal intervention and a major contributor to neonatal morbidity and mortality. Laser photocoagulation for twin-twin transfusion syndrome (TTTS) is no exception. As a result of both TTTS pathophysiology and complications from fetoscopic intervention, premature birth is expected and anticipated [1]. Prematurity not only leads to excess morbidity and mortality in neonates, it is an independent contributor to poor neurodevelopmental outcomes; in fact, it has been demonstrated that a lower gestational age at birth is the only factor independently associated with neurodevelopmental impairment [2].

Because of the important contribution that prematurity makes to the outcome in TTTS, we sought to further refine our understanding of the timing and indications for delivery after

laser photocoagulation from a large multicenter cohort of patients from within the North American Fetal Therapy Network (NAFTNet).

## Methods

This study was IRB approved by the Colorado Multiple Institutional Review Board and was IRB-approved in each of the participating centers. NAFTNet is a consortium of 35 medical institutions in the United States and Canada with interest and expertise in fetal surgery and other forms of multidisciplinary care for complex fetal disorders [3]. Eleven NAFTNet centers conducted a retrospective review of cases of TTTS that underwent laser photocoagulation. Demographic, clinical and ultrasound variables including TTTS stage as previously described [4] and gestational age (GA) at treatment and delivery were recorded by the participating center. Indications for delivery were divided into maternal or fetal and whether it was a primary or secondary indication for delivery. Secondary indications were defined as additional clinical diagnoses which were present and influenced the decision for delivery. Additionally, fetal indications were divided into whether it was related to the donor or recipient twin.

Data were collected and managed using REDCap electronic data capture tools hosted at the University of Colorado School of Medicine [5]. Each center was responsible for obtaining delivery outcomes from their respective cases and entering data within REDCap.

The association between variables of interest with gestational age at delivery and latency were examined using Cox regression or Kaplan-Meier analysis. All variables at a $p<0.20$ level from univariate analyses were included in the multivariable Cox regression analysis accounting for competing risk in order to model the relationship between GA and latency to significant candidate predictors and determine independent associations. Statistical analysis was performed utilizing SAS 9.4 (SAS Institute Inc., Cary, NC).

## Results

A total of 847 pregnancies were analyzed from years 2011 until 2017. Although this is a multicenter study, we accounted for center effect initially and dropped this in the final model due to non-significance. The average GA of delivery, including all dual demise and pre-viable deliveries, for the entire cohort was 30.65 +/− 4.46 weeks and the average latency time was 10.11 +/− 4.82 weeks. If all cases of dual fetal demise and pre-viable deliveries are excluded, the average GA at delivery is 31.1 +/− 4.02 weeks. Those who delivered with a single fetus (N=98), after a co-twin demise, had an average GA of delivery of 30.67 +/− 4.82 weeks. Indications for delivery after laser were 79% maternal and 21% fetal. The primary route of delivery was by cesarean section delivery (70.9 %). Whether vaginal delivery was planned, or spontaneous labor allowed to progress to vaginal delivery was not assessed.

Table 1 lists maternal demographics for the cohort. Table 2 lists treatment and delivery data. The average GA at evaluation was 20.07 +/− 2.57 weeks with mainly Stage III (57.5%) and Stage II (22.8%) disease. Stage I (N=106) delivered on average at 31.11 +/− 3.46 weeks, Stage II (N=185) 31.86 +/− 4.45 weeks, Stage III (N=467) 30.18 +/− 4.54 weeks and Stage IV (N=54) 29.48 +/− 5.02 weeks. Broken down by early (Stage I or II) or late (Stage III or

IV), there was a statistically significant difference in GA at delivery with early disease delivering later (31.58 +/−4.12 weeks versus 30.1 +/− 4.6, p <0.0001). The percentage of patients that underwent an amniocentesis or an amnioreduction prior to definitive laser treatment was 11.9% and 24.1% respectively. The average GA of delivery for these patients were 30.6 +/− 3.94 weeks and 30.19 +/− 3.95 weeks respectively. For the majority (72.4%) that did not undergo an amniocentesis or amnioreduction prior to laser, the average gestational age of delivery was 30.76 +/− 4.58 weeks and was not statistically significant from either the prior amniocentesis or prior amnioreduction groups. Those with a history of prior preterm birth had an average GA at delivery of 29.32 ± 4.36 weeks.

