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CLINICAL ARTICLE

Obstetrics

Timing of intra-fetal laser therapy for twin reversed arterial perfusion (TRAP) sequence: Retrospective series and systematic review and meta-analysis

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Abstract

Objective: To estimate the neonatal survival rate after intra-fetal laser (IFL) treatment for twin reversed arterial perfusion (TRAP) sequence, and to investigate the effect of gestational age at the time of procedure.

Methods: Retrospective cohort study of TRAP sequences followed at our institution from 2013–2020. Systematic review and meta-analysis of the neonatal survival rate after IFL was conducted. Both diamniotic and monoamniotic monochorionic pregnancies were included. A subgroup analysis to compare outcomes according to gestational age at procedure ($<16^{+0}$ weeks or $\geq 16^{+0}$ weeks) was planned.

Results: Thirteen pregnancies were followed at our center and seven were treated with IFL: the survival rate was 57%. Ten studies published between 2008 and 2020 for a total of 156 cases were included in the meta-analysis. The overall neonatal survival after IFL was 79% (95% CI 0.72–0.86, I^2 22%). A random-effects model comparing neonatal survival for IFL performed $<16^{+0}$ weeks versus $\geq 16^{+0}$ weeks showed no significant difference between the two groups (OR = 0.93; 95% CI 0.37–2.33).

Conclusion: IFL is a safe and minimally invasive technique for the treatment of TRAP sequence, with a survival rate of 79%. Gestational age at treatment (before or after 16 weeks) does not seem to affect neonatal survival rate.

KEYWORDS
fetal therapy, interstitial laser, meta-analysis, monochorionic twins, systematic review, TRAP sequence

1 | INTRODUCTION

Twin reversed arterial perfusion (TRAP) sequence is a unique complication of monochorionic multiple pregnancy in which an acardiac twin with multiple morphological anomalies and without a complete cardiovascular system is perfused by a structurally normal co-twin (the pump twin).[1] The acardiac twin is not viable, but it endangers the pump twin, causing an increased risk of congestive heart failure, intrauterine growth restriction (IUGR), preterm premature rupture of membranes (pPROM) and preterm delivery. The main goals in TRAP sequence management are preserving the survival of the pump twin and approaching a term delivery. If a conservative management is

not advisable, the treatment consists of stopping blood supply to the acardiac twin. Among such devascularization techniques, intra-fetal laser (IFL) treatment has gained momentum in recent years, due to its minimal invasiveness and the possibility to perform it as early as the first trimester of pregnancy.[2] However, there is ongoing debate regarding the best timing of the procedure, and its relative safety at early gestational ages.[3,4]

The first aim of this study was to review our center's experience in the management and treatment with IFL of monochorionic twin pregnancies complicated by TRAP sequence. The second aim was to perform a systematic review of the literature on pump twin neonatal survival after IFL treatment, with a planned subgroup analysis according to the timing of intervention (before 16^{+0} weeks versus at or more than 16^{+0} weeks).

2 | MATERIALS AND METHODS

2.1 | Cohort study

This retrospective study reviewed all consecutive cases of monochorionic twin pregnancies referred to ASST Spedali Civili of Brescia between January 2013 (when we switched from radiofrequency ablation to IFL) and December 2020 because of a suspicion or a diagnosis of TRAP sequence. Data were retrieved by searching the computerized ultrasound database. In case of missing data about pregnancy outcomes, the woman or referring physician were contacted. As this was a retrospective audit of anonymized data, no ethics committee approval was necessary according to national regulations; all women gave their written consent to use their routinely collected hospital data for retrospective studies without patient identifiers. Gestational age was confirmed in all cases by a first trimester ultrasound scan measuring the crown to rump length (CRL) of the pump twin. Chorionicity and amnionicity were assessed in the first trimester. At the first evaluation in our center, the diagnosis of TRAP sequence was confirmed by an ultrasound scan using color Doppler in the presence of an acardiac twin receiving a retrograde blood flow from the pump twin. All patients were counseled about the clinical significance of TRAP sequence, the natural history of this condition and the possibility of termination of pregnancy. We offered fetal therapy in cases in which a significant risk of death for the pump twin was assessed: persistent blood flow to the acardiac twin and an acardiac estimated fetal weight larger than 50% of the pump twin or an initial overload of pump twin indicated by mild polyhydramnios or ductus venosus pulsatility index for veins (DV-PIV) >95th centile. The main techniques used were fetoscopic cord coagulation and transection of the acardius umbilical cord (COT) and interstitial IFL. Interventional procedures were performed only by two different operators with more than 10 years' experience. Patients were admitted to the hospital the day before or the same day of the treatment in the early morning. They had been fasting for 6 h prior to the procedure. Before starting intervention, they received prophylactic antibiotics with i.v. cephalosporins; conscious sedation with midazolam i.v. and local anesthesia with mepivacaine were also performed.

