

## Perinatal Outcomes following Radiofrequency Ablation in Complicated Monochorionic Multiple Pregnancies

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### Abstract

#### Background

Radiofrequency ablation (RFA) is considered as an optional treatment method in complicated monochorionic (MC) twin pregnancies. The purpose of this study is to investigate the main factors of fetal death after such treatment procedure. The study also compares the perinatal outcomes among various groups of indication and gestational age (GA) at procedure.

**Materials and Methods:** This prospective cohort study considers 195 cases of MC multiple pregnancies including one twin with twin-twin transfusion syndrome, selective intrauterine growth restriction, severe anomaly and twin reversed arterial perfusion sequence (TRAP) which underwent selected reduction using RFA from 2016 to 2018 at Yas Hospital, Tehran, Iran. The GA at RFA categorized as 16-19<sup>+6</sup> wks., 20-23<sup>+6</sup> wks., and 24-28 wks. The analysis of risk factors of fetal death after RFA is based on multivariable logistic regression model.

**Results:** The result of analysis reveals that the rate of co-twin anemia after RFA in anomaly indication was higher than the other indications significantly ( $p=0.038$ ) while according to GA categories, it is significantly lower in 20-23<sup>+6</sup> weeks. ( $p=0.016$ ). Three independent significant factors contributing in fetal death after RFA were co-twin anemia after RFA, TRAP and anomaly indications of RFA and GA at RFA, respectively.

#### Conclusion

The co-twin anemia after RFA was found the most contributing factor of fetal death. As the results showed that the rate of co-twin anemia after RFA is significantly low in 20-23<sup>+6</sup> weeks of GA, such GA is suggested for RFA procedure to reduce the fetal death.

**Key Words:** Death, Radiofrequency ablation, Monochorionic multiple pregnancies, Co-twin anemia.

\*Please cite this article as: Rahimi-Sharbat F, Haghiri M, Shirazi M, Goshahi F, Arabipour A, Zolfaghari Z. Perinatal Outcomes following Radiofrequency Ablation in Complicated Monochorionic Multiple Pregnancies. Int J Pediatr 2021; 9(5): 13559-568. DOI: [10.22038/ijp.2020.48501.3904](https://doi.org/10.22038/ijp.2020.48501.3904)

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Received date: Jun.11, 2020; Accepted date: Jan.12, 2021

## 1- INTRODUCTION

Multiple births have a substantially increased perinatal mortality rate (PMR); especially monochorionic twins (MC) are at elevated risk of stillbirth, preterm birth and adverse outcomes (1). Adverse perinatal outcome in MC twin pregnancy increased due to placental anastomoses and associated complications such as twin-twin transfusion syndrome (TTTS), selective intrauterine growth restriction (sIUGR), and twin reversed arterial perfusion (TRAP). Single intrauterine fetal death (IUFD) in a multiple pregnancy puts the surviving co-twin in jeopardy (2). Selective fetal reduction is one of management options for complicated MC multiple pregnancies which is far more challenging (3). In this procedure, the ablation of blood flow in the umbilical cord of the anomalous or complicated fetus is needed to avoid back-bleeding through communicating vessels, which may participate death or neurologic injury in the surviving co-twin (3, 4).

At first Tsao et al. applied radiofrequency ablation (RFA) for 13 acardiac twin and reported that RFA is a minimally invasive, percutaneous novel technique that can effectively obliterate blood supply to an acardiac twin to preserve and protect the pump twin (5). Then seven case-series studies evaluated the efficacy and safety of radiofrequency in different population (6-11), the latest study is the largest sample size (n=100) by Kumar et al. (12) reported that RFA appears to be a reasonable option for selective fetal reduction in complex MC pregnancies with an overall survival rate of 78%. They found no statistical difference in outcomes with regard to gestation when the procedure was performed or the indication for RFA. Recently, sun et al. evaluated the risk factors for fetal death after radiofrequency ablation for 183 complicated MC twin pregnancies and found that the RFA coagulation more than 2 cycles is the only

independent risk factors of fetal death after RFA (13). Studies in this field are limited, so further researches could be helpful in parental counseling regarding predictive factors for pregnancy outcomes after RFA procedure. This cross-sectional study was conducted to investigate the perinatal outcomes and the risk factors of fetal death according to gestational age at procedure and indications RFA in complicated MC multiple pregnancies.

## 2- MATERIALS AND METHODS

### 2-1. Study design and population

In this prospective cohort study, all cases of complicated MC multiple pregnancy at gestational age 16 to 26 weeks underwent selective reduction using RFA from June 2016 through September 2018 in Yas hospital, a tertiary center for fetal medicine, related to Tehran University of Medical Sciences, Tehran, Iran, were evaluated.

### 2-2. Ethical consideration

Ethics Committee, Research Vice-President of Tehran University of Medical Sciences with code IR.TUMS.VCR.REC.1397.512, approves this study. Written informed consents were taken from all participants before enrollment.