A short cervical length (<25 mm) was present in 81 patients. The average GA of delivery for this group was significantly less (29.72 +/− 4.85 weeks versus 30.84 +/− 4.34 weeks, p=0.03) compared to those with a cervical length > 25 mm. A cerclage was placed in 6.4% of patients with an average GA at delivery of 28.78 +/− 4.12 weeks. Those with an intra-operative complication (N=157, 18.6%), had an average GA at delivery of 28.76 +/− 5.19 weeks compared to 31.08 +/− 4.16 weeks for those who did not have intra-operative complications, p< 0.0001. Intra-operative complications were recorded by the center performing the laser and included bleeding, premature rupture of membranes, chorioamniotic membrane separation, intertwin membrane disruption, fetal demise of one or both twins, inability to complete the procedure, and transplacental insertion of the cannula. If a chorioamniotic membrane separation occurred (N=135, 15.9%) the average GA at delivery was 29.43 +/− 3.88 weeks versus 30.89 +/− 4.52 weeks, p=0.0005 for those who did not have chorioamniotic membrane separation. Intertwin membrane disruption, or inadvertent septostomy, occurred in 68 (8.1%) of cases and the average GA at delivery was 29.8 +/− 3.17 weeks; this was not statistically significant compared to pregnancies that did not have intertwin membrane disruption, although its occurrence was found to be an independent predictor of both gestational age at delivery and latency.

Table 3 lists the primary indications (N= 799) for delivery in decreasing frequency. The indication listed is what prompted delivery or the decision for delivery. For example, co-twin demise was checked if that was what drove the primary indication for delivery. The top three primary maternal indications were spontaneous labor (46.8%), premature rupture of membranes (PPROM) (17.1%), and abruption (8.4%). The top three primary fetal indications were donor non-reassuring fetal status (20.5%), donor abnormal Dopplers (15.1%), and donor fetal growth restriction (14.5%). Table 4 lists the secondary maternal and fetal indications (N=447) for delivery.

Physician discomfort with the clinical picture was documented as the reason for delivery for 53 (6.3%) cases. All reasons stated were true maternal or fetal indications or a combination of maternal and fetal indications rather than primarily a clinical judgement call for delivery.

Institutional protocols triggered delivery in 60 (7.3%) patients when a particular GA was reached. The average GA for this was 34.69 +/− 4.32 weeks.

NAFTNet centers only made the decision to deliver in 90 cases, with an average delivery age of 29.14 +/− 5.62 weeks compared to the 727 cases where the decision was made by non-NAFTNet centers where the average GA of delivery was 30.82 +/− 4.22 weeks (p=.0007).

Table 5 and 6 provides univariate and multivariate analysis of candidate predictors for both gestational age at delivery and latency for all causes of delivery, spontaneous labor and indicated delivery with hazard ratios and 95% confidence intervals. Gestational age at diagnosis, stage, history of prior amnioreduction, cerclage, interwin membrane disruption, procedure complications and chorioamniotic membrane separation were found to be significant predictors for both gestational age at delivery and latency.

## Discussion

From this large multicenter cohort, patients may be counseled to expect approximately ten weeks of latency after laser treatment and deliver at an average GA at delivery of 31 weeks. Maternal indications for delivery predominate with spontaneous preterm labor and preterm premature rupture of membranes as the most common contributors to prematurity. Fetal indications, mainly relating to the donor, were responsible for 21% of deliveries. The high rate of placental abruption was surprising, accounting for 8% of maternal indications for delivery. Placental abruption occurs in 1–2% of multiple gestation, significantly less than what we report here [9]. Senat et al reported a 1% abruption rate as a direct complication from laser ablation [7]. Whether increased abruption results from aspects of the laser ablation procedure itself or for example high rates of premature rupture of membranes and the higher risk of abruption in that setting will require additional investigation.

Most institutional protocols triggered delivery at 34 weeks. The optimal timing of elective delivery after laser photocoagulation has not been determined. One investigation found that once 32 weeks GA is reached, the residual risk of an unexpected adverse event was found to be 1 in 17, which is similar to the rate in uncomplicated monochorionic twins [10].

