Original Paper

Fetal Diagnosis and Therapy

Fetal Diagn Ther 2014;35:267–279
DOI: 10.1159/000358593

Received: January 11, 2013
Accepted after revision: December 30, 2013
Published online: April 16, 2014

Optimal Method and Timing of Intrauterine Intervention in Twin Reversed Arterial Perfusion Sequence: Case Study and Meta-Analysis

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Key Words
Twin reversed arterial perfusion · Fetal therapy · Cord occlusion · Radiofrequency ablation · Laser coagulation

Abstract
Introduction: The objective of this study was to define the optimal method and timing of intervention in twin reversed arterial perfusion (TRAP) sequence. ***Material and Methods:*** During a period of 20 years (1993–2013), we performed endoscopic laser coagulation of umbilical cord vessels or intrafetal laser in 67 pregnancies with TRAP sequence. These data were combined with those reported in the literature to determine the survival rate of the pump twin for different methods and timing of interventions. ***Results:*** A variety of techniques were used to interrupt the blood supply to the acardiac twin. Most procedures were performed at or after 16 weeks, and with most methods the survival rate of the pump twin was about 80%. Good results were also obtained for triplet pregnancies. In 18 of 30 cases (60%) diagnosed at 11–14 weeks, there was spontaneous cessation of flow in the acardiac twin before planned intervention at 16–18 weeks, and in 11 of these (61.1%) the pump twin died or suffered brain damage. In 103 pregnancies treated by intrafetal laser at 12–27 weeks, there was no correlation between gestational age at treatment and survival rate, but there was an inverse association between gestational age at treatment and gestational age at birth. ***Discussion:*** In TRAP sequence, survival may be improved by elective intervention at 12–14 weeks.

Introduction

In twin reversed arterial perfusion (TRAP) sequence, the high risk of death for the normal pump twin [1] has led to the development of a wide range of intrauterine interventions to improve outcome. Early attempts were highly invasive and involved hysterotomy and removal of the acardiac twin [2–4]. Subsequently, a series of other less invasive intrauterine interventions aiming to arrest the circulation of the acardiac twin were introduced [5–75]. These included insertion of cord coils, ligation with or without transection of the umbilical cord, endoscopic laser coagulation of placental anastomoses between the pump and acardiac twins, endoscopic laser coagulation and endoscopic or ultrasound-guided monopolar or bipolar diathermy of vessels within the cord supplying the acardiac twin and, more recently, ultrasound-guided ablation of intrafetal vessels by injection of alcohol, monopolar diathermy, laser or radiofrequency. These interventions are usually carried out at or

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after 16 weeks' gestation, but this practice has recently been questioned because in a high proportion of cases the pump twin dies between 11–14 weeks, when TRAP sequence is diagnosed, and 16–18 weeks, when the intervention is scheduled to take place [61].

The objective of this study is to define the optimal method and timing of intrauterine intervention in TRAP sequence by examining the data of affected cases managed in our centre and those identified by a systematic review of the literature.

Material and Methods

Study Population in Our Centre

This study comprised all cases of TRAP sequence examined in our fetal medicine centre between April 1993, when we first introduced endoscopic laser coagulation of the umbilical cord vessels of the acardiac twin [25], and April 2013.

TRAP sequence was diagnosed in a monochorionic pregnancy by the coexistence of a normal fetus and an abnormal twin without functional cardiac activity and with reversed arterial flow in the umbilical artery as demonstrated by color Doppler. In each case, a detailed scan was carried out for biometry and the diagnosis of any major defects in the pump twin. The patients were managed expectantly or by either endoscopic laser coagulation of the umbilical cord vessels or intrafetal laser coagulation of the feeding vessels of the acardiac twin. Gestational age was determined by ultrasound measurements of the pump twin, crown-rump length before 14 weeks and head circumference at or after 14 weeks.

Maternal demographic characteristics, ultrasound findings and details of intrauterine intervention were recorded in a database. Pregnancy outcomes were collected into the same database when they became available from the referring hospitals, general practitioners or the patients themselves.

Laser Ablation of Blood Supply to the Acardiac Twin

Endoscopic laser surgery was performed as previously described [25]. Essentially, after the administration of prophylactic antibiotics and local anaesthesia, a rigid 2-mm-diameter fetoscope, housed in a 2.7-mm-diameter cannula (KeyMed, Southend, UK) was introduced transabdominally into the sac of the pump twin. The fetoscope was then advanced into the sac of the perfused twin, and neodymium-doped yttrium aluminum garnet laser (Dornier MedTech, Wessling, Germany) was used to coagulate the umbilical cord artery and vein. The procedure took 10–30 min to complete, and the patients were allowed home after a couple of hours.

For intrafetal laser, women received prophylactic antibiotics, and then ultrasound examination was carried out to select the best path for needle entry avoiding puncture of the amniotic sac of the pump twin. A transverse section of the lower fetal abdomen of the acardiac twin was obtained, and colour flow Doppler was used to visualize the feeding vessels. Local anaesthesia (10 ml of 1% lidocaine) was applied to the maternal skin, subcutaneous tissues and myometrium. An 18-gauge needle (Cook Ireland Ltd., Limerick, Ireland) was introduced, and under continuous ultrasound visualization it was guided to the fetal abdomen with the tip adjacent to the pelvic vessels. A 400-μm laser fiber was then inserted into the needle and advanced to a couple of millimetres beyond the tip of the needle. Laser coagulation was performed using neodymium-doped yttrium aluminum garnet laser (Dornier Med Tech) at 40 W. This resulted, within a few seconds, in hyperechogenicity of tissues in the lower abdomen and cessation of blood flow within the acardiac twin. The procedure took 5–10 min to complete, and after a period of rest for about 1 h, another ultrasound examination was carried out to confirm that there was normal heart activity in the pump twin and no flow within the acardiac twin. The patient was discharged home, and follow-up was usually undertaken in the referral hospital.

Systematic Review of the Literature

Searches of MEDLINE (October 2013) were performed, without any time or language restrictions, to identify all studies reporting on 'twin reversed arterial perfusion', 'acardiac twin' or 'acardiac triplet'. In addition, a manual search was performed from the reference lists of all identified articles. The inclusion criteria were studies reporting on intrauterine surgical intervention for TRAP sequence and providing data on survival to the neonatal period of the pump twin. In case of data duplication or overlap, only the largest or most recent study with available data was included. The first reviewer (P.C.) sorted all articles by citations and abstract for more detailed evaluation. Two reviewers (P.C., K.H.N.) independently extracted data on method, gestational age at intervention and outcome; any inconsistencies were discussed by the reviewers to reach consensus.