COT was adopted in monochorionic monoamniotic (MCMA) pregnancies at risk of cord entanglement.[5] In all remaining cases in which fetal therapy was indicated, IFL was performed. Under ultrasound guidance, an 18-gauge needle was inserted with a free-hand technique in the pelvis of the acardiac twin, very close to the intra-abdominal portion of the feeding vessels (umbilical artery and vein in proximity of the hilum); then, a 600-μm laser fiber was inserted into the needle and advanced a few millimeters in front of the needle tip. Laser coagulation was obtained with a diode laser generator. The initial power was set at 10 W to avoid thermal injury to the surrounding tissues. Multiple impulses of a few seconds were repeated until the tissue near the laser fiber became hyperechoic; when the cessation of reverse perfusion in the acardius was detected by color Doppler, the procedure was considered complete.

The day after the procedure, an ultrasound examination was performed to check the heart activity in the pump twin and to confirm the absence of reverse flow through the acardiac twin. Women were discharged in the absence of vaginal bleeding, amniotic fluid losses or uterine contractions. Ultrasound follow-up was planned after 1 week at our center, and in the referring hospital thereafter.

2.2 | Systematic review

The review was performed following an a-priori protocol (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=211452) and is reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement and checklist.[6] The study was registered with the PROSPERO database (registration number: CRD42020211452). The quality of the articles included in the review was assessed using the Newcastle-Ottawa Scale.[7] Medline, EMBASE and clinicaltrials.gov were searched on the 1 December 2020 using the following keywords: 'TRAP sequence', 'laser', 'interstitial', 'intrafetal'. Reference lists of relevant articles and reviews were manually searched. Two trained reviewers (A.V. and F.P.) independently screened titles and abstracts for relevance. The full text of relevant articles was evaluated independently and agreement about potential eligibility was reached by consensus. We included reports in English language about treatment of TRAP sequence by IFL that provided data on survival of the pump twin. Prospective and retrospective cohort studies, case–control studies and case series were included; editorials, case reports and personal communication were excluded. Only series with five or more cases were taken into account; we did not include smaller series in order to minimize selection bias. In case of data duplication, only the most recent and complete work was included. Discordance was resolved with consensus. An effort was made to obtain missing data by contacting the corresponding author of the publications; we subsequently excluded studies with incomplete outcomes of the cases. For each study we collected data on gestational age at IFL, pPROM, intrauterine fetal demise, gestational age at delivery, and neonatal survival.

A random-effects model was used to estimate weighted neonatal survival rates with 95% confidence intervals due to the heterogeneity between studies. We did not formally test for publication bias, given the low power of testing with the small number of studies included.[8] All analyses were performed with the statistical software OpenMetaAnalyst.[9]

3 | RESULTS

3.1 | Cohort study

In the study period, 15 women were referred to our center with a suspicion of TRAP sequence. Six pregnancies were MCMA and nine pregnancies were monochorionic diamniotic (MCDA). We confirmed the diagnosis of TRAP sequence in all cases. Details about the cohort are available in Table S1. The patient flow-chart is reported in Figure S1.

Eleven cases were considered eligible for treatment. In two cases of MCMA pregnancies, because of a long cord of the parasitic twin and the subsequent presence of cord entanglement, the treatment chosen was COT. The pregnancies delivered at 30^{+5} and 33^{+1} weeks, and both babies survived.