Rustico and colleagues reported spontaneous preterm birth (68%) and PPROM (28.7%) as the most frequent complications after laser ablation [11]. Snowise and colleagues determined a rate of PPROM of 39% occurring mainly around 27 weeks resulting in an average GA at delivery of 29 weeks [12]. Of these cases, 26.7% occurred prior to 24 weeks accounting for two-thirds of their dual demises.

In one single center series the rate of PPROM prior to 32 weeks increased from 15% to 40% over the course of fifteen years, resulting in more deliveries prior to 32 weeks. This was attributed to the higher number of procedures performed prior to 17 weeks gestation, from 4% to 10% over this same time period [13].

Intertwin membrane disruption was reported in 8.1% of our cases similar to Chmait (8.7%) and Cruz-Martinez (7.2%) [14,15]. In a series by Peeters et al, perforation of the intertwin membrane was suspected in 20% of cases resulting in a 31 week average GA of delivery [16].

Malshe and colleagues found an average GA at delivery of 30.9 weeks, similar to our cohort. Spontaneous preterm birth occurred in 48% of patients, indicated preterm birth in 32%, and 20% were elective deliveries. PPROM occurred in 39% of their patients. Risk factors for spontaneous preterm delivery were PPROM and shorter preoperative cervical length. PPROM was also a significant risk factors for indicated delivery [17].

Chorioamniotic membrane separation occurs frequently after these procedures and results in high rates of PPROM and prematurity. In one study, the rate was 28.6% which correlated with a two-fold increase in miscarriage, a three-fold higher rate of PPROM less than 32 weeks, and a reduction of single twin survival. Procedures performed prior to 18 weeks are significantly associated with this complication [18]. Higher rates of intertwin membrane disruption and a lower preoperative maximum vertical pocket of amniotic fluid has also been attributed to this complication [19].

Cerclage placement in the setting of TTTS and a short cervix remains controversial and there is no known consensus regarding its placement within NAFTNet. The indication for cerclage was not assessed in this retrospective study. In a retrospective analysis of cerclage versus no cerclage with a cervical length < 25 mm, there was no difference in average GA at delivery (28.8 +/− 5.4 weeks vs 29.1 +/− 5.6 weeks, p=.15). However, in a subset of patients with a cervical length between 16–20 mm there was a significant prolongation of pregnancy with cerclage (30.2 +/− 4.2 weeks versus 27.4 +/− 5.4 weeks, p=.04) [20]. Our data shows a lower GA at delivery with a cerclage, but we are not able to evaluate the efficacy of cerclage in a sub-population at increased risk of preterm birth and specifically compare those patients with a short cervix with and without cerclage placement. Whether progesterone was utilized was also not evaluated in our study.

The strengths of our study are the inclusion of a large number of patients from multiple centers across North America whose practice is to send patients back to the referring center for follow-up care and delivery. Additionally, the data was separated to determine whether fetal indications for delivery were based on the recipient or donor fetus.

The main limitation of the current study is that we did not collect extensive detail from ultrasound studies, fetal echocardiograms, operative reports, indications for amniocentesis or amnioreduction, amnioreduction volume, or on neonatal survival, as the focus was to determine the indications for delivery after laser photocoagulation. Other than stage, we do not have extensive information regarding initial indications for laser nor do we have knowledge of individual experience or expertise. Additionally, we do not have information with regard to the etiology of spontaneous preterm birth such as placental pathology and incidence of chorioamnionitis for example. With the Complicated Monochorionic Twin Pregnancy Registry (CMTPR) hosted by NAFTNet currently underway, further details regarding perioperative evaluation and treatment can be correlated with GA at delivery and latency.

Survival has improved over the last decade [7,8] with much of the current morbidity and mortality associated with TTTS associated with prematurity. Investigation in techniques to reduce spontaneous labor and PPROM are of paramount importance. Treatment at an earlier

stage was associated with an improved GA at delivery and prompt diagnosis remains a critical aspect of care. Refinement of the ideal GA for elective delivery after a successful laser photocoagulation, as well as further investigation into the interpretation of maternal and fetal "indications" in this setting will require additional multicenter efforts and prospective study.

