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Risk Factors Associated with Preterm Delivery after Fetoscopic Laser Surgery for Twin Twin Transfusion Syndrome

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Abstract

OBJECTIVE—Despite improved perinatal survival following fetoscopic laser surgery (FLS) for twin twin transfusion syndrome (TTTS), prematurity remains an important contributor to perinatal mortality and morbidity. The objective of the study was to identify risk factors for complicated preterm delivery after FLS.

STUDY DESIGN—Retrospective cohort study of prospectively collected data on maternal/fetal demographics and pre-operative, operative and post-operative variables of 459 patients treated in 3 U.S. fetal centers. Multivariate linear regression was performed to identify significant risk factors associated with preterm delivery, which was cross-validated using *K-fold* method. Multivariate logistic regression was performed to identify risk factors for early vs. late preterm delivery based on median gestational age at delivery of 32 weeks.

RESULTS—There were significant differences in case selection and outcomes between the centers. After controlling for the center of surgery, a multivariate analysis indicated a lower maternal age at procedure, history of previous prematurity, shortened cervical length, use of amnioinfusion, 12 Fr cannula diameter, lack of a collagen plug placement and iatrogenic preterm

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premature rupture of membranes (iPPROM) were significantly associated with a lower gestational age at delivery.

CONCLUSION—Specific fetal/maternal and operative variables are associated with preterm delivery after FLS for the treatment of TTTS. Further studies to modify some of these variables may decrease the perinatal morbidity after laser therapy.

Keywords

preterm delivery; predictors; twin-twin transfusion syndrome; laser photocoagulation; fetoscopy

Introduction

Twin twin transfusion syndrome (TTTS) affects approximately 10% of monochorionic diamniotic twin gestations. Fetoscopic laser surgery (FLS) has become the standard treatment for severe TTTS.[1] However, preterm delivery continues to be a challenge and determines perinatal survival and morbidity.[2–4] The average gestational age at delivery ranges from 29 weeks to 33 weeks with a wide variation between centers.[1, 5] European centers have reported a higher average gestational age at delivery compared to North American centers.[1, 5–7] Besides the obvious cost of caring for the premature infants, preterm delivery (PTD) is directly associated with long-term neurological deficit.[48] Differences in gestational age at delivery at different centers may be attributed to experience, case selection, patient population or other factors. Yet, there is a limited understanding of the risk factors for preterm delivery after FLS. The only pre-operative factor that has been associated with PTD is cervical shortening.[2, 9] However, the weakness of these studies was either a small sample size or variations in cerclage placement. There are no studies to date examining operative variables as a risk for preterm delivery after FLS. Post-operative variables such as chorioamnion separation and associated iatrogenic preterm premature rupture of membranes (iPPROM) significantly reduce the gestational age at delivery after FLS.[10, 11] Other preoperative factors such as maternal age, tobacco use, gestational age at procedure and stage of disease, and operative factors such as type of anesthesia, trocar size and amnioinfusion have not been evaluated as risk factors for PTD. Understanding these risk factors would be the first step in considering modifications that might help prolong these pregnancies.

The objective of this study was to evaluate various risk factors for preterm delivery after FLS in the treatment of TTTS.

Materials and Methods

This was a retrospective cohort study of prospectively collected data from three fetal treatment programs from United States. The study was approved by the institutional review boards of all participating institutions (Baylor College of Medicine, Houston, TX, University of Texas Health Science Center, Houston, TX, The Children's Hospital of Philadephia, Philadelphia, PA, and University of Maryland, Baltimore, MD). The data from the two centers (Baylor College of Medicine and University of Texas Health Science Center) were merged in the study as one center. The primary surgeons (AJ and KJM) moved from the former center to the nearby latter center during the study period. The important commonalities such as referral base, the patient selection and surgical protocol remained the same after translocation.

