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Comparison of Twin-to-Twin Transfusion Syndrome and Without Selective Fetal Growth Restriction Before Fetoscopic Laser Photocoagulation in Iran

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Authors
Dehghani Z.[1] *BC*
Rasekhi A.A.[1*] *PhD*
Marsoosi V.[2] *MD*
Mohammadi S.[3] *MD*

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[1]Department of Biostatistics, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran
[2]Department of Obstetrics and Gynecology, Dr. Ali Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Obstetrics and Gynecology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

***Correspondence**
Address: Department of Biostatistics, Faculty of Medical Sciences, Tarbiat Modares University, Jalal Al-e Ahmad, Tehran, Iran. Postal Code: 1411713116
Phone: +98 (21) 82884524
Fax: +98 (21) 82884524
rasekhi@modares.ac.ir

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ABSTRACT

Aims This study compared two groups of twin pregnancies complicated by twin-to-twin transfusion syndrome (TTTS), with and without selective fetal growth restriction (sFGR), and evaluated the survival rate at 30 days after birth treated with fetoscopic laser photocoagulation (FLP).

Materials & Methods The present study was a retrospective study of 164 diamniotic monochorionic twin pregnancies complicated with TTTS and treated with FLP. The sFGR was defined as an estimated fetal weight below the 10th percentile. The independent t-test, Chi-square test, or Fisher's exact test were used for statistical analysis. Multiple logistic regression analysis was performed to identify 30-day donor twin survival risk factors for the entire study population. The significance level was determined at $p<0.05$.

Findings Of the studied cases, 45.1% had only TTTS, while 54.9% had both TTTS and sFGR. There was a significant difference ($p<0.001$) in the distribution of Quintero stages and maternal age during the intervention ($p=0.01$) between the two groups. The sFGR before laser surgery in TTTS patients was associated with reduced donor survival. The multivariate analysis revealed that gestational age at delivery (OR=0.81, 95%CI:0.7-0.8) and sFGR (OR=0.43, 95%CI:0.2-0.8) were significantly associated with donor survival.

Conclusion The sFGR before FLP is present in approximately 55% of TTTS cases, which is caused by normal placental abnormalities. TTTS with sFGR is associated with reduced donor embryo survival. Gestational age at delivery and sFGR are important factors affecting donor survival 30 days after birth. Performing successive ultrasounds after diagnosing monochorionic twin pregnancies is essential for timely identification, correct management, and treatment.

Keywords Twins; Fetal Development; Blood transfusion; Lasers

CITATION LINKS

[1] Twin ... [2] Maternal hypotension during fetoscopic surgery: Incidence and its impact on fetal ... [3] Twin-to-twin transfusion syndrome: Controversies in the ... [4] Fetal medicine: Intrauterine fetal demise following laser treatment in ... [5] Twin-to-twin transfusion syndrome: prenatal ... [6] Influence of chorionicity and gestational age at single fetal loss on risk of preterm birth in twin pregnancy: analysis of ... [7] Solomon technique vs selective fetoscopic laser photocoagulation for twin-twin transfusion syndrome: Systematic review and ... [8] Selective intrauterine growth restriction in ... [9] Outcome of monochorionic twin pregnancy complicated by Type-III selective ... [10] The world of twins: an ... [11] Fetoscopic laser photocoagulation for twin–twin ... [12] Fetoscopic laser coagulation in 1020 pregnancies with twin–twin transfusion syndrome demonstrates improvement ... [13] Outcome after fetoscopic selective laser ablation of placental anastomoses vs equatorial laser dichorionization for the treatment ... [14] Molecular mechanisms underlying twin-to-twin ... [15] Perinatal survival in cases of twin–twin transfusion syndrome complicated by selective intrauterine ... [16] Outcome of monochorionic twin pregnancy with selective intrauterine growth restriction according to umbilical artery Doppler flow pattern of smalle ... [17] Twin-twin transfusion syndrome with and without selective fetal growth ... [18] 189: Perinatal survival in cases of twin-twin transfusion syndrome complicated by selective ... [19] Polyhydramnios: causes, diagnosis and ... [20] Staging of twin-twin transfusion ... [21] Impact of selective fetal growth restriction on laser therapy outcomes in ... [22] Fetal growth restriction in ... [23] Outcome of monochorionic twin pregnancy with selective fetal growth restriction at 16, 20 or 30 weeks ... [24] Outcome following laser surgery of twin–twin transfusion syndrome complicated by selective fetal growth ... [25] Comparison of prenatal and neonatal outcomes of selective fetal growth restriction in monochorionic twin pregnancies ...