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**Condensation**

After laser ablation, delivery occurs on average ten weeks later primarily due to spontaneous labor and premature rupture of membranes followed by fetal indications.

## AJOG at a Glance

**Why was this study conducted?**

Prematurity remains a main source of morbidity and mortality for twin-twin transfusion syndrome. We sought to further refine our understanding of the timing and indications for delivery after laser photocoagulation from a large multicenter cohort of patients from within the North American Fetal Therapy Network (NAFTNet).

**What are the key findings?**

Patients may be counseled to expect approximately ten weeks of latency after laser treatment and deliver at an average GA at delivery of 31 weeks. Maternal indications for delivery predominate with spontaneous preterm labor and preterm premature rupture of membranes as the most common contributors to prematurity. The high rate of placental abruption was surprising, accounting for 8% of maternal indications for delivery. Fetal indications, mainly relating to the donor, were responsible for 21% of deliveries.

**What does this study add to what is already known?**

When delivery was for fetal indications, concerns regarding the donor fetus predominated. After spontaneous labor and rupture of membranes, placental abruption was a significant contributor to maternal indications for delivery and requires further investigation as to the etiology. Finally, treatment of early stage twin-twin transfusion was associated with a later gestational age of delivery suggesting the benefit of prompt diagnosis and treatment of twin-twin transfusion syndrome.

**TABLE 1**

Maternal Demographics

| | |
|---|---|
| **Age, years** | 29.17 ± 5.55 |
| **Race/ethnicity** | |
| White non-Hispanic | 650 (76.7%) |
| Black non-Hispanic | 45 (5.3%) |
| Asian | 33 (3.9%) |
| Hispanic | 42 (5%) |
| Other/Unknown | 77 (9.1%) |
| **Body mass index at screening, kg/m$^2$** | 28.98 ± 6.19 |
| **Pregnancy History** | |
| Gravidity | 2.53 ± 1.53 |
| Parity | 1.07 ± 1.16 |
| **History of PTB or PPROM** | 55 (6.5%) |

Data presented as n (%) or mean ± SD

*kg*, kilograms*; m*, meters*; PTB, preterm birth; PPROM*, preterm premature rupture of membranes

**Table 2**

Treatment and Delivery Summary

| | |
|---|---|
| **GA at evaluation, weeks** | 20.07 ± 2.57 |
| **Stage at diagnosis** | |
| I | 106 (13.1%) |
| II | 185 (22.8%) |
| III | 467 (57.5%) |
| IV | 54 (6.7%) |
| **Amniocentesis prior to laser treatment** | 101 (11.9%) |
| **Amnioreduction prior to laser treatment** | 203 (24.1%) |
| **GA at Laser Treatment, weeks** | 20.63 ± 2.57 |
| **Pre-op cervical length, mm** | 38.57 ± 9.57 |
| **Intra-op complications** | 157 (18.6%) |
| **Intertwin membrane disruption** | 68 (8.1%) |
| **Chorioamniotic membrane separation** | 135 (15.9%) |
| **Cerclage** | 43 (6.4%) |
| **GA at Delivery, weeks** | 30.65 ± 4.46 |
| **Latency, weeks** | 10.11 ± 4.82 |
| **Method of Delivery** | |
| Cesarean | 581 (70.9%) |
| Vaginal | 233 (28.4%) |
| Both | 6 (0.7%) |
| **Primary Indication for Delivery** | |
| Maternal | 634 (79.2%) |
| Fetal | 167 (20.8%) |

Data presented as N (%) or N (mean ± SD)