The quality and integrity of this review were validated with Preferred Reporting Items for Systematic Reviews and Meta-Analyses, which focus on randomized trials but can also be used as a basis for reporting systematic reviews of other types of research, particularly evaluations of interventions [76]. The quality of case series (≥2 patients), in terms of inclusion in a meta-analysis, was evaluated by three assessors (P.C., L.C.P. and K.H.N.) by examining the following 8 criteria: (a) was there adequate reporting of selection/eligibility criteria, (b) was the selected population representative of that seen in normal practice, (c) was an appropriate measure of variability reported, (d) was loss to follow-up reported or explained, (e) were at least 90% of those included at baseline followed up, (f) were patients recruited prospectively, (g) were patients recruited consecutively and (h) did the study report relevant prognostic factors [77]. According to this scale, the quality rating is good if the answer is yes to all 8 criteria and satisfactory if the answer is yes to criteria b and d–f. In the case of meta-analysis, the criterion b for selection bias in the quality assessment scale is understood as differences in the baseline characteristics of individuals in different intervention groups, rather than whether the selected sample is representative of the population. Consequently, well-conducted and well-reported studies describing the use of different interventions were classified as being methodologically of poor quality if the choice of intervention was dependent on clinical findings. In contrast, if in the same study more than one technique was used but the selection was not based on findings but rather a change from one to another over time, such as from cord ligation to cord coagulation, then the answer to selection criterion b was yes.

Statistical Analysis

Data were pooled for each surgical method using meta-analytic techniques. Both fixed- and random-effects models were used to estimate weighted neonatal survival rates, with 95% confidence intervals, for each method of treatment for TRAP sequence. When

Table 1. Outcome of twin pregnancies with TRAP sequence managed expectantly or by endoscopic or intrafetal laser coagulation of the vessels of the acardiac twin according to gestational age at presentation in our centre

Presentation			Management	Outcome of pump twin		
group	n	GA, weeks		outcome	GA, weeks	GA <32 weeks
11–14 weeks	1[a]	13	pregnancy termination	termination (n = 1)	13	–
	9[a]	13 (11–14)	intrafetal laser at 12–14 weeks	alive (n = 6)	39 (32–40)	0
				dead (n = 3)	12 (12–14)	–
	10[a]	12 (11–14)	intrafetal laser at 16–18 weeks	alive (n = 8)	37 (32–41)	0
				dead (n = 2)	19	–
	14[a]	12 (11–14)	planned intrafetal laser at 16–18 weeks but blood flow stopped in acardiac twin in the intervening period	alive (n = 6)	39 (37–41)	0
				dead (n = 6)	15 (13–23)	–
				termination (n = 2)	16, 17	–
16–28 weeks	33[a]	19 (16–24)	intrafetal laser at 16–24 weeks	alive (n = 26)	36 (26–42)	4
				dead (n = 6)	20 (17–32)	–
				termination (n = 1)	22	–
	9[a]	20 (17–28)	endoscopic laser at 17–28 weeks	alive (n = 7)	38 (28–39)	3
				dead (n = 2)	23, 26	–
	4[a]	24 (19–28)	expectant management	alive (n = 4)	34 (32–36)	0
	5[b]	20 (17–26)	expectant management	alive (n = 3)	36 (32–39)	0
				dead (n = 1)	25	–
			pregnancy termination	termination (n = 1)	20	–

[a] Acardiac twin: blood flow presenst; [b] acardiac twin: blood flow absent. Values in parentheses represent ranges, except where indicated otherwise. GA = Gestational age.

the between-study heterogeneity was low, the fixed-effects model, which weighs each study by the inverse of its variance, was preferred over the random-effects model. Heterogeneity between studies was analyzed using both Higgins' I^2 and Cochrane's Q test. Heterogeneity was considered to be low if I^2 was below 0.50 [78, 79]. Publication bias was assessed by funnel plots of all the studies for each intrauterine intervention for TRAP sequence with survival rates on the x-axis in a linear scale and sample size on the y-axis.

Linear regression was used to assess the correlation between gestational age at treatment and survival rates and gestational age at birth.

The statistical software package SPSS 20.0 (IBM SPSS Statistics for Windows, version 20.0, IBM Corp., Armonk, N.Y., USA) and Meta-Analyst (Tufts Medical Center, Boston, Mass., USA) were used for data analysis.

Results

Findings in Our Centre

During the study period, we examined 96 twin and 12 triplet pregnancies with TRAP sequence presenting at a median gestational age of 16.5 weeks (range 11–30). Intrauterine intervention was undertaken in 67 cases and included endoscopic laser coagulation of the umbilical cord vessels of the acardiac twin (n = 11), which was essentially carried out between 1993 and 1996, and intrafetal laser coagulation (n = 56), which was carried out in or after 1996.

The twin pregnancies with TRAP sequence were referred either at 11–14 weeks' gestation or at 16–28 weeks (table 1). At presentation to our centre, in the 11–14 weeks group (n = 34), there was blood flow in the acardiac twin in all cases, whereas in the 16–28 weeks group (n = 51), blood flow in the acardiac twin was present in 46 cases and absent in 5.

In the 11–14 weeks group, 1 pregnancy was terminated at the request of the parents. In the remaining 33 cases, the management included, firstly, intrafetal laser coagulation at 12–14 weeks (n = 9), and in 6 of these (67%) the pump twin survived, and, secondly, delayed intrafetal laser planned for 16–18 weeks (n = 24). In the latter group, the planned procedure was carried out in 10 cases (42%), in 8 of which (80%) the pump twin survived, while in the other 14 (58%) there was spontaneous cessation of flow in the acardiac twin and the pump twin survived in 6 cases, died in 6 and was terminated in 2 because of fetal abnormalities (ventriculomegaly in one and dysplastic kidneys in the other).