Briefly, patients with TTTS who were referred to a fetal center underwent a comprehensive ultrasound examination, including Doppler studies for diagnosis and staging based on the Quintero system, performed by registered medical diagnostic sonographers supervised by experienced fetal medicine specialists. [12] Fetoscopic laser ablation was performed through a single-port fetoscopy under either local anesthetic in conjunction with intravenous sedation or regional or general anesthesia. The placental vascular equator was identified, and a neodymium-yttrium aluminum garnet (Nd-YAG) or diode laser used to ablate all vascular anastomoses using a selective method. In some cases amnioinfusion for improving the visualization was performed using Ringer's lactate solution or normal saline solution. All patients returned to their referring physicians for follow-up for the remainder of the pregnancy. Information about pregnancy outcomes was collected prospectively from the patients or the referring physicians as a part of follow-up care. Study data from all centers were de-identified and transferred to the investigator (R.P.) at the primary data center, where it was stored on a secure digital drive.

Exclusion criteria included triplet gestations and cases of selective reduction for a failed laser attempt. The following pre-operative variables were collected: maternal demographics (age, parity, previous preterm deliveries, smoking), staging using Quintero criteria and cervical length (measured transvaginally). Operative variables included type of anesthesia, cannula diameter for the trocar entry, entry method (Seldinger's[13] vs. direct entry with a sharp trocar) and volume of amnioinfusion. Post-operative variables included iPPROM (defined as clinical confirmation of rupture of membranes by positive pooling, nitrazine test and ferning prior to 34 weeks gestation), gestational age at delivery and live birth rate. Descriptive statistics were used appropriately for the distribution within the sample. The data for preoperative, intraoperative and postoperative variables were extracted and the analysis was performed using STATA 12.1 (StataCorp.; College Station, TX). Univariate analysis was performed as necessary using the following methods. Parameters were compared using the χ^2 test for categorical variables; the Fisher exact test was used when an expected frequency was less than five. The Mann-Whitney U test was used to compare non-parametric continuous variables. An unpaired t-test was performed for continuous variables which satisfied the criteria for normal distribution by histogram, kurtosis, skewness and Shapiro-Wilk test. If the data did not satisfy the criteria for normality, non-parametric analysis was performed. Multivariate linear regression was performed to evaluate potential independent predictors of gestational age at birth, the dependent variable.

Multivariate logistic regression was performed to evaluate the preterm delivery as a binary outcome based on the median gestational age at birth: early preterm delivery (≤32 weeks gestation) vs. late preterm delivery (> 32 weeks). Categorical variables were separated as individual variables. For example, the 4 stages of were divided into 4 binary variables, 3 treatment centers were into 3 binary variables, and the 3 cannula sized were divided into 3 variables. It resulted in a total of 25 independent variables. All variables were tested for inclusion with conventional regression model, followed by stepwise forward and backward process with p-value set at <0.1. In the final model, only the variables that were significant with p<0.05 were included. The assumptions for multivariate linear regression were tested including Shapiro- Wilk W test for normality of residuals, collinearity, Cook- Weisberg test for heteroscadasticity, and outliers in the predicted outcomes. The findings were internally cross- validated using *k-fold* x 10 method. The mean standard error and general trend in the co-efficients within each fold were evaluated. Additionally, a multivariate Cox proportional hazard model was conducted on the significant factors from both previous analyses and the assumptions were tested. There was less than 1% of the participants had missing data. Thus, no missing data imputation technique was adopted. Statistical significance was defined as a two-sided p value <0.05 for all analysis.

The sample size for the study was calculated using PASS 11 Statistical software (NCSS, LLC; Kaysville, UT, USA). Since, there were no prior studies on which to base calculations; conservative estimates were used for the sample size calculation. A sample size of 352 patient was required to achieve 90% power to detect an R^2 (multivariate linear regression) of 0.1 attributed to 25 independent variable(s) using an F-Test with a significance level (alpha) of 0.01.

Results

A total of 487 patients had FLS for TTTS during the study period. We excluded 16 triplet pregnancies and 12 pregnancies who underwent selective reduction due to failed laser surgery. A total of 459 patients were included in the study. The mean maternal age was 29.5 ± 6.2 years, while the median gravidity was 2 (range: 0 – 8) and the median parity was 1 (0 – 6). The mean BMI was 24.8 ± 8 Kg/m^2. Tobacco use was reported by 13% of the patients; 5% were noted to have a history of a previous preterm delivery. The mean gestational age at the time of laser was 145.6 ± 15.7 days. Ultrasound evaluation revealed a distribution of Quintero staging as follows; Stage I: 8%, Stage II: 39%, Stage III: 48%, and Stage IV: 5%. The mean cervical length was 36.3 ± 11.1 mm.

