



# Comparison of Prenatal and Neonatal Outcomes of Selective Fetal Growth Restriction in Monochorionic Twin Pregnancies with or Without Twin-to-Twin Transfusion Syndrome After Radiofrequency Ablation

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## What's Known

- Radiofrequency ablation is a practicable method for fetal reduction in complicated multiple pregnancy with a favorable outcome in the unaffected fetus.

## What's New

- Despite our last theory, the maternal and prenatal outcomes are comparable in selective fetal growth restriction in monochorionic twin pregnancies with or without twin-to-twin transfusion syndrome.

## Abstract

**Background:** This study aimed to investigate and compare the perinatal and neonatal outcomes of monochorionic twin pregnancies complicated with fetal growth restriction (sFGR) with or without twin-to-twin transfusion syndrome (TTTS) after cord occlusion by radiofrequency ablation (RFA).

**Methods:** This prospective cross-sectional study was conducted in women with monochorionic twin pregnancies of 16 to 26 weeks of gestational age (GA) in an academic hospital from 2016 to 2020. Demographic and obstetrical characteristics such as cervical length, GA of RFA and delivery, amnioreduction, cesarean section (C/S) rate, and maximum vertical pocket as well as perinatal, neonatal, and maternal outcomes were evaluated and compared between groups using Statistical Package for the Social Sciences (SPSS). Mann-Whitney U test or independent *t* test was used for quantitative data and Chi-square test was applied for comparing qualitative variables. The significance level of tests was 0.05.

**Results:** Totally 213 (106 sFGR and 107 TTTS+sFGR) cases were enrolled. The mean of maternal age ( $P=0.787$ ), body mass index ( $P=0.932$ ), gestational age at RFA ( $P=0.265$ ), as well as gestational age of delivery ( $P=0.482$ ), and C/S rate ( $P=0.124$ ) were not significant between the two groups, but a significant difference ( $P<0.001$ ) in cervical length was observed between the two groups. No significant differences were observed in newborn and fetal outcomes such as fetal demise ( $P=0.827$ ), PPROM ( $P=0.233$ ), abortion ( $P=0.088$ ), and admission to intensive care unit ( $P=0.822$ ) between the groups.

**Conclusion:** Although we expected worse fetal and neonatal outcomes in the TTTS+sFGR group after RFA, no significant difference was observed between groups.

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**Keywords** • Radiofrequency ablation • Twins, monozygotic • Fetofetal transfusion • Pregnancy, twin • Fetal growth retardation • Fetal death

## Introduction

Twin pregnancies has been on the rise in developed countries for the past 50 years.<sup>1, 2</sup> In Asia, the prevalence rate is less than 8

per 1000 births, but in Africa, it is 17 or more per 1000 births.<sup>3</sup> The use of assisted reproductive technologies, as well as women's delayed childbearing, are the primary causes of this growing trend.<sup>4</sup>

Monozygotic twins share an identical genetic, as they are descended from the same zygote.<sup>5</sup> The incidence of monozygotic and thus monochorionic diamniotic (MCDA) twins are common worldwide,<sup>6</sup> accounting for one in every three spontaneous twins.<sup>7</sup> Multiple pregnancies, particularly monochorionic monozygotic twins sharing the same placenta) twins,<sup>8</sup> have the greatest impact on the overall perinatal morbidity rate.

Although vascular anastomoses exist in all monochorionic placentas, most monochorionic pregnancies tolerate it without complications, suggesting an equilibrium in twin blood exchange.<sup>9</sup>

A particular challenge in monochorionic pregnancy is the risk of fetofetal vascular anastomoses and connections such as twin-to-twin transfusion syndrome (TTTS), the twin reversed arterial perfusion (TRAP) sequence, and the twin anemia polycythemia sequence (TAPS),<sup>10</sup> which may lead to fetal demise or hypotension in one fetus and cause fetal demise or severe permanent neurological injury in the cotwin.<sup>11</sup>

Selective intrauterine growth restriction (sFGR) is a fairly common situation associated with monochorionic (MC) pregnancies with the prevalence of almost 20%.<sup>12</sup> This means the fetal weight of one fetus below 3rd percentile or at least 2 of the 4 standards (the estimated weight or abdominal circumference under 10th percentile in the smaller twin, fetal weight discordance more than 25%, and umbilical artery pulsatility index of the smaller fetus upper than 95<sup>th</sup> percentile).<sup>13</sup> The relevant mechanisms are unequal placenta sharing<sup>14</sup> and the presence of anastomosis between arteries.<sup>9</sup> The mean number of anastomoses in sFGR placentas is similar to normal MC placentas. However, nearly all the placentas in sFGR have one artery-to-artery anastomosis with a significantly larger diameter than normal MC, which permits compensatory flow to the smaller twin promotes longer survival, but on the other hand, facilitates unexpected fetal demise or permanent neurological damage.<sup>9</sup>