Table 2. Outcome of triplet pregnancies with TRAP sequence managed expectantly or by endoscopic or intrafetal laser coagulation of the vessels of the acardiac triplet

Chorionicity/amnionicity	Presentation, weeks	Cessation of blood flow in acardiac triplet	Pump triplet	Other triplet
Dichorionic triamniotic	12.6	spontaneous in utero at 18.6 weeks	fetal death at 18.6 weeks	live birth at 28.6 weeks
Monochorionic triamniotic	14.7	spontaneous in utero at 22.3 weeks	fetal death at 22.3 weeks	fetal death at 22.3 weeks
Monochorionic triamniotic	16.3	spontaneous in utero at 17.0 weeks	fetal death at 17.0 weeks	fetal death at 17.0 weeks
Dichorionic triamniotic	19.9	spontaneous in utero at 19.9 weeks	fetal death at 24.0 weeks	live birth at 35.1 weeks
Dichorionic triamniotic	20.4	spontaneous in utero at 20.0 weeks	live birth at 27.9 weeks	live birth at 27.9 weeks
Monochorionic triamniotic	24.4	spontaneous at birth at 34.2 weeks	live birth at 34.2 weeks	live birth at 34.2 weeks
Dichorionic triamniotic	26.4	spontaneous at birth at 28.4 weeks	neonatal death at 28.4 weeks	neonatal death at 28.4 weeks
Dichorionic triamniotic	12.3	iatrogenic by intrafetal laser at 12.2 weeks	live birth at 27.5 weeks	live birth at 27.5 weeks
Monochorionic triamniotic	13.0	iatrogenic by endoscopic laser at 16.0 weeks	live birth at 35.6 weeks	live birth at 35.6 weeks
Dichorionic triamniotic	13.5	iatrogenic by intrafetal laser at 13.5 weeks	live birth at 37.0 weeks	live birth at 37.0 weeks
Dichorionic triamniotic	14.6	iatrogenic by intrafetal laser at 14.6 weeks	live birth at 36.1 weeks	live birth at 36.1 weeks
Monochorionic triamniotic	16.0	iatrogenic by intrafetal laser at 16.0 weeks	live birth at 37.0 weeks	live birth at 37.0 weeks
Dichorionic triamniotic	16.7	iatrogenic by endoscopic laser at 16.7 weeks	live birth at 35.4 weeks	live birth at 35.4 weeks

In the combined data from this and a previous study which includes most of our data [61], there were 30 pregnancies with TRAP sequence diagnosed at 11–14 weeks where fetal intervention was planned for 16–18 weeks; in 18 of these (60%) there was spontaneous cessation of flow in the acardiac twin, and in 11 (61.1% of the 18 or 36.7% of the 30) the pump twin also died or was terminated for ventriculomegaly.

In the 16–28 weeks group with blood flow in the acardiac twin at presentation (n = 46), the management included, firstly, intrafetal laser coagulation at presentation (n = 33), and in 26 of these (79%) the pump twin survived, secondly, endoscopic laser coagulation at presentation (n = 9), and in 7 of these (78%) the pump twin survived, and, thirdly, expectant management (n = 4), and in all of these cases the pump twin survived. In the cases of intrafetal laser, there was 1 pregnancy termination for fetal ventriculomegaly diagnosed 3 weeks after the procedure. In the 16–28 weeks group with no blood flow in the acardiac twin at presentation (n = 5), 1 pregnancy was terminated for major facial cleft and hypotelorism and the others were managed expectantly with survival of the pump twin in 3.

The triplet pregnancies were either monochorionic triamniotic (n = 5) or dichorionic triamniotic (n = 7; table 2). In 7 cases the pregnancies were managed expectantly, and cessation of blood flow in the acardiac triplet occurred spontaneously in utero (n = 5) or at birth (n = 2). In those with in utero cessation of blood flow in the acardiac triplet, there was also death of the 2 normal cotriplets in the monochorionic group (n = 2) and in the pump triplet in 2 of the 3 dichorionic triplets. In total, there were 2 pregnancies with 2 survivors, 2 with 1 survivor and 3 with no survivors, giving a survival rate of 6 of the 14 normal fetuses (42.9%). In 6 cases there was iatrogenic cessation of blood flow in the acardiac triplet by either endoscopic laser (n = 2) or intrafetal laser (n = 4) at a median gestational age of 15.3 weeks (range 12.2–16.7), and all 12 normal triplets survived.

Findings from the Systematic Review of the Literature

The literature search identified 375 articles on TRAP sequence, but after review, only 74 studies met the inclusion criteria of providing data on intrauterine interventions. Three of these studies used the technique of hysterotomy, and these were excluded from further analysis. After detailed assessment of the 71 remaining papers, we concluded that in some there was data duplication or overlap, and we therefore included only 53 studies for the final analysis. In the included 53 studies, 42 provided data for use of one intrauterine technique and 11 on more than one technique. Most studies reported data on 1 or 2 cases, and only 9 reported series of at least 10 cases [15, 20, 30, 33, 36, 55, 58, 60, 65].

The data from these studies on method, gestational age at intervention and survival of the pump twin or triplet together with our data are shown in tables 3–5. The weighted survival rates across studies and heterogeneity between studies for each intrauterine intervention are summarized in table 6 and illustrated in figures 1–3.

The quality of the case series is reported in tables 3 and 4, and this was assessed as being good or satisfactory in

Table 3. TRAP sequence in twins: reported extrafetal methods of treatment and survival rates