Nine patients were eligible for IFL treatment. On the day scheduled for the procedure, unfortunately two pump fetuses were found without cardiac activity (at 15^{+1} and 18^{+3} weeks, respectively); these fetuses had shown a reversed ductus venosus A wave in the ultrasound examination preceding surgery. Seven pregnancies were treated with IFL at a mean gestational age of 15^{+3} weeks (range 12^{+3}–19^{+5} weeks). Four pregnancies were MCDA and three MCMA without evidence of cord entanglement. In two cases, both MCMA, fetal demise was diagnosed at follow-up (1 and 54 days after the procedure). In three MCDA cases the pregnancy was uneventful, laser treatment was performed, and three healthy babies were delivered at term. In another MCDA pregnancy, IFL treatment was performed at 20^{+2} weeks. The day after the procedure, the pump twin presented a DV-PIV > 95th centile, that was not detected at the following examinations. At 26^{+1} weeks, the woman was admitted because of reduction of fetal movements. An emergency cesarean section for abnormal cardiotocography was performed at 26^{+2} weeks. A baby girl of 684 g was born; she was discharged from the neonatal intensive care unit without major morbidities, and is presently in good health.

In another MCMA pregnancy, the gestational age at procedure was 13^{+5} weeks. Cord coagulation and transection was excluded because of a body stalk anomaly of the acardius. During ultrasound follow-up in the referring hospital, a retrochorionic hematoma was detected; because of heavy vaginal bleeding an emergency cesarean section was performed at 24^{+5} weeks; the baby died on the following day.

Overall, we observed a 57% rate of neonatal survival rate (4/7) in the IFL treatment group. Details of the cases are shown in Table S2.

3.2 | Systematic review

We included in our systematic review a total of nine studies which met the selection criteria[3,4,10–16] (Figure 1), plus our current series. Newcastle-Ottawa Scale quality assessment is shown in Table 1: a maximum score of 9 can be assigned, based on selection (maximum 4), comparability (maximum 2) and outcome (maximum 3) items. In order to limit confounding bias, data about triplets were excluded from the meta-analysis. Outcomes of the 11 triplet pregnancies treated with IFL are separately reported in Table S3. The meta-analysis population included 156 monochorionic twin pregnancies complicated by TRAP sequence undergoing IFL. Data on pregnancy outcomes (survival or intrauterine demise of the pump twin) and gestational age at treatment are reported in Table S4. The overall neonatal survival rate of the pump twin estimated from meta-analysis was 79% (95% CI 0.72–0.86, I^2 22%). The Forest plot is reported in Figure 2a.

We further divided the IFL therapy cohort into two groups, according to the gestational age at treatment: at less than 16^{+0} weeks (early treatment group), and at 16^{+0} or more weeks of gestational age (late treatment group). Data about gestational age at delivery, pPROM and days between procedure and intrauterine demise of pump twin were incomplete; we report the available ones in Tables 2 and 3. The early treatment group included 60 pregnancies treated at a weighted mean gestational age of 13^{+5} weeks. In the late treatment group, 96 pregnancies were treated at a weighted mean gestational age of 19^{+6} weeks. The overall survival for each group was calculated trough a pooled proportion random-effects model, as shown in Figure 2b,c.

A meta-analysis (through a random-effects model) comparing the neonatal survival OR in each study showed no statistically significant difference between the two groups (OR = 0.927; 95% IC 0.37–2.33). Results are shown in Figure 3.

4 | DISCUSSION

We found that the neonatal survival rate of the pump twin after IFL for TRAP is approximately 80%. Timing of IFL (before or after 16 weeks of gestation) is not associated with differences in neonatal survival rate.

The major limitations of our systematic review are the small number of studies included and their retrospective non-randomized design. Indications for IFL treatment were not homogeneously reported in all studies and may have differed between studies and in the same study over time. One single study[14] contributed almost one third of the total cases, and 45% of those treated at or more than 16^{+0} weeks.