SFGRs are divided into three types based on Doppler results, which are essential in diagnosis and predicting fetal outcomes. In type I, both twins show positive end-diastolic flow (EDF) in the umbilical artery,<sup>15</sup> while in Type II, persistent absence or reversed EDF and in

Type III, intermittent absence or reversed EDF is detected.<sup>16</sup> Abnormal Doppler indices, umbilical artery, and severe oligohydramnios (stuck twin) might serve as significant predictors for mortality in sFGR MC twins.<sup>17</sup>

This phenomenon is observed in TTTS as well. TTTS is also a complication of monochorionic twins due to vascular anastomoses in the shared placenta. Approximately 9% to 15% of multiple pregnancies develop TTTS eventually.<sup>18</sup> Due to the unbalanced sharing of blood flow between twins, one of the fetuses would receive less blood, which reduces the urine volume and causes oligohydramnios and stuck.<sup>9</sup> The absence or low rate of artery to artery anastomoses in TTTS placentas result in deficient compensation of blood loss in the nonrecipient (donor) fetus and lead to polyhydramnios oligohydramnios sequence.<sup>9</sup> In some cases, TTTS besides sFGR is also observed. In contrast, an increase in the blood volume of another fetus, called the recipient, leads to raised urine production and polyhydramnios.<sup>19</sup>

Therefore, fetal intervention by selective fetal reduction may be a therapeutic option in morbid sFGR with oligohydramnios and abnormal Doppler findings or in the higher stages of TTTS (stage III) plus sFGR.<sup>17</sup>

Several methods are applied to occlude the blood flow in the umbilical cord.<sup>20</sup> One is the coagulation of the vascular anastomoses by laser in the placenta of TTTS.<sup>20</sup> However, in some cases that laser is not technically feasible or in intricate conditions such as congenital abnormalities, sFGR, or severe cerebral injury in recipient or donor, radiofrequency ablation may be the preferred method for fetal reduction in complicated MC pregnancies.<sup>20</sup> In the previous studies, the survival rate was estimated near to 75%.<sup>20, 21</sup> with the difference among the etiology of the RFA and was better in sFGR than TTTS.<sup>20</sup>

Although no research has been done on the fetus with both TTTS and sFGR, based on the more complicated etiology of TTTS than sFGR, we hypothesized worse outcome for TTTS+sFGR cases. To assess our hypothesis, this study aimed to investigate the perinatal and neonatal outcomes of monochorionic twin pregnancies complicated with sFGR with or without TTTS after cord occlusion by radiofrequency ablation.

## Materials and Methods

### Study Setting

This prospective cross-sectional study was recruited among pregnant women, who were referred to a tertiary educational hospital affiliated with Tehran University of Medical

Sciences from April 2016 to September 2020.

#### *Inclusion and Exclusion Criteria*

The inclusion criteria were the women with MC twin pregnancies between 16 and 26 weeks complicated with sFGR with or without TTTS, who were candidate for selective fetal reduction by RFA. Dichorionic twins or monochorionic triplet pregnancies were excluded from the study. Furthermore, cases of threatened abortion and membrane rupture were excluded.

#### *Data Gathering*

Maternal information including demographic information, pregnancy and illness records, and the used medications by the participants were collected. Besides, the perinatal and neonatal outcomes as well as maternal complications were evaluated and compared between groups. Obstetrical information such as amniotic fluid volume, cervical length measuring by vaginal ultrasound, RFA indication, fetal position, and anomaly scan of each fetus was gathered as well.

#### *RFA Procedure*

The day before the operation, an ultrasound examination was performed by an expert perinatologist to confirm RFA indication, biometric assessment including estimation of fetal weight, amniotic fluid volume, and Doppler study. Amoxicillin (Tolidaru, Iran) 1 gr was orally administered as a prophylactic antibiotic, and Indomethacin 50 mg suppositories were administered half an hour before the procedure.<sup>22</sup> For intramuscular sedation, 50 mg pethidine (Exir Company, Iran) and 25 mg promethazine (Tehranchimie, Iran) were prescribed before starting the procedure, and FHRs were measured.

RFA procedure was performed by the same perinatologist using a radiofrequency (RF) generator; RF um 2004 (manufactured by RF Medical Co., South Korea). The site of RF needle insertion was locally disinfected and anesthetized by administering lidocaine solution (Caspian Tamin, Iran). Under continuous ultrasound and Doppler guidance, the site of the intra-abdominal umbilical vein was determined, then the RF simple needle (gauge 17 and 2 cm exposed tip) was inserted, and, the umbilical vein was cauterized (power 100 Watt) for two minutes. The stop of blood flow was confirmed by color Doppler ultrasonography. If the blood flow was not stopped, the procedure was repeated, and FHR was assessed until cardiac asystole.