Method	Authors	Quality assessment	Mean GA (range), weeks	n	Pump twin survival, n
Cord coil	Hamada et al., 1989 [5]	NA	23	1	1 (100.0, 10.9–100.0)
	Porreco et al., 1991 [6]	NA	24	1	1 (100.0, 10.9–100.0)
	Tanawattanacharoen et al., 2002 [7]	NA	24	1	0 (0.0, 0.0–89.1)
	Total			3	2 (66.7, 20.8–93.9)
Cord ligation	McCurdy et al., 1993 [8]	NA	20	1	0 (0.0, 0.0–89.1)
	Foley et al., 1995 [9]	NA	22	1	1 (100.0, 10.9–100.0)
	Willcourt et al., 1995 [10]	NA	24	1	1 (100.0, 10.9–100.0)
	Deprest et al., 1998 [11][a]	satisfactory	(21–24)	3	2 (66.7, 15.4–95.7)
	Galinkin et al., 2000 [13]	NA	24	1	1 (100.0, 10.9–100.0)
	Bermúdez et al., 2003 [14]	NA	25	1	1 (100.0, 10.9–100.0)
	Quintero et al., 2006 [15][b]	poor	20 (16–26)	32	20 (62.5, 44.9–76.3)
	Total			40	26 (65.0, 49.5–77.9)
Cord coagulation – laser	Arias et al., 1998 [19]	NA	24	1	1 (100.0, 10.9–100.0)
	Hecher et al., 2006 [20][c]	poor	18 (14–24)	42	35 (83.3, 69.0–91.8)
	Quintero et al., 2006 [15][d]	poor	20 (18–23)	7	4 (57.1, 23.0–85.6)
	present study[e]	good	20 (15–28)	9	7 (77.8, 42.1–94.4)
	Total			59	47 (79.7, 67.7–88.0)
Cord coagulation – monopolar	Holmes et al., 2001 [26]	good	20 (16–24)	3	3 (100.0, 26.6–100.0)
	Chao et al., 2002 [27]	NA	23	1	1 (100.0, 10.9–100.0)
	Chang et al., 2004 [28]	satisfactory	(22–24)	2	1 (50.0, 5.9–94.1)
	Total			6	5 (83.3, 43.6–97.0)
Cord coagulation – bipolar	Deprest et al., 2000 [22]	good	19 (18–23)	5	4 (80.0, 30.9–97.3)
	Gallot et al., 2003 [29]	poor	23	2	2 (100.0, 19.4–100.0)
	Robyr et al., 2005 [30]	good	17 (16–27)	17	11 (64.7, 40.4–83.2)
	Gul et al., 2009 [31]	NA	20	1	1 (100.0, 10.9–100.0)
	He et al., 2010 [32]	good	(21–24)	4	2 (50.0, 12.3–87.7)
	Roman et al., 2010 [33]	poor	(15–26)	12	10 (83.3, 52.3–95.8)
	Yamamoto et al., 2010 [34]	NA	18	1	1 (100.0, 10.9–100.0)
	Corbacioglu et al., 2012 [35]	poor	20 (15–32)	4	2 (50.0, 12.3–87.7)
	Bebbington et al., 2012 [36]	poor	20 (16–25)	35	32 (91.4, 76.6–97.2)
	Lanna et al., 2012 [37][f]	poor	(24–27)	5	2 (40.0, 10.0–80.0)
	Total			86	67 (77.9, 68.1–85.4)
Placental anastomoses – laser	Hecher et al., 2006 [20][g]	poor	14–17	18	13 (72.2, 48.1–87.9)
	Quintero et al., 2006 [15]	poor	19 (15–23)	6	6 (100.0, 42.3–100.0)
	Nakata et al., 2008 [40]	NA	22	1	1 (100.0, 10.9–100.0)
	Total			25	20 (80.0, 60.9–91.1)

Values in parentheses represent percentages with 95% confidence intervals, except where indicated otherwise. GA = Gestational age; NA = not applicable.

[a] Includes all cases published in Deprest et al., 1996 [12].

[b] Includes cases published in Quintero et al., 1994 [16], Quintero et al., 1995 [17] and Quintero et al., 1996 [18].

[c] Includes cases published in Hecher et al., 1997 [21], Deprest et al., 2000 [22] and Lewi et al., 2006 [23].

[d] Includes a case published in Quintero et al., 2002 [24].

[e] Includes cases published in Ville et al., 1994 [25].

[f] Includes cases published in Nicolini et al., 2001 [38].

[g] Includes a case published in Hecher et al., 1996 [39].

the majority of studies. The funnel plots for the 4 most commonly used techniques are shown in figure 4, and they indicate low risk of bias. There was one outlier in the funnel plot for cord bipolar coagulation [36]. A likely explanation for this is that the quality of the study was methodologically poor because there was a selection bias in favour of bipolar coagulation, rather than radiofrequency ablation, in technically less challenging cases; radiofrequency ablation was preferred in cases involving earlier gestation, smaller fetal mass, presence of severe oligohy-

Table 4. TRAP sequence in twins: reported intrafetal methods of treatment and survival rates

Method	Authors	Quality assessment	Mean GA (range), weeks	n	Pump twin survival, n
Intrafetal alcohol	Tongsong et al., 2002 [41]	NA	25	1	1 (100.0, 10.9–100.0)
	Porreco, 2004 [42]	NA	17	1	1 (100.0, 10.9–100.0)
	Sepulveda et al., 2004 [43][a]	good	24 (20–32)	8	5 (62.5, 28.5–87.5)
	Ozeren et al., 2004 [46]	NA	16	1	0 (0.0, 0.0–89.1)
	Gul et al., 2009 [31][b]	satisfactory	20 (20–24)	4	2 (50.0, 12.3–87.7)
	Corbacioglu et al., 2012 [35]	poor	20 (15–32)	5	3 (60.0, 20.0–90.0)
	Miković et al., 2011 [48]	satisfactory	20, 29	2	1 (50.0, 5.9–94.1)
	Total			22	13 (59.1, 38.7–76.7)
Intrafetal MP coagulation	Rodeck et al., 1998 [49]	good	16–24	4	4 (100.0, 32.6–100.0)
	Holmes et al., 2001 [26]	good	20 (16–24)	8	6 (75.0, 37.7–93.7)
	Sepulveda et al., 2003 [50]	NA	29	1	1 (100.0, 10.9–100.0)
	Total			13	11 (84.6, 57.8–95.7)
Intrafetal laser	Jolly et al., 2001 [51]	poor	14–15	2	2 (100.0, 19.4–100.0)
	Soothill et al., 2002 [52]	poor	19–16	2	2 (100.0, 19.4–100.0)
	Sepulveda et al., 2004 [53]	NA	26	1	1 (100.0, 10.9–100.0)
	Weisz et al., 2004 [54]	poor	21–23	2	2 (100.0, 19.4–100.0)
	O'Donoghue et al., 2008 [55]	satisfactory	15 (12–21)	10	6 (60.0, 29.7–84.2)
	Scheier and Molina, 2012 [56]	good	16 (13–20)	6	5 (83.3, 36.9–97.7)
	Wegrzyn et al., 2012 [57]	NA	16	1	1 (100.0, 20.7–100.0)
	Berg et al., 2014 [58]	poor	15 (13–20)	11	8 (72.7, 41.4–91.0)
	Novak et al., 2013 [59]	NA	24	1	1 (100.0, 10.9–100.0)
	Pagani et al., 2013 [60]	satisfactory	18 (12–27)	16	13 (81.3, 55.3–93.8)
	present study[c]	good	17 (12–24)	52	40 (76.9, 63.6–86.4)
	Total			104	81 (77.9, 69.0–84.8)
Intrafetal RFA	Hirose et al., 2004 [62]	NA	27	1	1 (100.0, 20.7–100.0)
	Paramasivam et al., 2010 [63]	good	18 (15–21)	5	4 (80.0, 37.6–96.4)
	Berg et al., 2014 [58]	poor	23 (18–33)	7	6 (85.7, 48.7–97.4)
	Cabassa et al., 2013 [64]	good	17 (14–23)	7	5 (71.4, 35.9–91.8)
	Lee et al., 2013 [65][d]	poor	20 (16–25)	87	71 (81.6, 72.2–88.6)
	Weichert et al., 2013 [70]	NA	23	1	1 (100.0, 20.7–100.0)
	Total			108	88 (81.5, 73.1–87.7)

Values in parentheses represent percentages with 95% confidence intervals, except where indicated otherwise. GA = Gestational age; NA = not applicable; MP = monopolar coagulation; RFA = radiofrequency ablation.