*GA*, gestational age; *mm*, millimeters

**Table 3**

Primary Indications for Delivery

| **Primary Maternal Indication for Delivery** | | **N=633** | **GA at Delivery** |
|---|---|---|---|
| 1. | Spontaneous Onset of Labor | 296 (46.8%) | 30.29 ± 3.59 |
| 2. | Preterm Rupture of Membranes | 108 (17.1%) | 31.57 ± 3.47 |
| 3. | Placental Abruption | 53 (8.4%) | 29.05 ± 3.19 |
| 4. | Term Delivery | 40 (6.3%) | 36.77 ± 1.85 |
| 5. | Chorioamnionitis | 39 (6.2%) | 27.72 ± 3.79 |
| 6. | Other | 35 (5.5%) | 33.12 ± 4.5 |
| 7. | Previable Rupture of Membranes | 27 (4.3%) | 21.78 ± 3.67 |
| 8. | Preeclampsia | 17 (2.7%) | 33.41 ± 2.28 |
| 9. | Gestational Hypertension | 7 (1.1%) | 34.41 ± 2.8 |
| 10. | Significant Vaginal Bleeding | 5 (0.8%) | 30.54 ± 4.83 |
| 11. | Termination of Pregnancy | 4 (0.6%) | 26.18 ± 6.56 |
| 12. | Subsequent Intervention plication | 1 (0.2%) | 17.7 ± 0.0 |
| 13. | Mirror Syndrome | 1 (0.2%) | 24 ± 0.0 |
| **Primiary Fetal Indication for Delivery** | | **N = 166** | **GA at Delivery** |
| 1. | Donor NRFHTs | 34 (20.5%) | 29.99 ± 2.94 |
| 2. | Donor Abnormal Doppler | 25 (15.1%) | 31.33 ± 2.77 |
| 3. | Donor Fetal Growth Restriction | 24 (14.5%) | 33.43 ± 2.93 |
| 4. | Recipient NRFHTs | 18 (10.8%) | 30.80 ± 3.82 |
| 5. | Double Fetal Demise | 12 (7.2%) | 22.46 ± 4.28 |
| 6. | Both Twins, Other | 12 (7.2%) | 31.71 ± 2.69 |
| 7. | Donor Other | 8 (4.8%) | 31.43 ± 4.56 |
| 8. | Cord Entanglement | 5 (3%) | 30.69 ± 1.82 |
| 9. | Donor Demise | 4 (2.4%) | 33.32 ± 2.83 |
| 10. | Donor Poor Interval Growth | 4 (2.4%) | 32.07 ± 3.72 |
| 11. | TAPS | 4 (2.4%) | 28.96 ± 4.77 |
| 12. | Donor Hydrops Complication | 3 (1.8%) | 26.57 ± 2.1 |
| 13. | Recipient, Other | 3 (1.8%) | 38.1 ± 0.91 |
| 14. | Donor Cardiac Dysfunction | 2 (1.2%) | 32.57 ± 6.26 |
| 15. | Recipient Demise | 2 (1.2%) | 26.93 ± 7.37 |
| 16. | Recipient Abnormal Doppler | 2 (1.2%) | 32.5 ± 2.53 |
| 17. | Abnormal Dopplers, Both | 1 (0.6%) | 26.28 ± 0.0 |
| 18. | Donor Oligohydramnios | 1 (0.6%) | 27.42 ± 0.0 |
| 19. | Recipient Oligohydramnios | 1 (0.6%) | 37.85 ± 0.0 |
| 20. | Recipient Hydrops | 1 (0.6%) | 22.42 ± 0.0 |

Data presented as N (%) or N (mean ± SD)

*NRFHT*, non-reassuring fetal heart tones; *TAPS*, twin anemia polycythemia sequence