Several studies and reviews of literature tried to identify the technique of choice in TRAP treatment. Radiofrequency ablation (RFA) and IFL are currently the most commonly used techniques due to their reliability and safety. The previously published experience in TRAP sequence treatment at our center reported the use
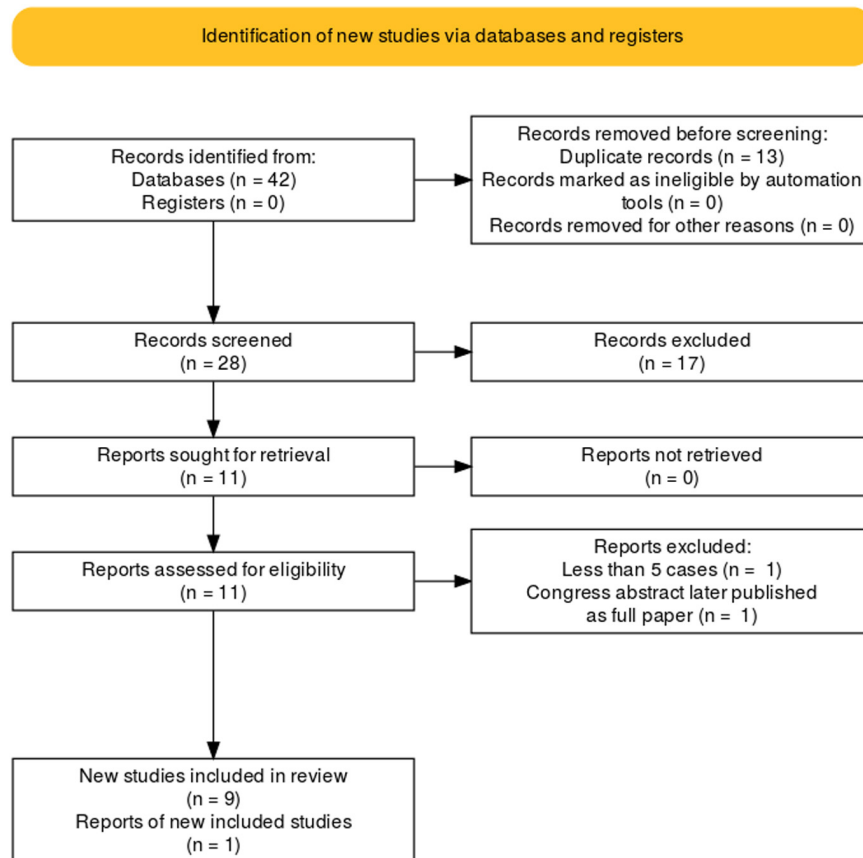
FIGURE 1 Flow chart of studies included in systematic review and meta-analysis

TABLE 1 Quality assessment of the included studies using the Newcastle-Ottawa Scale

Study	Selection	Comparability	Outcome
O'Donoghue et al. 2008	***	*	***
Scheier and Molina 2012	***	*	***
Berg et al. 2014	***	*	**
Pagani et al. 2013	***	*	***
Chaveeva et al. 2014	***	*	***
Roethlisberger et al. 2017	***	*	**
Tavares de Sousa et al. 2020	***	*	***
Shettikeri et al. 2019	***	*	**
Seshadri et al. 2020	***	*	**
Present study	***	*	***

Maximum **** for selection; ** for comparability; and *** stars for outcome assessment.

of RFA and reviewed the existing literature[17]: six studies were included for a total of 78 pregnancies (monochorionic twins or triplets with a monochorionic component). The overall neonatal survival in TRAP sequence treated by RFA was 85%. A rough pPROM rate was estimated at 22% (19/85), since not all studies reported specific details. Other large cohorts reported pump twin survival rates of 70%–80%.[14,18,19]

The other technique that appeared feasible since its first description by Jolly et al.[2] is IFL. Several publications have investigated its rate of success and the related outcomes of pregnancy. Overall neonatal survival rate was 80% in the systematic review by Pagani et al. based on 51 cases,[13] and 76% in the one by Chaveeva et al. based on 104 pregnancies.[14] Regarding the comparison between RFA and IFL, Pagani et al.[13] noted that, even though neonatal survival rate was similar, pPROM before 32 weeks' gestation was more common with RFA. Chaveeva[14] suggested that the risk of death for the pump twin using IFL is lower if treatment is undertaken at 12–14 weeks than at later gestational ages. A real comparison between RFA and IFL is not possible at such early gestational ages, since RFA is rarely performed before 15 weeks.
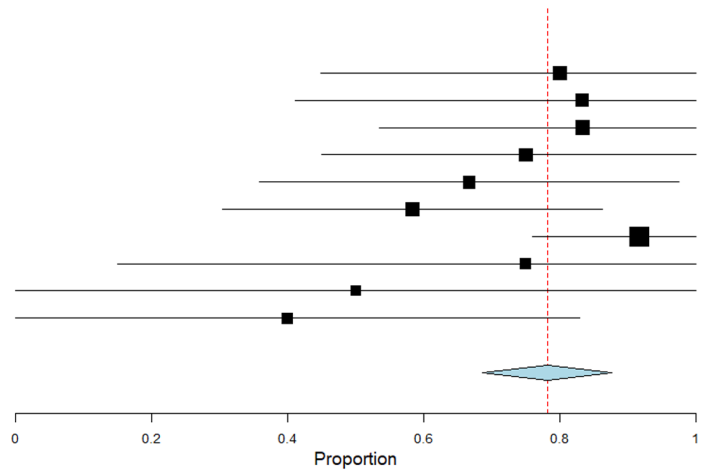
(a)