[a] Includes cases published in Sepulveda et al., 1995 [44] and Sepulveda et al., 2000 [45].

[b] Includes a case published in Gul et al., 2005 [47].

[c] Includes cases published in Lewi et al., 2010 [61].

[d] Includes cases published in Tsao et al., 2002 [66], Jelin et al., 2010 [67], Lee et al., 2007 [68], Livingston et al., 2007 [69], Roman et al., 2010 [33] and Bebbington et al., 2012 [36].

dramnios and where placental location created limited access for bipolar coagulation [36].

Individual Data Analysis on Intrafetal Laser

In the combined data from previous studies [51–60] and the current study there were 104 twin pregnancies treated by intrafetal laser. There was no significant association between the gestational age at treatment and survival rate (mean 77.9%, r = 0.066, p = 0.508). The survival rate was 77.4% for the 31 cases treated at 12–15 weeks, 78.6% for the 42 cases treated at 16–19 weeks and 77.4% for the 31 cases treated at 20–27 weeks.

In the survivors, there was a significant inverse association between gestational age at treatment and gestational age at birth (r = –0.297, p = 0.007; fig. 5). The mean gestational age at birth was 38 and 34 weeks when treatment was carried out at 13 and 27 weeks, respectively.

Table 5. TRAP sequence in triplets: reported methods of treatment and survival rates

Method	Authors	Mean GA (range), weeks	n	Pump twin survival, n
Cord coagulation – laser	Lewi et al., 2006 [23][a]	(16–19)	3 MC	3 (100.0, 43.9–100.0)
	present study	16	1 DC, 1 MC	2 (100.0, 34.2–100.0)
	Total		5	5 (100.0, 56.6–100.0)
Intrafetal MP coagulation	Holmes et al., 2001 [26]	19	1 DC	1 (100.0, 20.7–100.0)
	Sepulveda et al., 2003 [50]	16	1 MC	0 (0.0, 0.0–79.3)
	Total		2	1 (50.0, 9.5–90.5)
Intrafetal laser	Cavoretto et al., 2009 [72]	19	1 DC	1 (100.0, 20.7–100.0)
	Sepulveda et al., 2009 [73]	17	2 DC	1 (50.0, 9.5–90.5)
	Scheier and Molina, 2012 [56]	16	1 MC	1 (100.0, 20.7–100.0)
	Pagani et al., 2013 [60]	15	1 DC	1 (100.0, 20.7–100.0)
	present study	14 (12–16)	3 DC, 1 MC	4 (100.0, 51.0–100.0)
	Total		9	8 (88.9, 56.5–98.0)
Intrafetal RFA	Argoti et al., 2013 [74]	23	1 MC	1 (100.0, 20.7–100.0)
	Lee et al., 2013 [65]	19 (18–21)	5 DC, 6 MC	7 (63.6, 35.4–84.8)
	Total		12	8 (66.7, 39.1–86.2)

Values in parentheses represent percentages with 95% confidence intervals, except where indicated otherwise. GA = Gestational age; MP = monopolar coagulation; RFA = radiofrequency ablation; DC = dichorionic; MC = monochorionic.

[a] Includes cases published in Van Schoubroeck et al., 2004 [71].

Table 6. Pooled estimates of survival rate of each method of treatment for TRAP sequence

Method	Pooled estimate, %	Heterogeneity		
		I^2 statistic	Cochrane's Q	p value
Cord coil (n = 3)	59.1 (18.5–90.2)	0.000	0.547	0.270
Cord ligation (n = 40)	63.4 (48.3–76.3)	0.000	0.599	0.080
Cord coagulation – laser (n = 59)	78.4 (65.8–87.3)	0.000	0.700	0.000
Cord coagulation – monopolar (n = 6)	72.4 (32.1–93.5)	0.000	0.472	0.178
Cord coagulation – bipolar (n = 86)	73.4 (61.8–82.5)	0.154	0.917	0.003
Placental anastomoses – laser (n = 25)	75.7 (55.1–88.7)	0.000	0.516	0.022
Intrafetal alcohol (n = 22)	58.1 (37.9–75.9)	0.000	0.590	0.228
Intrafetal MP coagulation (n = 13)	78.8 (50.6–93.1)	0.000	0.304	0.051
Intrafetal laser (n = 104)	76.0 (67.0–83.1)	0.000	0.678	0.000
Intrafetal radiofrequency (n = 108)	80.8 (72.3–87.1)	0.000	0.383	0.000

The fixed-effects model was used in all cases because the heterogeneity was low. Values in parentheses represent 95% confidence intervals. MP = Monopolar coagulation.