### 2-3. Inclusion and exclusion criteria

Inclusion criteria were all MC multiple pregnancies with one twin complication including twin-twin transfusion syndrome (stage: 2-4 and in symptomatic stage) include patient with shortness of cervical length), selective intrauterine growth restriction (sIUGR) severe malformation and twin reversed arterial perfusion (TRAP) sequence. Exclusion criteria were dissatisfied patient to participate in the study, rupture of membrane, vaginal bleeding, uterine contraction, and cervical dilatation more than 1 centimeter.

### 2-4. Methods

After multidisciplinary consultation, parents opted for selective termination and gave written informed constant for this procedure. All possible complications including unsuccessful procedure, premature rupture of membrane, intra uterine co twin–death, abortion (during 4 weeks after procedure), preterm birth, and or thermal injury to the survived co twin were completely explained for the parents. All cases performed ultrasound examination at 11-14 weeks to determine the gestational age, chorionicity and nuchal translucency measurement. Gestational age calculated from the biggest fetus. In this study, all patients assessed for chromosomal abnormality screening tests and if they were high risk, they underwent amniocentesis; also, amnioreduction was done for polyhydramnios in TTTS cases before RFA if needed. Anomaly scan and fetal echocardiography were performed to exclude anomaly, also detail ultrasound was performed to confirm indication of intervention and assessment cervical length. Selective IUGR was defined as an estimated fetal weight  $<10^{\text{th}}$  (may be  $< 3\%$  if all patient less than  $3\%$ ) percentile in one twin and an intertwine weight difference of  $> 25\%$  was considered in the study. Doppler ultrasound of the umbilical artery was performed to demonstrate either absent or reversed diastolic flow based on Gratacos et al.'s study (14). Oligohydramnios was defined as a deepest vertical packet of  $\leq 20$  mm, and stuck twin defined no pocket of amniotic fluid around the fetus. TTTS was staged according to the scheme of Quintero et al. (15). For TRAP sequence, ultrasound was used to determine the parabiotic twin mass and inverse direction of blood flow in the umbilical artery and Aorta.

## 2-5. Intervention

All of the patients took two capsules of amoxicillin (500 mg) for prevention of infection thirty minute before the procedure. In addition, indomethacin rectal

suppository 50 mg was prescribed before the procedure and repeated after six hours to prevent uterine contraction. In the operating room pads was placed around the maternal thighs and place mother in a favorable position and convenience. After prepping and draping of the abdomen with Povidone-iodine, maternal sedation with intra muscular 50 mg meperidine and 25 mg promethazine was performed. The position of affected fetus was reinvestigated by ultrasound (Philips, affinity 50, made of UK). Under continuous ultrasound guidance, local anesthesia by 10 ml Lidocaine 2% was administered, and then radiofrequency simple needle 17-gauge, 20 cm in length, 2 centimeter tip expose (RF medical Co., Ltd. BT-2020, Belgium), with cool water center, (RF medical MYGEN made of South Korea) was inserted percutaneous through the uterus and into the fetal abdomen. The needle was crossed through intra-abdominal umbilicus vein (Targeted vessel for ablation).

Then the radiofrequency energy was applied by a generator that was set at 100 fixed Watts power and delivered for maximum 2 minutes. Usually the generator automatically stops the radiofrequency energy after coagulation was done in less than two minutes. Cessation of blood flow in the umbilical cord was confirmed by color flow and power Doppler. If the cessation of vascular flow did not occur needle, the location was rechecked and needle displaced a little slightly. The additional radiofrequency cycle was repeated for one to two times if needed. An area representing the probable zone of thermal injury was easily seen on ultrasound at conclusion of the procedure. Usually after 45 minutes of delivered energy, asystole was noted and was confirmed next day. Peak systolic velocity of middle cerebral artery with color Doppler ultrasound assessed for any evidence of anemia, before procedure and

next day for detection of anemia in remained twin. If co-twin anemia was diagnosed, especially when the embryo's movement was low, the parents were counseled about the higher probability of brain injury, and if the parents desire not to continue the pregnancy, labor was induced. A primatologist administered all procedure. The patients were discharged next day after procedure and suggested to terminate the pregnancy when 37 weeks of GA was completed. They were examined 1-2 weeks later in local hospital by her physician. Follow up continued until delivery by calling them or their physician and if needed checking their documents. The following perinatal variables were collected, including maternal age, conception mode, cervical length at RFA, indications for RFA, GA at RFA, duration of RFA, and pregnancy outcomes. Pregnancy outcomes included post-RFA miscarriage before 24 weeks of gestation death of the remaining co-twin before and after 1 weeks of gestation, co-twin IUFD, termination of pregnancies, Preterm Premature Rupture of Membranes (PPROM) defined as the leakage of amniotic fluid prior to the onset of labor before 37 week, GA at PPRM, GA at delivery, birth weight, and neonatal death (within the first 28 days of postnatal life). Fetal death after RFA included the miscarriage, co-twin death after 24 weeks of gestation, and the termination of pregnancy due to parents' request due to co-twin anemia following RFA. Survival rate was defined as survival beyond the first 28 days of postnatal life.