**Table 4**

Secondary Indications for Delivery

| **Secondary Maternal Indication for Delivery** | | **N= 344** | **GA at Delivery** |
|---|---|---|---|
| 1. | Preterm Rupture of Membranes | 250 (72.7%) | 29.85 ± 3.1 |
| 2. | Other | 60 (17.4%) | 28.42 ± 4.52 |
| 3. | Spontaneous Onset of Labor | 41 (11.9%) | 28.31 ± 4.18 |
| 4. | Chorioamnionitis | 22 (6.4%) | 27.44 ± 3.79 |
| 5. | Significant Vaginal Bleeding | 16 (4.7%) | 28.29 ± 3.85 |
| 6. | Preeclampsia | 15 (4.4%) | 31.27 ± 1.97 |
| 7. | Gestational Hypertension | 5 (1.5%) | 32.26 ± 2.61 |
| 8. | Placental Abruption | 3 (0.9%) | 23.33 ± 3.17 |
| 9. | Previable Rupture of Membranes | 1 (0.3%) | 18.43 ± 0.0 |
| 10 | Placenta Previa Without Bleeding | 1 (0.3%) | 28.0 ± 0.0 |
| 11 | Subsequent Intervention Complication | 1 (0.3%) | 27.14 ± 0.0 |
| **Secondary Fetal Indication for Delivery** | | **N = 103** | **GA at Delivery** |
| 1. | Donor Fetal Growth Restriction | 24 (23.3%) | 31.13 ± 2.69 |
| 2. | Recipient, Other | 20 (19.4%) | 30.45 ± 3.6 |
| 3. | Donor, Other | 17 (16.5%) | 30.91 ± 3.0 |
| 4. | Recipient NRFHTs | 12 (11.7%) | 28.30 ± 2.8 |
| 5. | Donor NRFHTs | 11 (10.7%) | 29.01 ± 3.1 |
| 6. | Donor Demise | 9 (8.7%) | 30.79 ± 4.84 |
| 7. | Recipient Abnormal Doppler | 6 (5.8%) | 31.33 ± 2.81 |
| 8. | Donor Oligohydramnios | 5 (4.9%) | 31.60 ± 4.02 |
| 9. | Donor Poor Interval Growth | 5 (4.9%) | 31.97 ± 1.05 |
| 10. | Donor Abnormal Doppler | 4 (3.9%) | 32.21 ± 2.09 |
| 11 | Recipient Oligohydramnios | 4 (3.9%) | 29.75 ± 4.15 |
| 12. | Recipient Demise | 3 (2.9%) | 23.95 ± 3.86 |
| 13. | Recipient Fetal Growth Restriction | 3 (2.9%) | 32.38 ± 1.81 |
| 14. | Recipient Cardiac Dysfunction | 3 (2.9%) | 33.52 ± 1.2 |
| 15 | Cord Entanglement | 2 (1.9%) | 26.71 ± 0.0 |
| 16. | Donor Cardiac Dysfunction | 2 (1.9%) | 28.5 ± 5.15 |
| 17. | Recipient Poor Interval Growth | 2 (1.9%) | 27.93 ± 7.78 |
| 18. | TAPS | 2 (1.9%) | 29.21 ± 4.14 |
| 19. | Double Fetal Demise | 1 (1%) | 18.43 ± 0.0 |
| 20. | Recipient Hydrops | 1 (1%) | 23.14 ± 0.0 |
| 21. | TTTS Recurrence | 1 (1%) | 30.57 ± 0.0 |

Data presented as N (%) or N (mean ± SD)

*NRFHT*, non-reassuring fetal heart tones; *TAPS*, twin anemia polycythemia sequence; *TTTS*, twin to twin transfusion syndrome

**Table 5.**

Candidate predictors for gestational age at delivery with hazard ratios for all causes, spontaneous delivery and indicated delivery.