Introduction

Twin pregnancies account for approximately 2-3% of all live births, 6.3% of stillbirths, and 12.7% of infant deaths. Complications of monochorionic twin pregnancy (monochorionic twins share a placenta) include selective fetal growth restriction (sFGR), twin-to-twin transfusion syndrome (TTTS), premature delivery, and high perinatal risks [1].

TTTS is a disorder caused by an imbalance in the blood flow between fetuses that share a single placenta. This condition can cause one embryo to dominate among other embryos. TTTS is a progressive condition that usually occurs between 16 and 26 weeks of gestation, affecting approximately 10-15% of all monochorionic pregnancies and becoming more severe if untreated. The Quintero *et al.*'s method is commonly used to stage disease severity [2-4]. Perinatal complications and mortality in monochorionic pregnancies with TTTS increase by 10-15% [5-7].

Selective fetal growth restriction (sFGR), also called selective intrauterine growth restriction (sIUGR), is a complication of monochorionic twin pregnancies. SFGR occurs when the placenta is unequally shared between twins, causing one of the twins to grow less than normal. In these cases, the estimated weight of the growth-restricted twin fetus usually reaches below the 10th percentile.

This usually results in more than 25% weight difference between twins. Approximately 20% of monochorionic pregnancies are associated with FGR. Early severe FGR complications are associated with intrauterine death or adverse neurologic outcomes for either twin [8-10]. Fetoscopic laser photocoagulation (FLP) is the most common and successful fetal intervention developed as the initial treatment for monochorionic twin pregnancy with TTTS. This procedure eliminates placental vessel anastomoses to treat TTTS [11]. Advances in FLP have contributed to significant improvements in perinatal survival in TTTS [12-14].

Both TTTS and FGR are common complications of monochorionic twin pregnancy. FGR complicates more than one-third of TTTS cases.

The statistical methods used in some previous similar studies include the Chi-square test or Fisher's exact test, Mann-Whitney U test or Student's t-test, one-way ANOVA, or Kruskal-Wallis test. The survival rate of each twin after laser surgery in pregnancies with TTTS+sFGR is lower than in pregnancies with only TTTS [15-18]. An abnormal increase in amniotic fluid volume is called polyhydramnios, which is associated with increased mortality [19]. Also, sFGR involves more than one-third of TTTS cases.

This study aimed to evaluate survival 30 days after birth and compare the TTTS and TTTS+sFGR groups that were treated with FLP. Here, for the first time in Iran, we compared TTTS+sFGR and TTTS-only in monochorionic twins.

Materials and Methods

Study Population

The present comparative cross-sectional study was done on 164 expectant mothers with monochorionic twin pregnancies with TTTS complications who were introduced to the medical center of Shariati Hospital in Tehran from January 2017 to May 2023 and were treated with FLP. It is the national reference center of FLP in Iran.

Inclusion and Exclusion Criteria

The inclusion criteria were pregnant women with twin pregnancies between 16 and 26 weeks of TTTS complications who were referred to this center for treatment by medical centers and specialist doctors in their city of residence. All patients underwent surgery. Monochorionic triplets were excluded from the study. Considering that the participants went to their city centers 48 hours after the laser, despite the follow-ups before and after the laser and delivery, some information remained incomplete and only 164 patients were eligible for analysis. Written informed consent was obtained from all patients before performing FLP.

Data Gathering and Treatment

The severity of the disease was determined using the Quintero staging method [20]. Due to the low observation in stages 1 and 4, we considered Quintero stages 1 and 2 as stage 1 and Quintero stages 3 and 4 as stage 2. Patients were divided into two groups: TTTS+sFGR and only TTTS. The TTTS+sFGR group was defined as TTTS patients with donor twin weight less than the 10th percentile before laser surgery.

The specialists of this center identified the abnormal vascular connections of the placenta and removed them using special medical technologies through a laser with an intrauterine photoscope. This operation was performed in the operating room with local anesthesia and sedation.

Amniotic fluid volume around the fetus, placenta position, cervical length, cerclage performed or not, the number of lasered placental anastomoses, gestational age (GA) at the time of intervention, GA at delivery, 30-day survival after birth, recipient survival, and donor survival were recorded and outcomes were compared and evaluated between the TTTS-only and TTTS+sFGR groups.

Statistical Analysis

Quantitative variables were displayed as mean and standard deviation and categorical variables were displayed as frequency and percentage. An independent t-test was used to analyze numerical data, and the Chi-square and Fisher's exact tests were used for categorical data. Multiple logistic regression analysis was performed to identify risk factors for 30-day donor twin survival. At First, univariate analysis was performed and only variables with a p-value less than 0.10 were entered in the multiple regression model. The odds ratio (OR) index with a 95%

confidence interval was used to show the relationship between independent variables and fetal survival. In all tests, p-values less than 0.05 were considered significant.