Regarding operative variables, cannula diameter distribution was 9F: 3%, 10F: 63% and 12F: 34%. The operative cannula was placed with a direct entry method in 30% of cases and a Seldinger method in the remaining cases. An amnioinfusion was used during the procedure in 41% of cases [median: 0 ml; quartile (25%–75%): 0 – 600 ml; range: 0– 6200 ml]. A Solomon laser method was employed in 44% of cases and a collagen plug was placed upon withdrawl of the operative cannula in 20% of cases.

The mean (± SD) gestational age at birth was 31.2 ± 4.9 weeks. 234 patients (51% delivered at or prior to 32 weeks gestation. iPPROM occurred in 147 patients (32%). The procedure-to-delivery interval was 73 ± 37.3 (mean ± SD) days. The total live births of 0, 1 and 2 fetuses were 35 (8%), 95 (20%) and 329 (72%), respectively. The differences in the case selection and surgical methods between the centers are illustrated in Table 1.

On multivariate linear regression, after controlling for the fetal center, followed by final regression analysis, the maternal age, history of prematurity, pre-operative cervical length, Stage 2 TTTS, cannula diameter of 12 Fr, amnioinfusion and placement of collagen plug, and iPPROM were significantly associated with gestational age at delivery (Table 2). By removing iPPROM from the analysis, the proportion of the total variability of the primary outcome that was described by the model changed from an R^2 value of 0.21 to 0.15, with minimal change in the co-efficient of other significant co-variates. The model satisfied all the assumptions for a multivariate linear regression, except for normality by Shapiro-Wilk W test for the residuals. Therefore, a robust regression was performed and the results were similar to the non-robust analysis (R^2= 0.21; F= 20.7; p<0.0001; root mean square error=30.5). On an internal *k*-fold cross-validation with 10 fold of the analysis, the results were consistent in all the folds, and the average (±SD) root mean square error was 30.2 (± 2.1). On a multivariate logistic regression model, maternal age, history of prematurity, TTTS Stage 2, cannula diameter of 12 Fr, amnioinfusion, collagen plug placement and iPPROM were significantly associated with early preterm delivery (Table 3). In a multivariate Cox proportional hazard regression model, history of preterm delivery, cervical length, cannula diameter 12 Fr, amnioinfusion, collagen plug placement, and iPPROM were significantly associated with gestational age at delivery (Table 4).

Discussion

The current multicenter cohort study investigated the potential role of multiple pre- and intraoperative factors in predicting the gestational age at delivery after FLS, including evaluating the effect of treatment center on the outcome. A younger maternal age, a history of previous prematurity, stage II TTTS, decreased cervical length, use of a 12F cannula, use of amnioinfusion and non-use of a collagen plug were all associated with a decreased gestational age at delivery. Using different regression models, the study was able to clearly demonstrate an association between different independent variables with the outcome variable. The model was able to predict 21% of the total variability of the gestational age at birth using the known preoperative, operative variables and iPPROM.

There were notable differences found in patient selection criteria, study population demographics (data not shown) and surgical methodologies among the 3 fetal centers. Although, there was a significant difference in the gestational age at delivery between the centers in the univariate analysis, in the multivariate analysis the center was not statistically significant factor after controlling for the other factors. One of the strengths of our investigation is that it points to some of the demographic factors that will be have to be taken into account to “risk adjust” any reported outcomes.