### 2-6. Data Analyses

All data were analyzed using SPSS software version 20 (SPSS Inc., Chicago, IL, USA). Data were presented as mean  $\pm$  standard deviation (SD) for continuous or frequencies for categorical variables. RFA outcomes were compared according to GA at procedure and RFA indication. The continuous variables compared by means

using analysis of variance (ANOVA) or Kruskal-Wallis tests as appropriate. The categorical variables compared with chi-squared test. Finally, the univariate were performed to identify the potential significant risk factors of fetal death following RFA in our study population. All of potential significant risk factors were entered in multivariable logistic regression model to determine the independent significant risk factors for fetal death. *P*-value less than 0.05 were considered as significant.

### 3- RESULTS

Totally, 195 cases of RFA were included in the study. The overall co-twin death, termination and live birth rates after RFA were 37/195 (18.9%), 4/195 (2.1%) and 154/195 (79%), respectively. The survival rate until 28 days of birth was 68.7 % (134 newborn) in general. The mean gestational age at birth after RFA was 33.2 $\pm$ 4.5 (24-39 weeks). The rate of co-twin death  $\leq$  2 week after RFA (30/195; 15.4%) was significantly higher than that of in  $>$  2 weeks after RFA (7/195; 3.6%). The rates of co-twin death and co-twin anemia next day after RFA were (17/195; 8.7%) and 10/195 (5.1%), respectively. The overall PPRM rate was 28.7% (56/195) which 25% (14/56) of them was occurred less than 2 week after RFA.

**Table.1** shows the overall maternal characteristics and indications for RFA. The most common indications of RFA were TTTS (39.5%, n=77) and sIUGR (36.4%, n=71). The most type of multiple pregnancies was MCDA (94.4%, n=184), and the rate of triple pregnancies was very low (2.5%, n=5). The type of conception in most pregnancies was spontaneous (90.3%). The mean of gestational age at RFA procedure was 21.5  $\pm$  2.5 (rang: 16-28 wks.). All cases of RFA were technically successful, there were no maternal complications related to the procedures.

**Table-1:** Overall maternal characteristics and indications for radiofrequency ablation.

| Variables  |                     |
|--|---------------------|
| Maternal age (rang), year.   | 30.39 ± 5.5 (17-45) |
| BMI at RFA procedure, (kg/m <sup>2</sup> )   | 28.30 ± 4.26        |
| Gravidity  | 2.0± 1.18           |
| Type of conception   |                     |
| Spontaneous  | 176 (90.3%)         |
| Induction ovulation  | 11 (5.6%)           |
| IVF  | 8 (4.1%)            |
| Type of multiple pregnancy   |                     |
| MCMA   | 6 (3.1 %)           |
| MCDA   | 184(94.4 %)         |
| MCTA   | 2(1 %)              |
| DCTA   | 3 (1.5%)            |
| RFA indication   |                     |
| TTTS   | 77 (39.5 %)         |
| Selective IUGR   | 71 (36.4 %)         |
| Anomaly  | 33 (16.9 %)         |
| TRAP   | 14 (7.2 %)          |
| GA at RFA, (range), week   | 21.5 ± 2.5 (16-28)  |
| Cervical length at RFA, (mm)   | 32.1 ± 7.46         |
| Duration of RFA, (sec)   | 139.2 ± 73.49       |
| DCTA, dichorionic triamniotic; IUGR, intrauterine growth restriction; GA, gestational age; IVF, in vitro fertilization; MCDA, monochorionic diamniotic; MCMA, monochorionic monoamniotic; IUFD, intrauterine fetal death, MCTA, monochorionic triamniotic; MFPR, multifetal pregnancy reduction; RFA, radiofrequency ablation ;TRAP, twin reversed arterial perfusion; TTTS, twin-twin transfusion syndrome. * The quantitative and qualitative data were presented as mean ± SD and number (%), SD: standard deviation. |                     |

The comparison of perinatal outcome was presented according to RFA indications in **Table.2**. The mean of GA at RFA in anomaly group was significantly lower than other groups ( $p=0.023$ ). The rate of co-twin anemia after RFA in anomaly group was higher than other groups significantly ( $p=0.038$ ). The rate of IUFD  $\geq 24$  week in anomaly indication group was higher than other groups, but it did not reach to statistical significant level ( $p=0.077$ ). In similar way, the termination of pregnancy rate in TRAP group was higher than TTTS and sIUGR groups (7.1% versus 0% and 1.4% respectively) and this trend *was not* statistical significance ( $p=0.051$ ). The co-twin death  $> 2$  week after RFA in TRAP and anomaly groups was significantly higher than TTTS and sIUGR groups (14.2% and 9.1% versus 1.3% and 1.4 % respectively,

$p=0.021$ ). The total PROM rate after RFA in TRAP indication group was higher than other groups, but it did not reach to statistical significant level ( $p=0.076$ ). Meanwhile, the rate of PROM  $\leq 2$  week after RFA in TRAP group was significantly higher than that of in other groups ( $p=0.008$ ), which may be clinically important. In addition, NICU admission rate and the duration of hospitalization in NICU in sIUGR group was lower than other group ( $p= 0.03$  and  $p=0.13$ ). There is no significant difference in terms of duration of RFA, cervical length at RFA, miscarriage, co-twin death  $\leq 2$  weeks after RFA, PROM rate, RFA-to-delivery after 24-week interval, GA at birth, overall birth weight, neonatal mortality rate and overall survival rates, the duration of hospitalization and coexist of obstetrics complication among groups.