Studies	Estimate (95% C.I.)	Ev/Trt
O Donghue et al 2008	0.600 (0.296, 0.904)	6/10
Scheirer and Molina 2012	0.857 (0.598, 1.000)	6/7
Pagani et al 2013	0.812 (0.621, 1.000)	13/16
Berg et al 2014	0.727 (0.464, 0.990)	8/11
Chaveeva et al 2014	0.769 (0.655, 0.884)	40/52
Roethlisberger et al 2017	0.583 (0.304, 0.862)	7/12
Tavares de Sousa et al 2019	0.917 (0.760, 1.000)	11/12
Shettikeri et al 2019	0.938 (0.770, 1.000)	7/7
Seshadri et al 2020	0.727 (0.541, 0.913)	16/22
Current study 2020	0.571 (0.205, 0.938)	4/7
Overall (I^2=21.97 % , P=0.241)	0.790 (0.717, 0.862)	118/156

Proportion
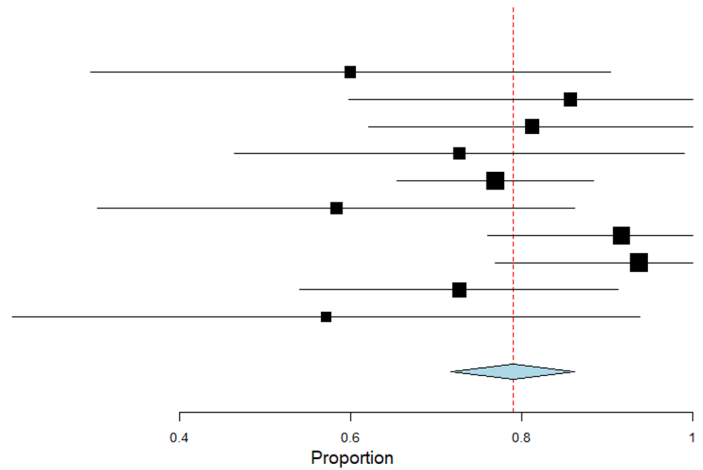
(b)

Studies	Estimate (95% C.I.)	Ev/Trt
O Donghue et al 2008	0.800 (0.449, 1.000)	4/5
Scheirer and Molina 2012	0.833 (0.412, 1.000)	2/2
Pagani et al 2013	0.833 (0.535, 1.000)	5/6
Berg et al 2014	0.750 (0.450, 1.000)	6/8
Chaveeva et al 2014	0.667 (0.359, 0.975)	6/9
Roethlisberger et al 2017	0.583 (0.304, 0.862)	7/12
Tavares de Sousa et al 2019	0.917 (0.760, 1.000)	11/12
Shettikeri et al 2019	0.750 (0.150, 1.000)	1/1
Seshadri et al 2020	0.500 (0.000, 1.000)	0/0
Current study 2020	0.400 (0.000, 0.829)	2/5
Overall (I^2=0 % , P=0.444)	0.781 (0.686, 0.877)	44/60

Proportion

(c)

| Studies	Estimate (95% C.I.)	Ev/Trt
O Donghue et al 2008	0.400 (0.000, 0.829)	2/5
Scheirer and Molina 2012	0.800 (0.449, 1.000)	4/5
Pagani et al 2013	0.800 (0.552, 1.000)	8/10
Berg et al 2014	0.667 (0.133, 1.000)	2/3
Chaveeva et al 2014	0.791 (0.669, 0.912)	34/43
Roethlisberger et al 2017	0.500 (0.000, 1.000)	0/0
Tavares de Sousa et al 2019	0.500 (0.000, 1.000)	0/0
Shettikeri et al 2019	0.929 (0.738, 1.000)	6/6
Seshadri et al 2020	0.727 (0.541, 0.913)	16/22
Current study 2020	0.833 (0.412, 1.000)	2/2
Overall (I^2=0 % , P=0.684)	0.786 (0.708, 0.864)	74/96