| GA at Delivery | Hazard Ratios (95%CI) | | | | | |
|---|---|---|---|---|---|---|
| **Candidate Predictors** | **All Causes** | | **Spontaneous Delivery** | | **Indicated Delivery** | |
| | **Univariate** | **Multivariate** | **Univariate** | **Multivariate** | **Univariate** | **Multivariate** |
| GA at Diagnosis | **0.79(0.94, 0.99)** * | **0.96 (0.93, 0.99)** * | 0.99 (0.95, 1.05) | NS | **0.95 (0.92, 0.99)** * | **0.95 (0.91, 0.99)** * |
| RACE | | | | | | |
| Black vs. White | 1.16 (0.86, 1.58) | NS | 1.21 (0.74, 1.98) | NS | 1.14 (0.77, 1.69) | NS |
| Black vs. Other | 1.02 (0.73, 1.44) | | 1.18 (0.68, 2.06) | | 0.94 (0.61, 1.45) | |
| White vs. Other | 0.88 (0.73, 1.06) | | 0.98 (0.72, 1.34) | | 0.82 (0.65, 1.04) | |
| TTTS Stage | | | | | | |
| I vs. II | **1.42 (1.10, 1.82)** ** | NS | 1.45 (0.95, 2.23) | NS | **1.41 (1.03, 1.93)** * | NS |
| I vs. III | **0.99 (0.79, 1.23)** | | 0.88 (0.62, 1.25) | | 1.06 (0.81, 1.40) | |
| I vs. IV | **0.88 (0.63, 1.23)** | | 0.72 (0.43, 1.22) | | 1.00 (0.65, 1.56) | |
| II vs. III | **0.70 (0.58, 0.84)** | | **0.60 (0.44, 0.83)** * | | **0.76 (0.60, 0.95)** * | |
| II vs. IV | **0.62 (0.45, 0.86)** | | **0.50 (0.30, 0.82)** * | | 0.71 (0.47, 1.08) | |
| III vs. IV | **0.89 (0.67, 1.19)** | | 0.83 (0.54, 1.28) | | 0.94 (0.64, 1.39) | |
| Prior Amnioreduction, Y vs. N | **1.25 (1.06, 1.47)** * | NS | **1.41 (1.10, 1.82)** * | **1.38 (1.07, 1.79)** * | 1.15 (0.93, 1.42) | NS |
| Prior Preterm Birth, Y vs. N | **1.48 (1.11, 1,96)** * | **1.54 (1.16, 2.05)** * | **2.01 (1.34, 3.01)** ** | **1.80 (1.20, 2.72)** * | 1.16 (0.77, 1.73) | NS |
| Cerclage, Y vs. N | **1.84 (1.34, 2.53)** *** | **1.95 (1.40, 2.71)** *** | 1.64 (0.96, 2.82) | NS | **1.96 (1.32, 2.92)** * | **2.08 (1.38, 3.04)** ** |
| Procedure Complication, Y vs. N | **1.30 (1.09, 1.55)** ** | **1.26 (1.05, 1.51)** * | 1.21 (0.90, 1.64) | NS | **1.35 (1.09, 1.69)** * | **1.30 (1.04, 1.62)** * |
| Interwin Membrane Disruption, Y vs. N | **1.53 (1.18, 1.98)** * | NS | **1.69 (1.15, 2.49)** * | **1.72 (1.17, 2.54)** * | **1.42 (1.01, 2.00)** * | NS |
| Choriamniotic Membrane Separation, Y vs. N | **1.59 (1.32, 1.93)** *** | **1.53 (1.26, 1.86)** *** | **1.45 (1.06, 1.98)** * | NS | **1.69 (1.33, 2.15)** ** | **1.58 (1.34, 2.02)** ** |

* <.05

** <.001

*** <.0001

Taking multivariable modeling for spontaneous delivery, examples of interpretation of the direction of effect are as follows:

The hazard of having an earlier gestational age at delivery for patients who had a prior amnioreduction is 1.38 times higher than patients who did not have a prior amnioreduction before treatment after controlling for other covariates.

The hazard of having an earlier gestational age at delivery for patients who had a prior preterm birth is 1.80 times higher than patients who did not have a prior preterm birth after controlling for other covariates.

**Table 6.**

Candidate predictors for latency with hazard ratios for all causes of delivery, spontaneous delivery and indicated delivery.