**Table-2:** Compression of Pregnancy outcomes based on indications for RFA.

| Variables   | TTTS<br>(n=77) | Selective IUGR<br>(n=71) | Anomaly<br>(n=33) | TRAP<br>(n=14) | P value        |
|---|----------------|--------------------------|-------------------|----------------|----------------|
| GA at RFA   | 21.5 ± 2.2     | 22.0 ± 2.6               | 20.5 ± 2.4        | 22.4 ± 3.0     | <b>0.023**</b> |
| Duration of RFA, (sec)  | 131.9 ± 50.9   | 132.8 ± 59.4             | 148.3 ± 100.3     | 182.1 ± 133.2  | 0.215          |
| Cervical length at RFA  | 29.7 ± 7.4     | 32.6 ± 7.0               | 37.1 ± 7.0        | 35.3 ± 2.5     | 0.060          |
| Termination of pregnancy *  | 0% (0:77)      | 1.4% (1:71)              | 6% (2:33)         | 7.1% (1:14)    | <b>0.051</b>   |
| Miscarriage < 24 weeks  | 14.3% (11:77)  | 12.7% (9:71)             | 15.2% (5:33)      | 21.4% (3:14)   | 0.861          |
| IUFD ≥ 24 week  | 1.2% (1:77)    | 5.6% (4:71)              | 12.1% (4:33)      | 0% (0:14)      | 0.077          |
| Co-twin death ≤ 2 week after RFA  | 14.3% (11:77)  | 16.9% (12:71)            | 18.2% (6:33)      | 7.1% (1:14)    | 0.771          |
| Co-twin death > 2 week after RFA  | 1.3% (1:77)    | 1.4% (1:71)              | 9.1% (3:33)       | 14.2% (2:14)   | <b>0.021</b>   |
| Anemic co-twin after RFA  | 5.2% (4:77)    | 1.4% (1:71)              | 15.1% (5:33)      | 0% (0:14)      | <b>0.038</b>   |
| RFA-to-delivery after 24-week interval—weeks  | 11.6 ± 5.8     | 11.5 ± 5.6               | 12.7 ± 6.1        | 12.0 ± 5.5     | 0.844          |
| Live birth rate   | 84.4% (65:77)  | 80.3% (57:71)            | 66.7% (22:33)     | 71.4% (10:14)  | 0.177          |
| GA at birth, weeks <sup>a, b</sup>  | 33.0 ± 4.7     | 33.4 ± 4.4               | 33.2 ± 4.5        | 34.9 ± 3.1     | 0.697          |
| GA at birth, <sup>a, b</sup>  |                |                          |                   |                |                |
| 24-27 <sup>+6</sup> wks.  | 15.1% (10:66)  | 14.7% (9:61)             | 19.2% (5:26)      | 0% (0:10)      | 0.576          |
| 28-31 <sup>+6</sup> wks.  | 19.6% (13:66)  | 19.6% (12:61)            | 15.3% (4:26)      | 20% (2:10)     | 0.969          |
| 32-33 <sup>+6</sup> wks.  | 10.6% (7:66)   | 4.9% (3:61)              | 3.8% (1:26)       | 20% (2:10)     | 0.297          |
| ≥ 34 wks.   | 54.5% (36:66)  | 60.6% (37:61)            | 61.5% (16:26)     | 60% (6:10)     | 0.892          |
| Total PROM rate   | 44.6% (25:56)  | 43.7% (21:48)            | 20% (4:20)        | 60% (6:10)     | 0.076          |
| PROM ≤ 2 week after RFA   | 9.0% (7:77)    | 4.2% (3:71)              | 0% (0:33)         | 28.5% (4:14)   | <b>0.008</b>   |
| PROM > 2 week after RFA   | 23.3% (18:77)  | 25.3% (18:71)            | 12.1% (4:33)      | 14.2% (2:14)   | 0.402          |
| Neonatal mortality  | 11.6% (9:77)   | 12.6% (9:71)             | 6.0% (2:33)       | 0% (0:14)      | 0.537          |
| Overall survival rate   | 72.7% (56:77)  | 67.6% (48:71)            | 60.%(20/33)       | 71.4% (10:14)  | 0.694          |
| Overall Birth weight (gr)   | 2105 ± 852.5   | 2316 ± 864.4             | 2227 ± 810.9      | 2447 ± 886.6   | 0.494          |
| NICU admission/live birth, n (%)  | 47.7% (31:65)  | 22.8% (13:57)            | 45.4% (10:22)     | 40% (4:10)     | <b>0.031</b>   |
| Duration of hospitalization in NICU, day  | 10.1 ± 16.8    | 4.2 ± 9.7                | 7.6 ± 13.3        | 6.9 ± 14.2     | 0.130          |
| Coexist of obstetrics complication (preterm labor, preeclampsia, chorioamnionitis, placenta detachment) | 42.9% (33:77)  | 36.6% (26:71)            | 27.3% (9:33)      | 42.9% (6:14)   | 0.461          |

\*\*Kruskal–Wallis test analysis.