Proportion
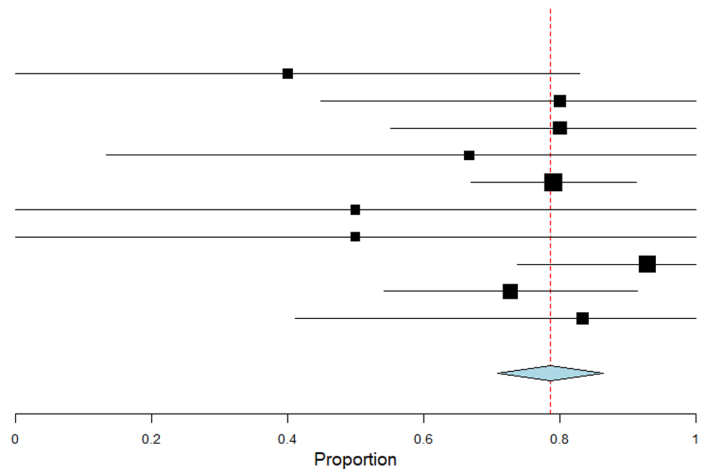
FIGURE 2 Pooled neonatal survival rates after intrafetal laser treatment. Overall (a), treatment at <16^{+0} weeks of gestation (b), treatment at ≥16^{+0} weeks of gestation (c)

At our center, in the last 6 years the technique of choice has been IFL, because of the possibly lower rate of complications and easier availability of the laser generator. In our series, we had a 57% neonatal survival rate, 29% of late post-procedure fetal demise and 14% perinatal death rate. As opposed to RFA,[17] we did not observe pPROMs after IFL, which is in keeping with the findings of Pagani et al.[13] The overall neonatal survival rate in our series was lower than other previously published studies. Possible reasons of this difference can be the small sample size and the presence in the treatment group of three MCMA pregnancies in which we observed the

TABLE 2 Outcomes with IFL treatment at $<16^{+0}$ weeks of gestation

Study	N. cases treated $<16^{+0}$	Mean GA at treatment (range)	N. pump alive (%)	Mean GA at delivery (range)	N. pPROM (%)	N. pump IUFD (%)	N. pump neonatal death
O'Donoghue et al. 2008	5	14^{+2} (12^{+2}–15^{+1})	4 (80%)	38^{+2} (37^{+1}–39^{+1})	1 (20)	1 (20)	0
Scheier and Molina 2012	2	13^{+1} (13^{+1}–13^{+2})	2 (100%)	39^{+4} (38^{+0}–40^{+6})	0	0	0
Pagani et al. 2013	6	14^{+3} (12^{+6}–15^{+5})	5 (83%)	38^{+1} (37^{+0}–40^{+5})	0	1 (17)	0
Berg et al. 2014	8	14^{+3} (13^{+0}–15^{+6})	6 (75%)	38^{+5} (36^{+3}–40^{+6})	0	2 (25)	0
Chaveeva et al. 2014	9	13^{+0} (11^{+0}–14^{+0})	6 (66.6%)	39 (32^{+0}–40^{+0})	NR	3 (33.4)	0
Roethlisberger et al. 2017	12	13^{+2} (12^{+6}–13^{+6})	7 (58.3%)	40^{+0} (38^{+6}–40^{+0})	0	5 (41.7)	0
Tavares de Sousa et al. 2020	12	13^{+4} (12^{+3}–14^{+3})	11 (91.7%)	39^{+1} (32^{+0}–42^{+1})	0	1 (8.3)	0
Shettikeri et al. 2020	1	15^{+0}	1 (100%)	NR	0	0	0
Seshadri et al. 2020	-	-	-	-	-	-	-
Present study	5	13^{+5} (13^{+0}–14^{+1})	2 (40%)	33^{+6} (24^{+5}–39^{+1})	0	2 (40)	1
Total	60	13^{+5}	44			16	