The day after the procedure, the participants were evaluated by Doppler ultrasound for FHR,

fetal activity, middle cerebral arterial (MCA) peak, and systolic velocity measurements. Moreover, the cases were visited one week after the procedure in our center or at a local hospital. Prenatal routine care was continued until delivery as follow-up visits once a month in the second trimester, twice a month from 28 to 36 weeks of pregnancy, and weekly until delivery. They were asked to come in for regular obstetrics visits and were referred to the hospital, if any complications arose. A trained midwife followed up on all participants via phone until delivery, and all information and potential maternal, fetal, and neonatal complications were recorded.

#### *Ethical Considerations*

The study was conducted in compliance with all the ethical considerations of Helsinki related to human studies. All patients were consulted on how to conduct the study, and the necessary training was provided. Written informed consents were obtained from all patients, and no additional costs were imposed on patients. The study protocol was approved by the Ethics Board of the Tehran University of Medical Sciences (Registration number: IR.TUMS.MEDICINE.REC.1399.813).

#### *Statistical Analysis*

To analyze the data, first, the distribution of quantitative variables was checked for normality and then to compare quantitative data based on the type of distribution, Mann-Whitney U test or independent t-test was used. To compare qualitative variables, a Chi-square test was applied. The significance level in tests was considered 0.05.

## **Results**

Totally 213 participants (106 in sFGR and 107 in TTTS+sFGR) were enrolled. The RFA procedure was successful in all cases. About 25% of the cases performed the procedure before the 20<sup>th</sup> week of gestation. The demographic and clinical characteristics of the participants are listed in table 1. A significant difference ( $P < 0.001$ ) in the cervical length was observed between the two study groups. The newborn and fetal characteristics and complications in the two groups are compared in table 2. As seen, there are no significant differences between the two groups. The survival rate was about 75%. The mean gestational age at delivery was 35w+2days with no difference between groups ( $P = 0.629$ ). The mean birth weight was 2370±860 grams with no difference between groups ( $P = 0.424$ ).

**Table 1:** Comparison of the demographic and clinical characteristics between selective fetal growth restriction and twin-to-twin transfusion syndrome+selective fetal growth restriction groups

Variables	sFGR (n=106) (mean±SD)	TTTS+sFGR (n=107) (mean±SD)	P value
Maternal age (year)	28.63±5.23	28.81±5.27	0.787
BMI (kg/m <sup>2</sup> )	26.0±3.2	26.04±3.18	0.932
Gestational age at RFA (week)	21.56±2.31	21.16±2.93	0.265
Cervical length (mm)	31.66±4.81	29.01±6.35	<0.001
MVP (mm)	44.82±13.15	101.64±22.48	<0.001
Amnioreduction*	0	35 (32.7)	<0.001
Gestational age at delivery (week)	32.40±5.71	33.04±5.45	0.482
Gestational age at delivery (week)			
	<24	4	3
	24-28	13	15
	28-34	18	20
	34-37	27	15
	>=37	36	45
Cesarean rate*	54 (50.9)	66 (61.6)	0.124
Live birth*	77 (72.6)	81 (75.7)	0.610

\*These variables are described as n (%); BMI: Body mass index; RF: Radiofrequency ablation; MVP: Maximum vertical pocket; SD: standard deviation; TTTS: Twin-to-twin transfusion syndrome; sFGR: Selective fetal growth restriction

**Table 2:** Comparison of newborn and fetal characteristics and complications in selective fetal growth restriction and twin-to-twin transfusion syndrome+selective fetal growth restriction groups

Variables	sFGR (n=106) n (%)	TTTS+sFGR (n=107) n (%)	P value
IUFD	17 (16.0)	16 (14.9)	0.827
PPROM	27 (25.5)	20 (18.7)	0.233
Abortion	13 (12.3)	6 (5.6)	0.088
Newborn weight (gram) *	2318.54±843.82	2423.63±879.01	0.424
NICU admission	32 (30.1)	32 (29.9)	0.822
NICU admission time (days) *	6.913±1.53	6.672±1.46	0.911

\*These variables are described as mean±SD; IUFD: Intrauterine fetal death; PPROM: Premature preterm rupture of membrane; NICU: Neonatal intensive care unit; TTTS: Twin-to-twin transfusion syndrome; sFGR: Selective fetal growth restriction

## Discussion

In the present study, despite our idea and the fact that sFGR±TTTS fetuses are suffered from placental unbalanced sharing, abnormal placental anastomosis, and a proportion of them need amnioreduction, no significant differences in most fetal, maternal and perinatal outcomes were observed in sFGR patients with or without TTTS. It could be explained that after performing the radiofrequency procedure, the pathology of vascular anastomosis and placental sharing in both groups would eliminate and lead to the same outcome in both groups.