IUGR: intrauterine growth restriction; GA: gestational age; IUFD: intrauterine fetal death; RFA, radiofrequency ablation; TRAP: twin reversed arterial perfusion; TTTS: twin-twin transfusion syndrome; Overall survival rate: survival beyond the first 28 days of postnatal life. PROM: premature rupture of membranes prior to the onset of labor before 37 weeks.

<sup>a</sup> Only pregnancies with live born were included in this analysis.

<sup>b</sup>Data were shown as median (interquartile range).

\* Pregnancy termination after RFA due to co-twin anemia was optional based on the viewpoint of parents.

**Table.3** compares the pregnancy outcomes among different groups according to the gestational age at RFA procedure. Three groups were defined: group 1 (RFA at 16-19 weeks), group 2 (RFA at 20-23 weeks), and group 3 (RFA at 24-28 weeks). The termination of pregnancy in group 1 was significantly higher than two other groups (p=0.025). The rates of co-twin anemia after RFA and IUFD ≥ 24 week in group 2 were lower than other groups significantly (p=0.016 and p=0.046, respectively). The

rate of co-twin death > 2 week after RFA in group 2 was lower than other groups; however, it did not reach to statistical significant level (p=0.081). GA at birth in group 1 and 2 was significantly higher than group 3 (p=0.005 and p=0.06). So that the number of births at GA (24-27 wks.) and GA (28-31 wks.) in group 3 were significantly higher than those of in two other groups (p=0.044 and p=0.011). The duration of hospitalization in NICU in group 2 (RFA at 20-23 wks.) was lower

than other group ( $p= 0.10$  and  $p=0.027$ ). There is no significant difference in terms of co-twin death  $\leq 2$  weeks after RFA, survival rates, total PROM rate ( $\leq 2$  and  $>$

2 weeks after RFA), coexist of obstetrics complication, neonatal mortality rate, NICU admission rate and overall birth weight among groups.

**Table-3:** Compression of pregnancy outcomes based on gestational age at RFA (weeks).

| Variables   | Group 1<br>(16-19 wks.+ 6 days)<br>(n=65) | Group 2<br>(20-23 wks.+ 6 days), (n=99) | Group 3<br>(24-28 wks.)<br>(n=31) | P-value         |
|---|---|---|-----------------------------------|-----------------|
| Duration of RFA, (sec)  | 126.9 $\pm$ 68.56                         | 143.1 $\pm$ 77.72                       | 152.5 $\pm$ 66.96                 | 0.415           |
| Cervical length at RFA  | 34.0 $\pm$ 7.6                            | 31.0 $\pm$ 7.2                          | 31.5 $\pm$ 7.7                    | 0.360           |
| Termination of pregnancy *  | 6.1% (4:65)                               | 0%(0:99)                                | 0%(0:31)                          | <b>0.025***</b> |
| Miscarriage < 24 weeks  | 18.5% (12:65)                             | 16.2%(16:99)                            | -----                             | 0.420           |
| IUFD $\geq 24$ week   | 4.6% (3:65)                               | 2.0% (2:99)                             | 12.9% (4:31)                      | <b>0.046**</b>  |
| Co-twin death $\leq 2$ week after RFA   | 15.4% (10:65)                             | 16.2% (16:99)                           | 12.9% (4:31)                      | 0.908           |
| Co-twin death > 2 week after RFA  | 7.7% (5:65)                               | 2.0% (2:99)                             | 0% (0:31)                         | 0.081           |
| Anemic co-twin after RFA  | 9.2% 6 (6:65)                             | 1.0% 1 (1:99)                           | 9.7% (3:31)                       | <b>0.016***</b> |
| Live birth rate   | 70.8% (46/65)                             | 81.8% (27/31)                           | 87.1% (27/31)                     | 0.114           |
| GA at birth, weeks <sup>a, b</sup>  | 34.5 $\pm$ 4.2                            | 33.4 $\pm$ 4.3                          | 31.3 $\pm$ 4.7                    | <b>0.008**</b>  |
| GA at birth <sup>a, b</sup>   |   |   |                                   |                 |
| 24-27 <sup>+6</sup> wks.  | 12.2% (6:49)                              | 12.0% (10:83)                           | 25.8% (8:31)                      | <b>0.044</b>    |
| 28-31 <sup>+6</sup> wks.  | 8.2% (4:49)                               | 21.6% (18:83)                           | 29.0% (9:31)                      | <b>0.011</b>    |
| 32-33 <sup>+6</sup> wks.  | 8.2% (4:49)                               | 8.4% (7:83)                             | 6.4% (2:31)                       | 0.973           |
| $\geq 34$ wks.  | 71.4% (35:49)                             | 57.8% (48:83)                           | 38.7% (12:31)                     | 0.381           |
| Total PROM rate   | 34.7% (16:46)                             | 33.3% (29:87)                           | 40.7% (11:27)                     | 0.525           |
| PROM $\leq 2$ week after RFA  | 4.61%(3:65)                               | 7.07%(7:99)                             | 12.9%(4:31)                       | 0.933           |
| PROM > 2 week after RFA   | 20%(13:65)                                | 22.2%(22:99)                            | 22.5%(7:31)                       | 0.338           |
| Neonatal mortality  | 7.7% (5:65)                               | 11.1% (11:99)                           | 12.9% (4:31)                      | 0.620           |
| Overall survival rate   | 63.1% (41:65)                             | 70.7% (70:99)                           | 74.2% (23:31)                     | 0.305           |
| Overall birth weight (gr)   | 2105 $\pm$ 852.5                          | 2316 $\pm$ 864.4                        | 2227 $\pm$ 810.9                  | 0.494           |
| NICU admission /live birth (%)  | 43.5% (20:46)                             | 36.8% (32:87)                           | 59.3% (16:27)                     | 0.108           |
| Duration of hospitalization in NICU, day  | 10.1 $\pm$ 16.8                           | 4.172 $\pm$ 9.7                         | 7.6 $\pm$ 13.3                    | <b>0.027*</b>   |
| Coexist of obstetrics complication<br>(preterm labor, preeclampsia,<br>chorioamnionitis, placenta detachment) | 30.8% (20:65)                             | 37.4% (37:99)                           | 51.6% (16:31)                     | 0.161           |