Advancing maternal age had a protective effective on the gestational age delivery after FLS. This is a novel finding in relation to the latency period after FLS. One possible explanation could be a better coping style and social support in the older pregnant woman. A similar protective effect has been previously reported to the prolong the latency period after spontaneous PPROM. [14–16] A history of prematurity in the prior pregnancy was significantly associated with earlier delivery after FLS. This is consistent with the prior knowledge of an increased recurrent risk for preterm delivery.[17] Stage II disease, which is absence of donor bladder with normal Doppler studies in both fetuses, prolonged the pregnancy. One of the possible explanation for longer pregnancy after FLS in stage II disease compared to stage I is that FLS is usually offered to stage I patients who have a short cervix or symptomatic from severe polyhydramnios, which may independently play a role in early delivery. Whereas in Stage III and IV, where there is an existing cardivascular manifestation of the disease, which may play a role in early delivery after FLS. This needs to be further investigated. A pre-operative short cervical length was a significant factor in decreasing the gestational age at birth. This adds further support to this association reported in previous studies, irrespective of the placement of a cerclage. [2, 9, 18]

The increased outer diameter of the operative cannula to 12 F was associated with an earlier gestation age at delivery and a higher rate of iPPROM. The corresponding iPPROM rates for 9Fr, 10Fr and 12 Fr cannulas were 15%, 27% and 42%, respectively (p=0.002). A possible explanation for the increasing rate of iPPROM rates with increasing cannula diameter is the non-healing nature of fetal membrane.[19] The advantage of using a larger cannula diameter, 12 Fr, is to accommodate different scopes for diffucult cases. For example, a 3.0-mm 0° rod lens (Richard Wolf Medical Instruments Corporation; Vernon Hills, IL, USA) fetoscope allows for better visualization of placental anastomoses as compared to non-rod lenses and has the advantage of its length in cases of extreme polyhydramnios, or a 2.0-mm 30° rod lens fetoscope (Karl Storz GmbH, Tuttlingen, Germany) that incoporates an Albarran mechanism that is used to deflect the laser fiber upwards in patients with anterior placentation.

Better visualization using larger diameter fetoscopes results in a lower rate of “failed laser”. This is an important outcome, because recurrent TTTS after laser therapy has a dismal prognosis with few effective treatments.[20] Thus, the use of a larger cannula must be balanced against the higher risk for early delivery after the procedure.

Surprisingly, amnioinfusion increased the risk for preterm delivery. Amnioinfusion is typically employed during FLS due to poor visibility from debris or bleeding or the need for restoration of the amniotic fluid volume of intraperitoneal loss of fluid occurs during the procedure. These factors in themselves may contribute to an increased risk for preterm delivery. Another possible hypothesis is that the amnioinfusion replaces the normal amniotic fluid and dilutes the proteins and other nutrients that the amniotic membrane depends on for its survival through endocytosis.[21, 22] The alteration of the normal amniotic fluid environment may cause membrane damage, leading iPPROM and preterm birth.

Use of a collagen plug prolonged the pregnancy duration. Although, on a subgroup analysis there was no difference in iPPROM rates between with or without collagen plug placement (39% vs. 32%, respectively; p=0.42), which needs futher investigation. Finally, iPPROM reduced the gestational age by 3 weeks; 32.2 ± 5 weeks vs. 29.2 ± 4 weeks (p<0.0001). After controlling for other significant covariates, it reduced the pregnancy duration by 18 days. iPPROM had the most significant effect on the gestational age at birth: 80% of those who had iPPROM delivered within 10 days. This is in consistent with our previous published finding of 2– 3 week shorter pregnancy interval after iPPROM.[11]

The strength of our study is that we included a large population of patients from three different yet experienced fetal centers. This allowed us to compare a variety of pre and intraoperative variables on the outcome of gestational age at delivery. We included 25 pre-and operative variables into our model to predict the gestational age at delivery. There are some limitations to our study. Spontaneous vs indicated preterm delivery was not assessed.. In addition, other intra-operative variables that may have contributed to the primary outcome such as turbidity of fluid, complexity and duration of the procedure, intra-operative complications (septostomy, intramniotic bleeding and chorioamnion separation), and acute fetal demise were not always recorded in the databases of the fetal centers and therefore were not included in the model.