Abbreviations: GA, gestational age; pPROM, preterm premature rupture of membranes; IUFD, intrauterine fetal death; NR, not reported.

worst outcomes. In approximately 5% of cases of TRAP sequence the pregnancy is monoamniotic and this represents a challenge in the choice of the optimal therapeutic option. If the cord of the cardiac twin is long, it will become entangled with the umbilical cord of the pump twin and, if RFA or ILF is employed, the acardius's cord may constrict that of the pump twin, leading to its demise; in such cases, devascularization of the acardiac twin is better achieved by coagulation of the acardiac twin cord by means of fetoscopic laser or ultrasound-guided bipolar coagulation, followed by transection of the coagulated cord performed fetoscopically with a laser fiber or miniature scissors.[5,20] However, often the umbilical cord of the acardiac twin is very short and cord coagulation and transection is not feasible. In these cases, treatment options are not different from those in MCDA pregnancies, i.e. RFA or IFL.[21,22] Therefore, we included in our series MCMA cases suitable for IFL treatment. Moreover, among the among the nine studies included in our meta-analysis, two expressly also treated MCMA twins,[10,11] four only treated MCDA pregnancies with IFL,[3,4,13,15] three others did not report amnionicity.[12,14,16] It was therefore not possible to confidently exclude MCMA pregnancies from the analysis.

As for the results of our systematic review and meta-analysis, in the population of 156 TRAP pregnancies treated with IFL the estimated pump twin survival rate was 79%. The second part of our analysis was undertaken in order to highlight possible differences in outcome between treatment before or after 16 weeks, since the debate about the optimal time of intervention is still open. In 2010, a retrospective study by Lewi et al.[23] described a pump twin loss rate of 33% (8/24) in the time elapsed from the first trimester diagnosis and the elective intervention at 16–18 weeks, showing an important disadvantage of delayed procedures. Pagani et al. showed a significantly lower adverse pregnancy outcome in the group in which the treatment was undertaken before 16 weeks.[13] Conversely, in the retrospective series of TRAP cases treated by Roethlisberger et al. with IFL before 14^{+0} weeks, fetal loss was more common in cases treated in the first trimester.[3] The work by Tavares de Sousa et al.[4] reported a live birth rate of 92% at a median gestational age of 39^{+6} weeks (interquartile range 37^{+1} to 41^{+2}) in 12 TRAP cases treated before 14^{+3} weeks. The recent series by Shettikeri[15] et al. included laser treatment in the second and in the third trimester, all with good outcome. Since there is equipoise between early and delayed treatment, a randomized controlled trial has been launched to compare treatment at 13–15 weeks versus 16 weeks or later (TRAP Intervention Study, TRAPIST; ClinicalTrials.gov: NCT02621645). As we were expecting to find between 100 and 200 cases of IFL treatment for TRAP from our systematic review, we considered it reasonable to plan only one subgroup analysis for gestational age at treatment. The 16 weeks cut-off chosen is the one more frequently reported in the literature to separate between early and late treatment.

Our meta-analysis suggests no significant difference in pump survival rate between IFL performed before or after 16 weeks. Since gestational age at delivery and pPROM rate were not reported in all studies, a comparison between the two groups in terms

TABLE 3 Outcomes with IFL treatment at $\geq 16^{+0}$ weeks of gestation

Study	N. cases treated $\geq 16^{+0}$	Mean GA at treatment (range)	N. pump alive (%)	Mean GA at delivery (range)	N. pPROM (%)	N. pump IUFD (%)	N. pump neonatal death
O'Donoghue et al. 2008	5	18^{+6} (16^{+6}–20^{+5})	2 (40)	34^{+1} (30^{+2}–38^{+0})	0	3 (60)	0
Scheier and Molina 2012	5	17^{+5} (16^{+2}–20^{+3})	4 (80)	36^{+0} (29^{+2}–39^{+1})	1 (20%)	1 (20)	0
Pagani et al. 2013	10	21^{+6} (17^{+4}–25^{+4})	8 (80)	34^{+6} (27^{+5}–38^{+0})	0	2 (20)	0
Berg et al. 2014	3	17^{+3} (16^{+0}–20^{+0})	2 (66.6)	38^{+5} (36^{+3}–40^{+6})	0	1 (33.4)	0
Chaveeva et al. 2014	43	19^{+0} (16^{+0}–24^{+0})	34 (79.1)	36^{+0} (26^{+0}–42^{+0})	NR	9 (20.9)	0
Roethlisberger et al. 2017	–	–	–	–	–	–	–
Tavares de Sousa et al. 2020	–	–	–	–	–	–	–
Shettikeri et al. 2020	6	19^{+6} (16^{+0}–30^{+0})	6 (100)	NR	0	0	0
Seshadri et al. 2020	22	22 (16^{+0}–26^{+3})	16 (73)	37^{+0} (36^{+1}–38^{+0})	2 (9%)	5 (22)	1
Present study	2	18^{+4} (17^{+1}–20^{+2})	2 (100)	NR	0	0	0
Total	96	19^{+6}	74		3	21	1