\*\*\* Kruskal–Wallis test analysis. \*\* One-way analysis of variance (ANOVA). Group 1 vs. Group 3 ( $P=0.005$ ), Group 2 vs. Group 3 ( $P=0.06$ ), Group 1 vs. Group 2 ( $P=0.35$ ). The P-values between groups were determined by post-hoc analysis (Tukey). GA: gestational age; RFA: radiofrequency ablation; PROM: premature rupture of membranes; NICU: neonatal intensive care unit. Overall survival rate: survival beyond the first 28 days of postnatal life. PROM: premature rupture of membranes prior to the onset of labor before 37 weeks.

<sup>a</sup> Only pregnancies with live born were included in this analysis.

<sup>b</sup> Data were shown as median (interquartile range).

\* Pregnancy termination after RFA due to co-twin anemia was optional based on the viewpoint of parents.

The univariate and multivariable logistic regression was performed to determine significant predictive factors for fetal death after ARF. In univariate analysis, maternal age ( $P=0.045$ ), gestational age at RFA ( $P=0.045$ ), TRAP indication ( $P=0.037$ ), Anomaly indication (0.010), co-twin anemia after RFA ( $P=0.008$ ), and coexist

of obstetrics complication ( $P=0.061$ ) were related important variables. In multivariable regression model, TRAP and anomaly indications of RFA, GA at RFA and twin anemia after RFA were remained as significant independent contributing factors of fetal death after RFA (**Table.4**).

**Table-4:** Univariate and multivariable regression analysis to identify risk factors of perinatal mortality following RFA.

| Variables   | OR crude (95% CI)    | P-value | Adjusted OR (95% CI) | P-value |
|---|----------------------|---------|----------------------|---------|
| Maternal age  | 0.93 (0.86 - 0.99)   | 0.045   | N/A                  | N/A     |
| BMI at procedure  | 0.94 (0.86 - 1.03)   | 0.228   | N/A                  | N/A     |
| Gravidity   | 0.82 (0.58 - 1.15)   | 0.264   | N/A                  | N/A     |
| Gestational age at RFA  | 0.82 (0.67 - 0.99)   | 0.045   | 0.83 (0.702-0.973)   | 0.023   |
| <b>Indication of RFA</b>  |                      |         |                      |         |
| TTS   | Reference group      |         | Reference group      |         |
| Selective IUGR  | 1.88 (0.742 - 4.795) | 0.182   | 2.41 (0.90-6.45)     | 0.080   |
| Anomaly   | 3.92 (1.377 - 11.16) | 0.010   | 4.65 (1.07- 20.23)   | 0.040   |
| TRAP  | 3.92 (1.083 - 14.18) | 0.037   | 5.94 (1.53-23.04)    | 0.010   |
| Type of conception  |                      |         | N/A                  | N/A     |
| Assisted  | Reference group      |         |                      |         |
| Spontaneous   | 0.57 (0.11-2.80)     | 0.491   |                      |         |
| Twin anemia after RFA   | 8.52 (1.74-41.65)    | 0.008   | 9.85 (2.13-45.40)    | 0.003   |
| Duration of RFA-sec   | 1.79 (0.70 - 4.58)   | 0.220   | N/A                  | N/A     |
| Coexist of obstetrics complication<br>(preterm labor, preeclampsia,<br>chorioamnionitis, placenta detachment) | 0.44 (0.18 - 1.041)  | 0.061   | N/A                  | N/A     |

BMI: body mass index; IUGR: intrauterine growth restriction; RFA: radiofrequency ablation; TTS: twin-twin transfusion syndrome; TRAP: twin reversed arterial perfusion; OR: odds ratio; CI: confidence interval.