Conclusion

In conclusion, while the advancing maternal age and placement of a collagen plug during FLS prolonged the gestational age at delivery, a history of prematurity, cervical length shortening, amnioinfusion, larger operating cannula and iPPROM shortened the duration of pregnancy. In spite of significant variations between centers in case selection and operative methods, several variables are strong predictors of early delivery. Understanding of these significant factors will aid in the counseling patients and should guide future research. Future research should focus on refinements of operative technology to allow for smaller diameter cannulas to be used. Intra-operative methods to seal the iatrogenic entry site into the amniotic cavity should be developed. The role of pessary for the short cervix in cases of TTTS also deserves further investigation.[23]

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Table 1

Laser candidates and methodology by Center

Parameter	Center 1	Center 2	Center 3
Candidate stages for laser	I – IV	II – IV	I – IV
Cannula size used			
9F			√
10F	√	√	√
12F	√		√
Entry method			
Direct	√		√
Seldinger	√	√	
Solomon technique	√		√
Collagen plug placement	√		

Table 2

Results from the multivariable linear regression model evaluating the association between the gestational age at birth and independent variables.

All co-variates included			Selected co-variates			
	Co-efficient (Std. Err)	p-value	Stepwise forward and backward (p<0.1) R^2= 0.24; P<0.0001		*Final included variables R^2= 0.21; p<0.0001*	
Maternal demographics R^2 = 0.257; P<0.0001, F=9.98			Co-efficient (Std. Err)	p-value	*Co-efficient (Std. Err)*	*p-value*
Constant	184 (23)	<0.0001	**196 (8.6)**	**<0.001**	***195 (8.4)***	***<0.001***
Maternal age (years)	0.80 (0.26)	0.002	**0.8 (0.25)**	**0.001**	***0.72 (0.2)***	***0.003***
Gravidity	−2 (1.07)	0.06	− 2.02 (1)	0.06	-	-
History of prematurity	−14.6 (7)	0.036	**−13 (6.8)**	**0.047**	***−16.3 (6.8)***	***0.02***
BMI	−0.15 (0.2)	0.47	-	-	-	-
History of tobacco use	2.68 (4.5)	0.59	-	-	-	-
Gestational age at procedure	0.08 (0.1)	0.4	-	-	-	-
Fetal growth discordance	−0.056 (0.11)	0.62	-	-	-	-
Anterior placenta	−2.3 (3.2)	0.48	-	-	-	-
Stage 2	12.3 (6.2)	0.05	**9.3 (3)**	**0.002**	***7.4 (3)***	***0.02***
Stage 3	3.8 (6)	0.5	-	-	-	-
Stage 4	−0.37 (8.6)	0.97	-	-	-	-
Cervical length	0.35 (0.15)	0.02	**0.36 (0.14)**	**0.008**	***0.34 (0.14)***	***0.01***
Cerclage	−0.97 (9.1)	0.92	-	-	-	-
Center 2	17.7 (9.1)	0.05	-	-	-	-
Center 3	0.38 (9.4)	0.97	-	-	-	-
Cannula 10Fr	−12 (10)	0.23	-	-	-	-
Cannula 12Fr	−17 (7)	0.02	**−14 (4.1)**	**0.001**	***−10.7 (4)***	***0.01***
Amnioinfusion	−9.1 (4.3)	0.036	**−10.8 (3.8)**	**0.004**	***−13.1 (3.5)***	***<0.001***
Trocar entry (direct)	−4 (6.1)	0.5	-	-	-	-
Collagen plug	17.9 (5.8)	0.002	**15.2 (4.7)**	**0.001**	***11.4 (4.7)***	***0.02***
Solomon technique	6.9 (5.2)	0.19	-	-	-	-
iPPROM	−19.5 (3.2)	<0.0001	**−18.9 (3.1)**	**<0.001**	***−18 (3.1)***	***<0.0001***

Note: Stage 1, Center #1 and Cannula 9Fr were omitted in the regression due to collinearity with their respective co- categorical variables; iPPROM- iatrogenic preterm premature rupture of membranes, BMI- Body mass index (Kg/m^2); Fr- French

Table 3

Results from the univariate and multivariable logistic regression model evaluating the association between early vs. late preterm delivery and independent variables.