Monochorionic pregnancies may have high complications due to vascular anastomosis of the placenta. Twin complications depend on the cause and the gestational age.<sup>23</sup> Understanding the pathology, diagnosis, and management of complications and the use of appropriate treatment methods such as RFA may prevent fetal and consequently neonatal complications.

Currently, available treatments in complicated MC pregnancies are laser photocoagulation for selective reduction.<sup>24</sup> In the Laser

photocoagulation method, the laser is guided to cut the vascular connection. The survival rate for TTTS cases is 70% for both twins. However, there is a near to 15% risk of long-term neurological damage.<sup>25</sup> Another method is to selectively reduce a twin by coagulation in the umbilical cord (BCC) or radiofrequency ablation,<sup>26</sup> but it is gradually giving way to more effective methods. Therefore, RFA may be the better option here to save the life of one fetus and prenatal care may be the same as normal single pregnancy and decrease the further risk of neurological damage.

The overall survival rate after RFA in this study was equal to 75%, which was near the previous studies that reported a survival rate between 76.8% and 78%.<sup>27</sup> This lower survival rate may be due to the study populations in terms of twin complications. In another study, the survival in TTTS (58%) was statistically lower than sFGR (80%).<sup>21</sup> Indeed, in a study assessing only sFGR twins; the survival rate was reported at 83%, although the type of sFGR with or without TTTS hasn't been indicated accurately.<sup>28</sup> On the other hand, referrals from our center have delayed the

transfer of many cases from distant countries and even from Middle Eastern countries, losing the golden age and even in the end stages of TTTS and sFGR.

The PPROM rate in this study was 22.1 %, which is comparable to other studies and was confirmed in a review by Gaerty et al., in which the rate of PPROM in MC twins and survival after RFA were reported to be 17.7 % and 76.8 %, respectively.<sup>29</sup> In another study performed by the same researcher, the mean PPROM in all complicated twins after RFA was 16.7% that was lower in anomaly (6%) and TRAP (10%) than the TTTS (21.2%) or sFGR (20.8%) groups.<sup>20</sup> The higher PPROM in TTTS could be due to the possibility of polyhydramnios and uterine distention, but the reason is not clear in FGR. None of the cases that were born before 28 weeks of gestational age did survived. That may be because of nonoptimal equipped neonatal intensive care units (NICUs) in most small towns in this region.

Overall, the mean gestational age at delivery was 35.2 weeks. Childbirth at <32 weeks occurred in 17.9 % of cases. In the Sun et al. study, the mean gestational age at delivery was around 36 weeks in TTTS and 38 weeks in sFGR.<sup>28</sup> It is obvious that the mean gestational age at delivery was lower in TTTS cases in the mentioned study. In another study by Wang et al., the gestational delivery in TTTS (35.5 weeks) and sFGR (36.5 weeks) was significantly different.<sup>21</sup> Otherwise, there was no statistically significant difference in outcomes considering gestational age at the time of the procedure or RFA indication in our cases. Preterm birth may be a consequence of PPROM after the procedure.<sup>21</sup> We used to terminate pregnancies after the RFA procedure at 37 weeks, and that is the reason for the average preterm age of delivery in our study, but according to the new protocol, the termination date is determined by obstetrical indications.

In this study near 16.5% of cases were IUFD with no difference between groups. In another study, the perinatal outcomes were correlated with the stages of TTTS, and sFGR and they were worst in stage IV TTTS and sFGR III due to the larger arterial anastomosis and more blood exchange during ablation.<sup>21</sup>

The weight of newborns in the two groups was not significantly different, but their mean was LBW due to their sFGR history of all cases. NICU admission and duration did not differ between our study groups.

The main strengths of this study were the prospective nature of the study and relatively larger sample size, a standardized technique,

and a single operator.

The limitation of this study was the lack of a long-term follow-up in children and evaluation of the neurodevelopmental standard scaling in infants.

## Conclusion

Although we expected the worse results in the case of TTTS+sFGR, because of the overdistended uterus and also the probability of preterm increases, the prenatal and maternal complications were not significantly different in sFGR with or without TTTS. Further studies are recommended to compare the outcomes in various stages of TTTS and sFGR. Indeed, designing the potential clinical trial to reduce the fetomaternal complications is recommended.

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**Conflict of Interest:** None declared.

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