#### 4- DISCUSSION

The parental counseling regarding predictive factors for pregnancy outcomes after RFA is vital before decision of RFA procedure. Then, this study was designed to report the clinical outcome of a large cohort of complicated MC multiple pregnancies managed with RFA and to compare them according to GA at procedure and RFA indications and finally to identify the potential risk factors of fetal death following RFA. Our outcomes of selective reduction using RFA are comparable with the data from other centers. In present study, the overall PPROM and live birth rate for this reason were 28.7% and 79%; recently, Gaerty et al., in a systematic review reported overall rates of PROM and survival following RFA in MC twins being 17.7% (CI:12.9-24.3%) and 76.8% (CI: 67.6-87.2) respectively (3). We compared our outcomes with Sun et al. (13) study due to similar sample size. The overall PPROM and survival in their cohort were 15% and 77% respectively. The reason of higher PPROM in our study may lie in different

proportion of TTS (39.5%), and TRAP (7.2%) indications of RFA in this series, which is 19% and 19% in sun et al. analysis. The multivariable logistic regression analysis demonstrated that twin anemia after RFA, TRAP and anomaly indications of RFA, GA at RFA were the significant independent risk factors for fetal death in our study population. It was found that with one-week increase in gestational age at RFA, the probability of fetal death decreased by 17%. Also, in the cases with occurrence of anemia following RFA, the possibility of fetal death increased by 9.8 times. Elsewhere, Sun et al. evaluated risk factors for fetal death after radiofrequency ablation for 183 complicated MC twin pregnancies and they found that in the multivariable regression analysis, the cycles of RFA coagulation > 2 is related to the fetal death after RFA (13). In our study, in multivariable analysis TRAP and anomaly indications of RFA had higher risk of fetal death in compared to TTS indication. The multiple pregnancies with TTS indication for RFA seem to be most likely



to benefit from RFA, and the fetal death in this indication is lower than, others. In contrast, Sun et al, reported that fetal death is associated with indications such as sIUGR and TTTS in univariable analysis. They assumed that the post RFA deterioration of the wellbeing of the remaining twin may be also associated with the preexisting fetal complication itself, such as the cardiac dysfunction of the recipient with TTTS and pump twin with TRAP(13). Elsewhere, Kumar et al, found no statistical difference in outcomes with regard to gestation when the procedure was performed or the indication for RFA (12). The main reason of different results was the different proportion of various indications of RFA between our study and others analysis.

The possible reasons of increased fetal death in pregnancies with anomaly indication for RFA might be as follows: 1) the apparently healthy co-twin in cases of anomaly indication may have been accompanied by the chromosomal disorders such as the micro deletion and micro duplication syndrome which has worsened the condition, 2) in anomaly indication, the needle was inactive in the liquid medium such as hydropic fetus with ascites or omphalocele, coagulation of the umbilical vein should be down adjacent to the fetal liver, which is accompanied by more bleeding and co-twin anemia, 3) it is likely that in the fetal and placental vessels of complicated twin with TTTS, sIUGR and TRAP, there are a compensatory mechanism for regulating the sudden pressure fluctuations between fetuses.

It seems that in the case of anomalies, this defensive mechanism is not active, and as a result, these fetuses were more prone to anemia. However, our speculations should be confirmed in larger studies. The main strengths of this study are the relatively larger sample size, longer follow up until three month after birth, a single operator and analysis of contributing factors of fetal

death after RFA. However, there are some limitations in the present study. One is the relatively small sample size in each subgroup; this is reasonable given a single-center study and the rarity of these conditions. In addition, we only recorded the whole RFA procedure time, and the number of coagulation cycles was not recorded, so we could not comment on this subject. In conclusion RFA is a minimal invasive technique for management in complicated MC multiple pregnancies and it was found the main risk factors for fetal death following RFA in our study population were the occurrence of co-twin anemia, TRAP indication and gestational age at RFA. In present study, the best prognosis according to GA at procedure and RFA indication was for GA at 20-23 weeks and TTTS indication. The findings demonstrate that whereas the rate of co-twin anemia after RFA is the most important in fetal death, the anemia rate is low in 20-23<sup>+6d</sup> weeks of GA. This finding is clinically intriguing because such GA is suggested for RFA procedure to reduce the fetal death. The result of this study is useful in consultation with parents, allowing them to select the appropriate decision before RFA procedure in complicated MC multiple pregnancies.