	Early preterm delivery (≤ 32 weeks)	Late preterm delivery (>32 weeks)	p-value	Multivariate logistic regression (Odds ratio (95% CI))	
				All covariates included	Only significant factors after stepwise forward and backward process
	234 (51%)	225 (49%)		*χ^2 =148; p<0.0001*	*χ^2 =127; p<0.0001*
Maternal age (years)	28.7 ± 6.1	30.4 ± 6.2	**0.003**	**0.94 (0.9–0.98)**	**0.94 (0.9 –0.98)**
Gravida	2 (1–7)	2 (1–8)	0.78	1.1 (0.94 – 1.3)	-
History of prematurity	18 (8%)	4 (2%)	**0.004**	**5.2 (1.5 – 18)**	**4.5 (1.4 – 15)**
BMI (Kg/m^2)	25.8 ± 7.9	23.7 ± 7.9	**0.006**	1.0 (0.97–1.04)	-
TTTS Stage 1	21 (9%)	14 (6%)	0.27	Collinear	-
TTTS Stage 2	68 (29%)	114 (51%)	**<0.0001**	**0.21 (0.07– 0.58)**	**0.4 (0.25 – 0.64)**
TTTS Stage 3	132 (56%)	86 (38%)	**<0.0001**	0.53 (0.2 – 1.4)	-
TTTS Stage 4	14 (6%)	11 (5%)	0.75	0.38 (0.1 – 1.5)	-
Cervical length (mm)	33.9 ± 12	36.9 ± 12	**0.01**	**0.98 (0.96 – 1)**	-
Anterior placenta	100 (43%)	83 (37%)	0.18	1 (0.63 – 1.7)	-
Center #1	106 (45%)	47 (21%)	**<0.0001**	Collinear	-
Center #2	84 (36%)	127 (56%)	**<0.0001**	**0.14 (0.03–0.57)**	-
Center #3	44 (19%)	51 (23%)	0.3	0.9 (0.2 – 4.2)	-
Cannula diameter 9 Fr	4 (2%)	9 (4%)	0.02	Collinear	-
Cannula diameter 10 Fr	123 (53%)	164 (73%)	**0.001**	4.1 (0.82 – 20.7)	-
Cannula diameter 12 Fr	107 (46%)	52 (23%)	**<0.0001**	**5.3 (1.73 – 16)**	**3 (1.6 – 5.7)**
Trocar entry Seldinger's type	74 (32%)	64 (28%)	0.44	1.5 (0.56 – 3.9)	-
Amnioinfusion	125 (54%)	61 (28%)	**<0.0001**	**1.9 (1 – 3.6)**	**2.3 (1.4 –3.9)**
Solomon technique	117 (51%)	79 (35%)	**0.003**	**0.42 (0.2 – 0.94)**	-
Collagen plug placement	60 (26%)	33 (15%)	**0.003**	**0.2 (0.07 – 0.56)**	**0.34 (0.16 – 0.74)**
Cerclage placement	9 (4%)	6 (3%)	0.48	0.9 (0.2 – 4.2)	-
iPPROM n (%)	110 (47%)	17 (16%)	**<0.0001**	**6.4 (3.8 – 10.8)**	**5.8 (3.5 – 9.6)**

Numbers are expressed as n(%), mean ± SD. BMI- Body mass index (Kg/m^2); TTTS- Twin twin transfusion syndrome; iPPROM- iatrogenic preterm premature rupture of membranes, Fr- French; CI- Confidence interval.

Table 4

Results from the Cox proportional hazards regression analyses predicting gestational age at birth from significant factors from multivariate regression analysis. (χ^2 = 118; p<0.0001)

	Hazard ratio	**95% Confidence interval**	**p-value**
Maternal age (years)	0.98	0.97 –1	0.1
History of prematurity	1.7	1.11– 2.91	**0.015**
Cervical length	0.98	0.98–0.997	**0.004**
Stage 2 TTTS	0.88	0.73 – 1.07	0.21
Cannula 12 Fr	1.33	1.01 – 1.74	**0.04**
Amnioinfusion	1.5	1.2 – 1.9	**<0.0001**
Collagen plug	0.69	0.5 – 0.94	**0.02**
iPPROM	2.42	1.93 – 3.03	**<0.0001**