Findings

Of 164 patients, 45.1% (74 cases) were classified as TTTS and 54.9% (90 cases) as TTTS+sFGR.

Tables 1 and 2 present the demographic and clinical characteristics and 30-day postnatal survival for TTTS+sFGR and TTTS-only patients.

Table 1. The frequency of baseline maternal and neonatal characteristics and survival rate 30 days after birth in the TTTS+sFGR (Selective Fetal Growth Restriction) and TTTS (Twin-Twin Transfusion Syndrome) groups

Parameter	TTTS+sFGR (n=90)	TTTS (n=74)	p-Value
Placenta orientation			
Anterior	37 (41.1)	34 (45.9)	0.5
Others	53 (58.9)	40 (54.1)	
Cerclage placement			
Yes	8 (8.9)	10 (13.5)	0.3
No	82 (91.1)	64 (86.5)	
Quintero stage			
Stage I	17 (18.9)	39 (52.7)	<0.001
Stage II	73 (81.1)	35 (47.3)	
Polyhydramnios			
Yes	86 (95.6)	68 (91.9)	0.3
No	4 (4.4)	6 (8.1)	
Survival 30 days after birth			
No survivor	31 (34.4)	21 (28.4)	0.3
One survivor	31 (34.4)	21 (28.4)	
Two survivors	28 (31.1)	32 (43.2)	
Donor survival	29 (32.2)	37 (48.6)	0.04
Recipient survival	57 (63.3)	47 (63.5)	0.9
Double survival	31 (34.4)	32 (43.2)	0.1
At least one survivor	62 (68.9)	53 (71.6)	0.4

The TTTS+sFGR group mainly included stages 3 and 4 (81.1%), while the TTTS group mainly included stages 1 and 2 (52.7%). A significant difference (p<0.001) was observed in the Quintero stages between the two groups. There was a significant difference in maternal age during the intervention (p=0.01) between the TTTS+sFGR and TTTS groups, with an average age of 28.9±5.3 weeks and 31±5 weeks, respectively.

Table 2. Mean of baseline maternal characteristics of the TTTS+sFGR (Selective Fetal Growth Restriction) and TTTS (Twin-Twin Transfusion Syndrome) groups

Parameter	TTTS+sFGR (n=90)	TTTS (n=74)	t	df	p-Value
Maternal age at operation (year)	28.9±5.3	31.0±5.0	-2.62	162	0.01
GA intervention (week)	21.3±2.2	21.2±2.5	0.37	162	0.7
GA at delivery (week)	31.8±6.0	31.7±4.8	0.20	162	0.8
Anastomoses (number)	38.3±22.7	33.6±21.6	1.33	162	0.1
Pre-op cervical length (cm)	31.8±9.1	31.4±7.9	0.17	162	0.8

The mean GA at delivery was 31.8±4.9 and 31.7±4.8 weeks in the c, respectively (p=0.1).

Table 1 compares the survival rate 30 days after birth between the TTTS and TTTS+sFGR groups. Double survival was higher in the TTTS group (43.2%) compared to the TTTS+sFGR group (31.1%; p=0.1). The survival of at least one infant in the two groups was almost similar (71.6% and 65.6% for the TTTS and TTTS+sFGR groups, respectively).

The survival of the recipient twin was not different between the groups (p=0.9), but the survival of the donor embryo was 32.2% in the TTTS+sFGR group and 48.6% in the TTTS group, and there was a significant difference between the two groups (p=0.04).

Univariate logistic regression analysis indicated that GA at delivery and sFGR were important factors; hence, they were included in the model (Table 3).

Table 3. Univariate and multiple logistic regression of factors affecting the donor survival at 30 days after birth

Parameter	Coeff.	SD	OR	95% CI	p-Value
Placenta orientation					
Anterior	Ref	0.3	1.09	0.58-2.05	0.7
Others	0.08				
Cerclage placement					
Yes	Ref	0.51	0.96	0.3-2.6	0.94
No	-0.03				
Quintero stage					
Stage I	Ref	0.33	0.97	0.5-1.8	0.94
Stage II	-0.02				
Polyhydramnios					
Yes	Ref	1.06	4.45	0.54-36.1	0.16
No	1.49				
Selective fetal growth restriction (sFGR)					
Yes	Ref	0.32	0.50	0.26-0.9	0.03
No	0.68				
Gestational age at intervention (weeks)	-0.04	0.06	0.95	0.8-1	0.5
Gestational age at delivery (weeks)	-0.19	0.04	0.82	0.7-9.03	<0.001
Anastomoses	0.0008	0.007	1	0.9-1.01	0.9
Pre-op cervical length (cm)	0.08	0.3	1.09	0.58-2.05	0.7
Gestational age at delivery (weeks)	-0.2	0.04	0.81	0.2-0.8	<0.001