| **Latency** | **Hazard Ratios (95%CI)** | | | | | |
|---|---|---|---|---|---|---|
| **Candidate Predictors** | **All Causes** | | **Spontaneous Delivery** | | **Indicated Delivery** | |
| | **Univariate** | **Multivariate** | **Univariate** | **Multivariate** | **Univariate** | **Multivariate** |
| GA at Diagnosis | **1.22 (1.18, 1.26)** *** | **1.23 (1.19, 1.27)** *** | **1.24 (1.18, 1.30)** *** | **1.23 (1.16, 1.29)** *** | **1.21 (1.17, 1.27)** *** | **1.21 (1.16, 1.27)** *** |
| RACE | | | | | | |
| Black vs. White | 1.34 (0.99, 1.82) | NS | 1.33 (0.81, 2.18) | NS | 1.35 (0.91, 2.00) | 1.32 (0.89, 1.96) |
| Black vs. Other | 1.09(0.77, 1.53) | | 1.21 (0.70, 2.12) | | 1.02 (0.66, 1.57) | 0.99 (0.64, 1.54) |
| White vs. Other | **0.81 (0.67, 0.98)** * | | 0.92 (0.67, 1.26) | | **0.75 (0.60, 0.95)** * | **0.75 (0.59, 0.95)** * |
| TTTS Stage | | | | | | |
| I vs. II | **1.91 (1.48, 2.46)** *** | NS | **2.01 (1.30, 3.09)** * | **1.56 (1.04, 2.42)** * | **1.87 (1.36, 2.57)** ** | **1.50 (1.08, 2.08)** * |
| I vs. III | **1.37 (1.10, 1.71)** | | 1.22 (0.85, 1.74) | 1.08 (0.75, 1.55) | **1.48 (1.12, 1.95)** ** | 1.22 (0.92, 1.62) |
| I vs. IV | 1.14 (0.81, 1.59) | | 0.92 (0.55, 1.56) | 0.90 (0.53, 1.51) | 1.31 (0.84, 2.03) | 1.19 (0.76, 1.85) |
| II vs. III | **0.72 (0.60, 0.87)** | | **0.61 (0.44, 0.83)** * | **0.56 (0.35, 0.95)** | **0.79 (0.63, 0.99)** ** | 0.82 (0.65, 1.03) |
| II vs. IV | **0.59 (0.44, 0.82)** | | **0.46 (0.28, 0.76)** * | 0.83 (0.54, 1.29) | 0.88 (0.60, 1.30) | 0.79 (0.52, 1.21) |
| III vs. IV | **0.83, (0.62, 1.10)** | | 0.76 (0.49, 1.18) | 0.78 (0.51, 1.21) | 0.87 (0.60, 1.27) | 0.97 (0.66, 1.43) |
| Prior Amnioreduction, Y vs. N | **1.44 (1.23, 1.70)** *** | NS | **1.66 (1.29, 2.14)** *** | **1.43 (1.09, 1.88)** * | **1.32 (1.06, 1.63)** * | NS |
| Prior Preterm Birth, Y vs. N | **1.45 (1.09, 1.92)** * | **1.57 (1.18, 2.09)** * | **1.93 (1.29, 2.88)** * | **1.94 (1.27, 2.96)** * | 1.15 (0.77, 1.72) | NS |
| Cerclage, Y vs. N | **3.11 (2.24, 4.31)** *** | **2.09 (1.50, 2.91)** *** | **2.74 (1.58, 4.74)** ** | **1.83 (1.04, 3.19)** * | **3.36 (2.23, 5.05)** *** | **2.38 (1.56, 3.63)** *** |
| Procedure Complications, Y vs. N | 1.18 (0.99, 1.42) | **1.27 (1.06, 1.52)** * | 1.08 (0.80, 1.46) | NS | **1.25 (1.01, 1.56)** * | NS |
| Interwin Membrane Disruption, Y vs. N | **1.31 (1.01, 1.69)** * | NS | **1.55 (1.05, 2.28)** * | **1.71 (1.14, 2.54)** * | 1.16 (0.82, 1.63) | NS |
| Choriamniotic Membrane Separation, Y vs. N | **1.26 (1.05, 1.53)** * | **1.48 (1.22, 1.80)** *** | 1.20 (0.88, 1.64) | NS | **1.30 (1.02, 1.65)** * | **1.44 (1.13, 1.85)** * |

* <.05

** <.001

*** <.0001

Taking multivariable modeling for spontaneous delivery, examples of interpretation of the direction of effect are as follows:

For each week later in diagnosis of TTTS, the hazard of having a shorter latency increases by 23% after adjusting for other covariates.

For TTTS stage comparison, the hazard of having a shorter latency for TTTS stage I is 1.56 times higher (with 95% confidence interval of (1.04, 2.42)) than TTTS stage II, while the hazard of having shorter latency for those with TTTS stage II is 0.56 times that of Stage III (with 95% confidence interval of (0.35, 0.95)) after controlling for other covariates.

The hazard of having shorter latency for patients who had a prior amnioreduction is 1.43 times higher than patients who did not have a prior amnioreduction before treatment after controlling for other covariates.