Discussion

A study in the early 1990s highlighted that in 49 expectantly managed pregnancies with TRAP sequence the perinatal mortality rate was 55% [1]. In the past 3 decades, several methods for intrauterine intervention have been developed, aiming to improve the outcome for the pump twin [2–75]. Most studies in the literature have reported treatment in 1–10 cases, with only a handful examining larger series. In the combined data, the survival rate of the pump twin was about 80% for most techniques, including ablation of umbilical cord vessels by laser or diathermy, coagulation of placental anastomoses by laser or ablation of intrafetal vessels by monopolar diathermy, laser or ra-

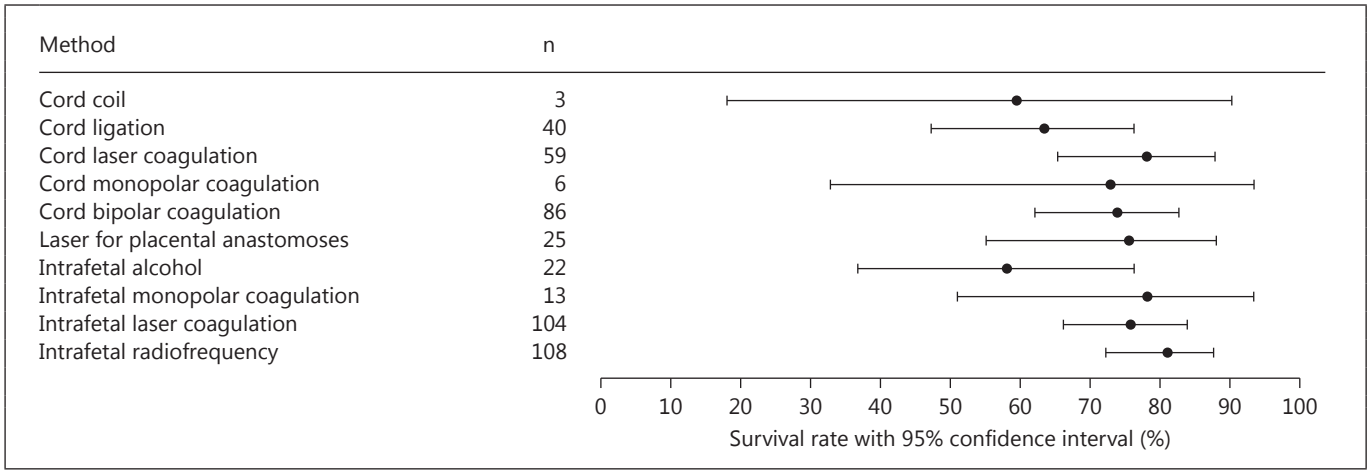

Fig. 1. Pooled estimates of survival rates across studies and heterogeneity between studies for each intrauterine intervention for TRAP sequence.

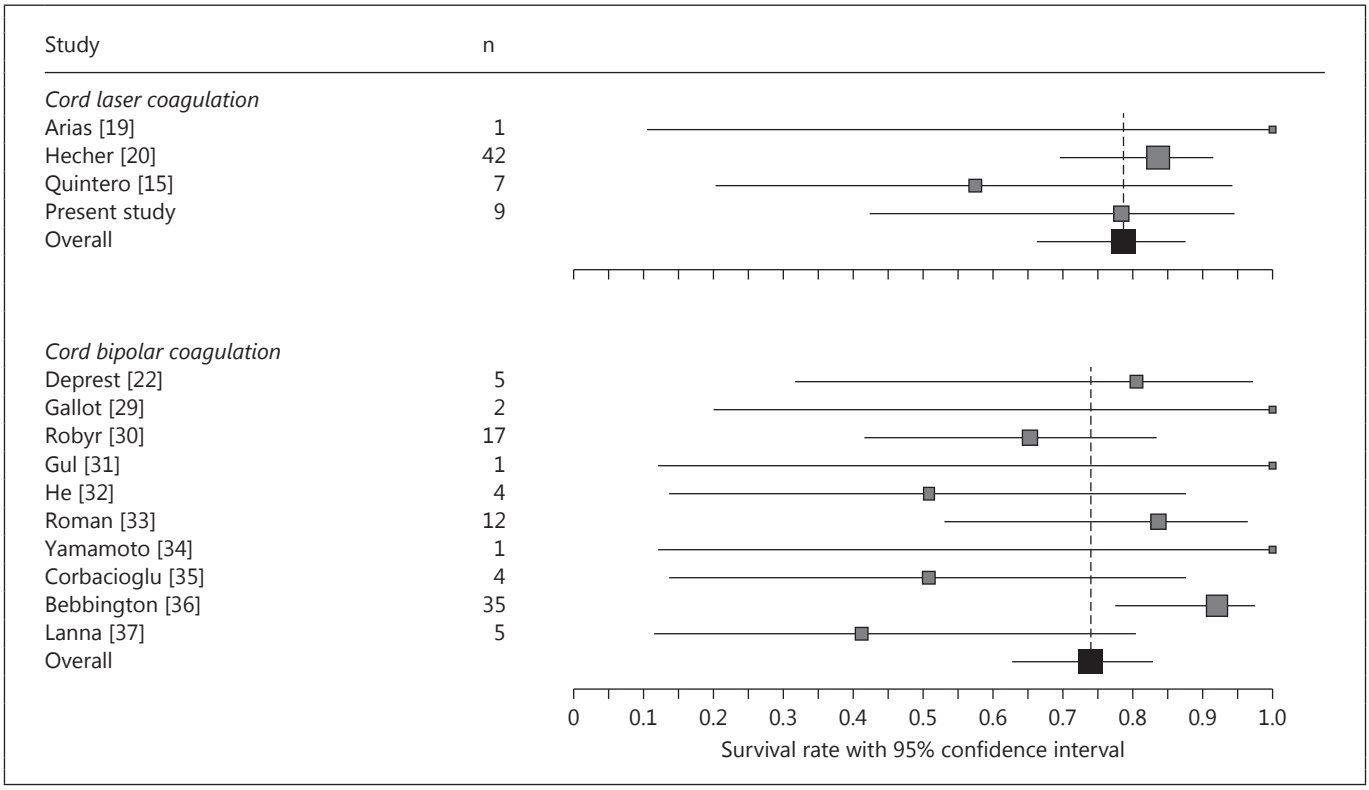

Fig. 2. Forest plots with pooled proportion (fixed-effects model) of reported neonatal survival in pregnancies with TRAP sequence treated by umbilical cord laser or bipolar coagulation.