## 5- CONCLUSION

In conclusion RFA is a minimal invasive technique for management in complicated MC multiple pregnancies and it was found the main risk factors for fetal death following RFA in our study population were the occurrence of co-twin anemia, TRAP indication and gestational age at RFA. In present study, the best prognosis according to GA at procedure and RFA indication was for GA at 20-23 weeks and TTTS indication. The findings demonstrate that whereas the rate of co-twin anemia after RFA is the most important in fetal death, the anemia rate is low in 20-23<sup>+6d</sup> weeks of GA. This finding is clinically intriguing because such GA is

suggested for RFA procedure to reduce the fetal death. The result of this study is useful in consultation with parents, allowing them to select the appropriate decision before RFA procedure in complicated MC multiple pregnancies.

## 6- ACKNOWLEDGEMENTS

The author would like to thank Yas Hospital personnel's and patients for their invaluable contributions to present research.

**7- CONFLICT OF INTEREST:** None.

## 8- REFERENCES

1. James DK, Steer PJ, Weiner CP, Gonik B, Robson SC. High-risk pregnancy: management options: Cambridge University Press; 2017.
2. Gabbe SG, Niebyl JR, Simpson JL, Landon MB, Galan HL, Jauniaux ER, et al. Obstetrics: Normal and Problem Pregnancies E-Book :Elsevier Health Sciences; 2016.
3. Gaerty K, Greer RM, Kumar S. Systematic review and metaanalysis of perinatal outcomes after radiofrequency ablation and bipolar cord occlusion in monochorionic pregnancies. *Am J Obstet Gynecol.* 2015 Nov;213(5):637-43. doi: 10.1016/j.ajog.2015.04.035. Epub 2015.
4. Quarello E, Molho M, Ville Y. Incidence, mechanisms, and patterns of fetal cerebral lesions in twin-to-twin transfusion syndrome. *The Journal of Maternal-Fetal & Neonatal Medicine.* 2007;20(8):589-97.
5. Tsao K, Feldstein VA, Albanese CT, Sandberg PL, Lee H, Harrison MR, et al. Selective reduction of acardiac twin by radiofrequency ablation. *Am J Obstet Gynecol.* 2002;187(3):635-40.
6. Lee H, Wagner AJ, Sy E, Ball R, Feldstein VA, Goldstein RB, et al. Efficacy of radiofrequency ablation for twin-reversed arterial perfusion sequence. *Am J Obstet Gynecol.* 2007;196(5):039.
7. Moise KJ, Jr., Johnson A, Moise KY, Nিকেleit V. Radiofrequency ablation for selective reduction in the complicated monochorionic gestation. *Am J Obstet Gynecol.* V2008;198(2): 198.e1-198.e5.
8. Cabassa P, Fichera A, Prefumo F, Taddei F, Gandolfi S, Maroldi R, et al. The use of radiofrequency in the treatment of twin reversed arterial perfusion sequence: a case series and review of the literature. *Eur J Obstet Gynecol Reprod Biol.* 2013;166(2):127-32.
9. Lee H, Bebbington M, Crombleholme TM. The North American Fetal Therapy Network Registry data on outcomes of radiofrequency ablation for twin-reversed arterial perfusion sequence. *Fetal Diagn Ther.* 2013;33(4):224-9.
10. Berg C ,Holst D, Mallmann MR, Gottschalk I, Gembruch U, Geipel A. Early vs late intervention in twin reversed arterial perfusion sequence. *Ultrasound Obstet Gynecol.* 2014;43(1):60-4.
11. Wang HM, Li HY, Wang XT, Wang YY, Li L, Liang B, et al. Radiofrequency ablation for selective reduction in complex monochorionic multiple pregnancies: A case series. *Taiwan J Obstet Gynecol.* 2017;56(6):740-4.
12. Kumar S, Paramasivam G, Zhang E, Jones B, Noori M, Prior T, et al. Perinatal- and procedure-related outcomes following radiofrequency ablation in monochorionic pregnancy. *Am J Obstet Gynecol.* 2014;210(5):4.
13. Sun L, Zou G, Yang Y, Zhou F, Tao D. Risk factors for fetal death after radiofrequency ablation for complicated monochorionic twin pregnancies. *Prenat Diagn.* 2018 Jun;38(7):499-503. doi: 10.1002/pd.5269. Epub 2018 May 9. PMID: 29675904.
14. Gratacos E, Lewi L, Munoz B, Acosta-Rojas R, Hernandez-Andrade E, Martinez J, et al. A classification system for selective intrauterine growth restriction in monochorionic pregnancies according to umbilical artery Doppler flow in the smaller twin. *Ultrasound in Obstetrics & Gynecology.* 2007;30(1):28-34.
15. Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin-twin transfusion syndrome. *J Perinatol.* 1999;19(8 Pt 1):550-5.