Abbreviations: GA: gestational age; pPROM: preterm premature rupture of membranes; IUFD: intrauterine fetal death; NR: not reported.
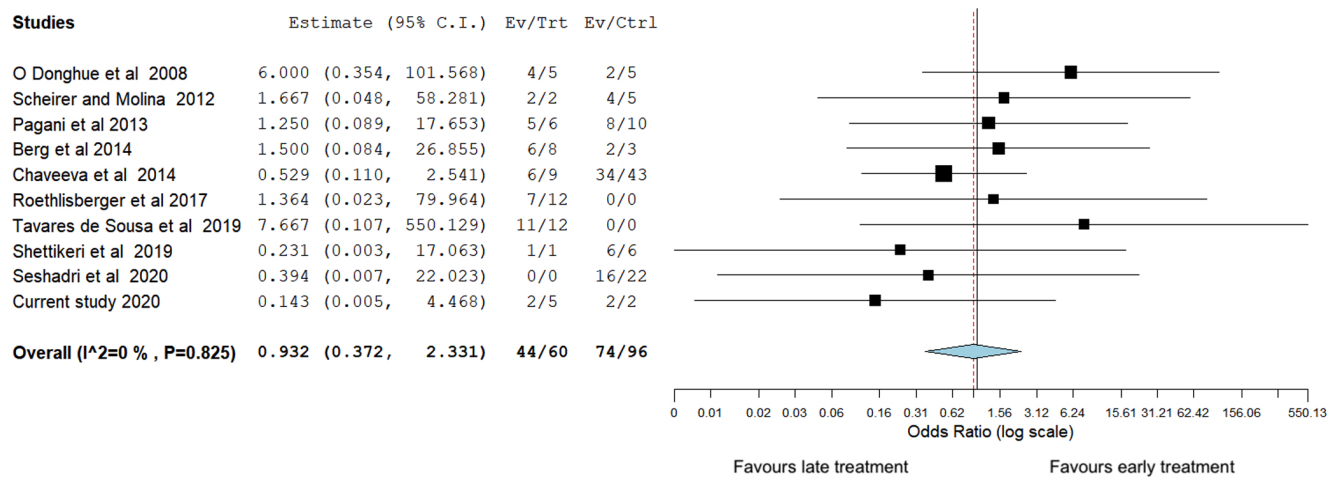

FIGURE 3 Forest plot for subgroup analysis (early treatment at $<16^{+0}$ weeks of gestation versus late treatment at $\geq 16^{+0}$ weeks of gestation) of overall intrafetal laser treatment neonatal survival

of pregnancy complications was not possible. Consequently, given the risk of spontaneous pump twin loss with delayed procedures, our data may suggest an advantage for early treatment of TRAP sequence. However, this finding must be interpreted with caution, since timing of the procedures in non-randomized studies is influenced by several unmeasured confounders related to operator's experience and judgment, patient's preference, and of course gestational age at referral.

In conclusion, IFL is a safe and minimally invasive technique that allows a satisfactory treatment of TRAP sequence. Gestational age at treatment (before or after 16 weeks) does not seem to affect neonatal survival rate. This would favor early treatment but needs to be confirmed by ongoing randomized controlled studies.

INFORMED CONSENT

Written consent was obtained from all women.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

AV, AF and FP conceived and designed this study. AV, NF, AF and FP contributed substantially to the acquisition of the data. AV and FP performed statistical analyses. AV, NF, AF, ES and FP contributed to the interpretation of the results. AV and FP drafted the paper. AV, NF, AF, ES and FP revised and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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