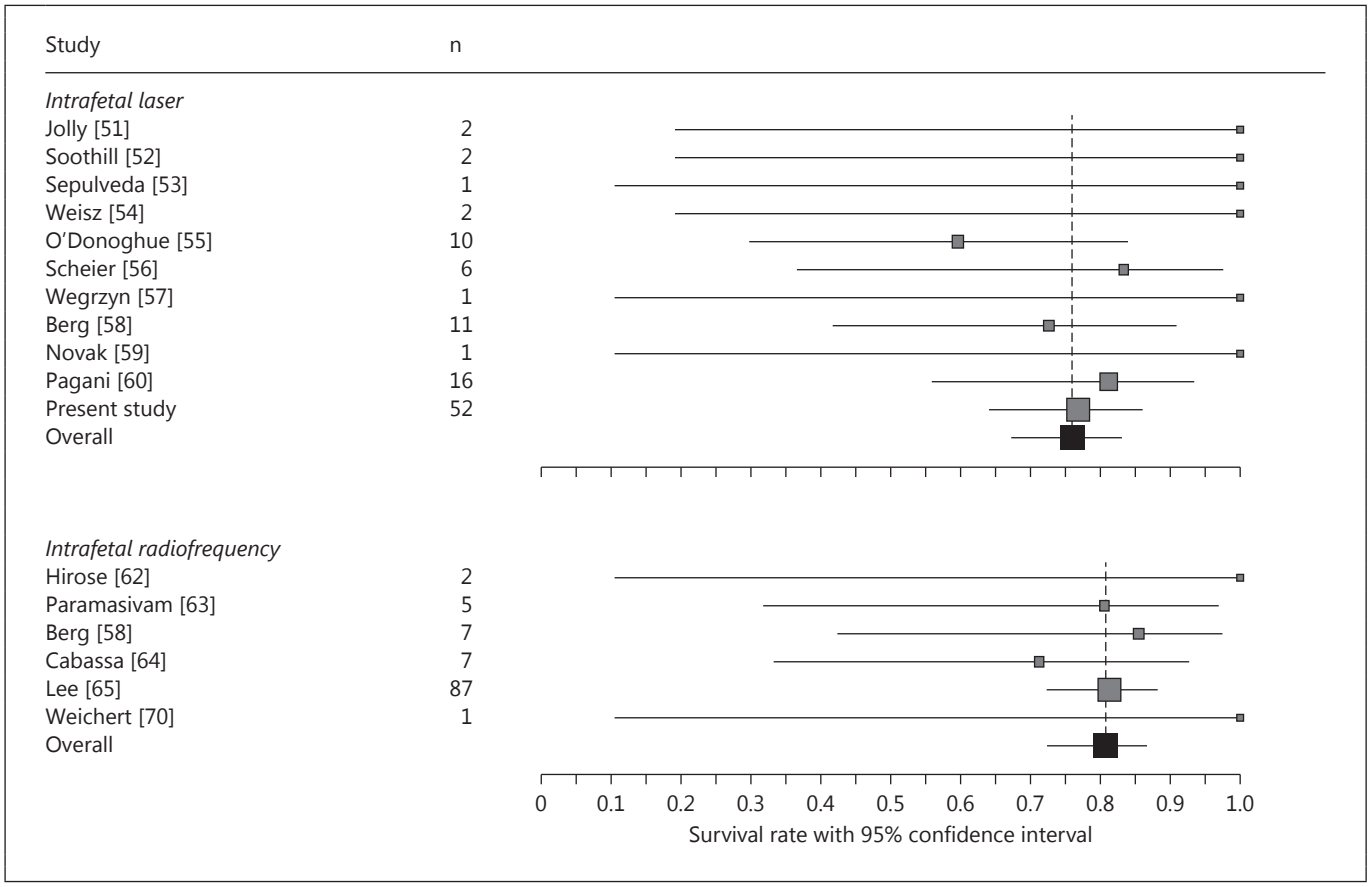

Fig. 3. Forest plots with pooled proportion (fixed-effects model) of reported neonatal survival in pregnancies with TRAP sequence treated by intrafetal laser or intrafetal radiofrequency ablation.

diofrequency. Lower survival rates were achieved after cord ligation and the use of cord coils or intrafetal injection of alcohol.

On the basis of publications within the last 3 years, it appears that the most commonly used techniques now are ultrasound-guided bipolar cord coagulation and ablation of intrafetal vessels by laser or radiofrequency, rather than endoscopic procedures, presumably because of their less invasive nature. Two studies comparing bipolar cord coagulation and intrafetal radiofrequency for a variety of complications in monochorionic twins reported similar rates of survival for the two techniques [33, 36].

In both dichorionic and monochorionic triplet pregnancies with TRAP sequence, a few case reports and small series have demonstrated the feasibility of intrauterine interventions, mainly endoscopic laser coagulation of umbilical cord vessels and ablation of intrafetal vessels by laser or radiofrequency, with good results. In contrast, in our 7 triplet pregnancies that were managed expectantly, only 6 of the 14 normal babies survived. These findings suggest that the management of triplet pregnancies with TRAP sequence should be the same as in twin pregnancies.

The survival rate of about 80% following interruption of the blood supply to the acardiac twin is higher than the reported rate of 45% with expectant management [1]. However, these survival rates relate to pregnancies with TRAP sequence diagnosed at or after 16 weeks' gestation. More recently, with the widespread introduction of an ultrasound scan at 11–13 weeks' gestation, as part of early screening for fetal aneuploidies, many cases of TRAP sequence are now diagnosed during the first trimester of pregnancy [80]. Despite this earlier diagnosis, intrauterine therapeutic interventions were delayed until after 15 weeks' gestation, because the risks of amniorrhexis and miscarriage were considered to be too high if carried out before obliteration of the celomic cavity [81–83].

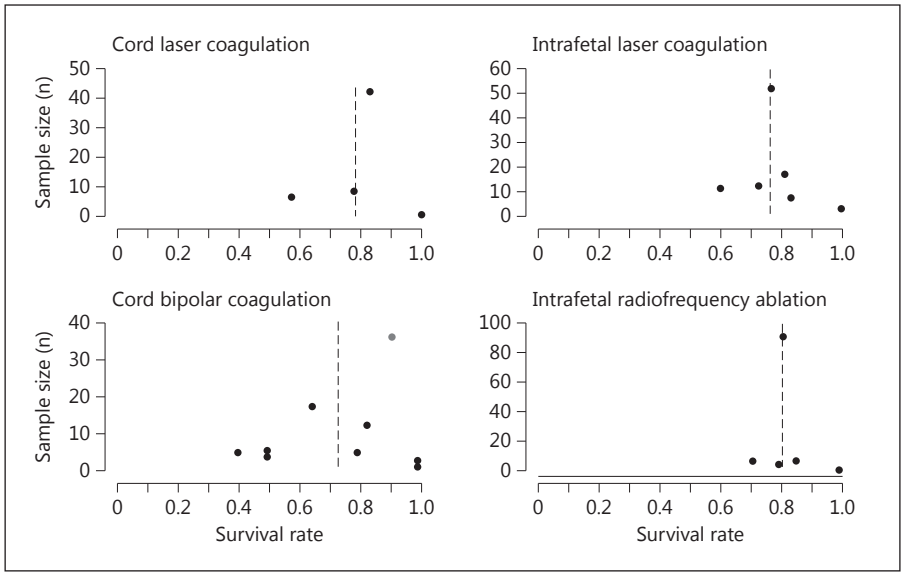

Fig. 4. Assessment of publication bias for the 4 most commonly used techniques of intrauterine intervention for TRAP sequence, with survival rates on the x-axis in a linear scale and sample size on the y-axis. The grey dot is an outlier from a study of poor methodological quality.