The results of the multiple analysis showed that GA at delivery (OR=0.81, 95%CI: 0.7-0.8, p<0.001) and sFGR (OR=0.43, 95%CI: 0.2-0.8, p=0.01) had a significant relationship with the survival of the donor. For every week increase in GA at delivery, the odds of donor survival increased by 19%. Additionally, the odds of donor survival in the TTTS group were 0.43 times higher than in the TTTS+sFGR group. The constructed receiver operating characteristic (ROC) curve had an area under the curve (AUC) of 66% (95%CI:0.58-0.75).

Discussion

This study analyzed the outcomes of twin pregnancies complicated by TTTS with and without sFGR. The study included 237 twin pregnancies that underwent FLP, but only 164 patients were eligible for analysis due to incomplete data. Of these, 45.1% were classified as TTTS-only and 54.9% as

TTTS+sFGR. The prevalence of sFGR and TTTS coexistence in our study was similar to another report [17] and higher than another one [21] and also compared to some studies [15, 18], it had a lower percentage. These differences in studies may be because there are different definitions for sFGR, and the use of different definitions makes it difficult to compare the results between studies [21, 22].

Many studies use sFGR as a difference in estimated fetal weight (EFW) greater than 20% or 25% for definition, some define sFGR as EFW below the 10th percentile in at least one fetus, some combined cases of growth failure and growth below the 10th percentile are used as EFW<10th percentile [23]. Using consistent definitions to diagnose intrauterine growth restriction across centers enables easy comparison of study results and useful information acquisition.

There was a significant difference in the distribution of Quintero stages and maternal age during the intervention between the two groups.

TTTS pregnancies complicated by sFGR had a higher Quintero stage, as confirmed by studies [12, 24]. The reason can be explained that the most commonly used staging system for TTTS is the Quintero staging system, which is usually used for TTTS based on two-dimensional ultrasound and Doppler studies [20]. Similar to some studies [15, 17, 21], the findings of our study also indicated that TTTS combined with sFGR before laser surgery has a negative effect on the survival of the donor twin. Twins with growth restriction have a smaller portion of the placenta, which over time, causes abnormal blood flow and less growth [8, 25].

According to Shinar et al. [9], laser surgery is a commonly used treatment for TTTS, which can save the lives of both twins. However, the procedure can also cause damage to the placenta. Even a small loss of the placenta can have adverse effects on the growth and survival of the smaller twin, who is usually the donor.

According to the multivariate logistic regression, donors in the TTTS group had a 43% higher likelihood of achieving 30-day survival, which is consistent with other findings [8]. Additionally, our finding is similar to another study [17], which reported that GA at delivery is an important factor in the survival of donor twins.

Rahimi et al. [25] compared prenatal and neonatal outcomes between complicated monochorionic twin pregnancies in two groups: sFGR-only and sFGR+TTTS. The survival rate was found to be 75.7% in the sFGR+TTTS group and 72.6% in the sFGR-only group. However, there was no significant difference in survival rates between the two groups. Although generally worse fetal outcomes were expected in the TTTS+sFGR group, no significant difference was observed between the groups. But in our study, TTTS with sFGR was associated with reduced donor embryo survival. To better understand the impact of sFGR on survival, further studies comparing the three groups of TTTS-only, only sFGR, and sFGR+TTTS are suggested.

This study had some limitations, including the limited number of patients due to the nature of the disease and the number of pregnancies analyzed. Additionally, there was a lack of complete information on mothers and babies before and after delivery as patients were referred to the center from various locations.

Conclusion

Monochorionic twin pregnancy carries a high risk of severe complications such as the coexistence of TTTS and sFGR. This is a serious issue, and conducting studies in these cases is associated with increasing the awareness of healthcare workers and parents, and causes timely identification and correct management, including consecutive ultrasounds after the diagnosis of monochorionic twin pregnancy. Based on the results of our study, interventions are necessary in the studied community. Due to the small number of patients (due to the rarity of the disease), conducting more multicenter studies is recommended to improve the quality of health education services in this country and in other countries in the future.

These studies will be useful for the obstetrics and gynecology community, also parents' information about this disease and its results is low. By conducting these studies, parents can be better guided about intrauterine surgery. Further studies are recommended to confirm or refute the results of TTTS+sFGR.

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