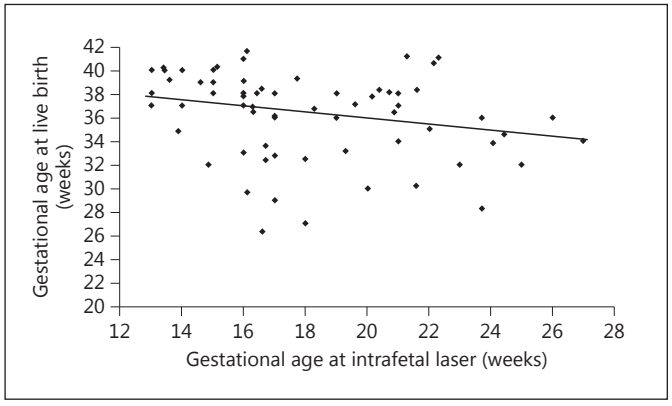

Fig. 5. Individual data analysis on intrafetal laser. Association between gestational age at treatment and gestational age at birth.

As demonstrated in this and in our previous study [61], the delay in intervention between the diagnosis of TRAP sequence at 11–13 weeks until 16–18 weeks is associated with spontaneous cessation of flow in the acardiac twin in 60% of cases, and in about 60% of these there is also death or brain damage in the pump twin. This finding has raised the possibility that the outcome may be improved by elective intervention at the time of the first-trimester diagnosis. Two factors have contributed to this concept. The first of these is the realization that at 11–13 weeks' gestation there are no sonographic features, including discordance in fetal size and nuchal translucency thickness, that could help distinguish between the pregnancies resulting in death of the pump twin and those that would survive until prophylactic intervention at 16–18 weeks [56, 61], and the second is that ultrasound-guided intrafetal laser is less invasive than endoscopic interventions and therefore less likely to cause amniorrhexis and miscarriage when undertaken at 12–14 weeks [40, 44].

In the 104 pregnancies treated by intrafetal laser, the survival rate was unrelated to the gestational age at intervention, suggesting that in cases diagnosed at 11–13 weeks there is no benefit in delaying intervention until 16–18 weeks. An additional benefit in favour of early intervention is reduced risk of preterm birth because there is an inverse association between gestational age at treatment and gestational age at birth.

The technique of choice for early intervention is likely to be intrafetal laser or radiofrequency, which require the intrauterine insertion of 17- to 18-gauge needles, rather than ultrasound-guided bipolar cord coagulation, which is carried out through trocars of 3.3–3.8 mm in diameter [33, 36, 37]. In this study we provided some evidence that with intrafetal laser the risk of death for the pump twin may not be higher if the intervention is undertaken at 12–14 weeks than at later gestational ages. However, there is a scarcity of data on the use of radiofrequency ablation before 15 weeks' gestation. A large multicentre study reported that the rate of intrauterine death of the pump twin was significantly higher in the cases undergoing radiofrequency ablation at 15–19 weeks that in those treated after 19 weeks (33.3 vs. 10.7%) [65]. Similarly, a large single-centre study on selective feticide by ultrasound-

guided bipolar cord coagulation for a variety of indications in monochorionic twins reported that the rate of miscarriage was significantly higher when the intervention was performed at 16–19 weeks compared to those treated after 19 weeks (45 vs. 3%) [37]. It is therefore likely that with bipolar coagulation of the cord and intrafetal radiofrequency ablation, the risk of miscarriage would be even higher if the intervention is undertaken at 12–14 weeks. Another technique that could potentially be useful for early intervention in TRAP sequence is high-intensity focused ultrasound from outside the maternal abdomen to achieve cessation of blood flow within the acardiac twin, but the effectiveness and safety of this approach requires investigation [75, 84].

A major limitation of pooling data from case series is that they are highly prone to several sources of bias, including selection, performance, attrition and reporting, and the direction of the effect of these biases may be variable and unpredictable, which is commonly reflected in the high heterogeneity between such studies [85, 86]. Nevertheless, it is acceptable that systematic reviews can include case series on new technologies [87] or interventions which are unlikely to be studied in randomized controlled trials [85]. In fact, case series have been used in 30% of the National Institute for Clinical Excellence health technology assessment reports [86]. In these instances, the risk of bias can be reasonably contained by following a firm protocol which addresses methodological differences and other potential confounders. In our review, the risk of most of the common sources of bias was low. For example, the risk of selection and measurement bias was low because both the disease, TRAP sequence, and the outcome, neonatal survival of the pump fetus, are well-defined and objectively ascertained conditions. Attrition bias was also low, because included studies reported on consecutive cases with known outcome. Case reports and small case series are generally regarded as particularly susceptible to publication bias. However, an extensive health technology assessment report has shown that there is a consistent lack of association between sample size and outcome and recommended that size limitations should not be used as inclusion criteria [86, 87]. The low risk of bias in our review is supported by the findings of the funnel plots and the markedly low heterogeneity between studies.

In summary, this study has demonstrated the evolution in intrauterine interventions aiming to improve the outcome of pump twins in TRAP sequence. These interventions have traditionally been undertaken at or after 16 weeks' gestation, and with most techniques the neonatal survival rate of the pump twin has been about 80%. In the last decade, the widespread introduction of a routine first-trimester ultrasound examination has created a new challenge in the management of TRAP sequence because it has exposed a hidden mortality in this condition in the period between 11–13 and 16–18 weeks' gestation. Preliminary data have demonstrated the feasibility, effectiveness and potential safety of intrafetal laser at 12–14 weeks. Randomized studies are needed to compare intervention at 12–14 versus 16–18 weeks' gestation and the use of intrafetal laser versus radiofrequency ablation for such intervention.

Acknowledgement

This study was supported by grants from the Fetal Medicine Foundation (Charity No. 1037116).

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