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# The Management of Acardiac Twinning: Twin Reverse Arterial Perfusion Sequence – An International Survey

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## Mini-Summary

What does this study add to current knowledge?

- Our survey is the first to document the differences in the management of twin reverse arterial perfusion (TRAP) sequence among fetal intervention centers worldwide, incorporating responses from five continents and 29 countries.

What are the main clinical implications?

- This survey discloses a lack of consensus among the international fetal therapy community in the management of TRAP sequence regarding the ultrasound surveillance eligibility for surgery, optimal surgical technique, and the earliest gestational age for an in utero intervention.

## Keywords

Acardiac twin · Twin reversed arterial perfusion · Prenatal diagnosis · Fetal therapy · Ultrasonography · Monochorionic twin pregnancy

## Abstract

**Introduction:** The optimal approach and therapy method for the acardiac twin with a reverse arterial perfusion sequence has not yet been established. The aim of this study was to determine the clinical practice patterns among international fetal therapy units in their management of these cases.

**Methods:** A survey was sent to fetal centers across the world via email between December 2020 and December 2021. **Results:** Responses were obtained from 77% contacted centers. The most frequent ultrasound variables used in the evaluation of twin reverse arterial perfusion sequence include echocardiographic assessment of the pump twin and umbilical artery Doppler waveforms in the acardiac and pump twins, in 90% and 80% of the centers, respectively. Most centers in Europe and Latin America propose an in utero intervention in all cases. Most centers in Europe and Latin America prefer interstitial laser ablation, whereas radiofrequency ablation (RFA) is preferred in North America. The earliest gestational age for an intervention is on mean 13 weeks in Europe, which is earlier than the other geographic areas ( $p = 0.001$ ). **Conclusions:** Most centers agreed that antenatal evaluation should include echocardiography along with the UA Doppler waveform measurements, and the most frequently used interventions were interstitial laser ablation or RFA at a median between 14 and 26 weeks.

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## Introduction

Twin reverse arterial perfusion (TRAP) sequence is a unique complication that occurs in 1% of monochorionic (MC) twin pregnancies [1, 2]. However, some authors suggest that the incidence may be higher, up to 2.6% of all MC twin pregnancies, due to the early undetected death of the pump twin or early arrest of perfusion to the acardiac twin and the increased rate of MC twinning associated with assisted reproductive technologies [3]. The acardiac twin, as its name suggests, does not have a functioning heart and entirely depends on the blood flow it receives from a normal co-twin (also called the pump twin) through an arterio-arterial (AA) anastomosis [1]. The acardiac twin is the true parasite that puts the pump twin at risk of perinatal morbidity and mortality from cardiac overload and polyhydramnios-related preterm birth [4]. The presence of AA and deep veno-venous (VV) placental vascular anastomoses is an essential component for the development of TRAP sequence, and two hypotheses have been proposed for the pathophysiologic etiology of this unique disorder in MC twinning. In the first one, the reversed flow through the umbilical artery results in preferential perfusion of the lower portion of the evolving acardiac twin, causing morphogenic disruption of its body due to oxygen deprivation [5, 6], after which deoxygenated blood is returned via VV anastomoses to the pump twin [7]. The second theory attributes the disorder to a primary defect in embryo-

genesis, resulting in an acardiac twin with retrograde blood flow through the placental vascular anastomoses [8]. Regardless of the actual etiology, the pump twin is at increased risk of perinatal morbidity and mortality from premature delivery, due to the development of cardiac overload and polyhydramnios [4].

The prenatal management of TRAP sequence aims to prevent a very preterm birth of pump twin and maximize its probability of intact survival. In the absence of randomized controlled trials, management strategies have been based on meta-analyses and single-center case series [9–11]. In the absence of poor prognostic predictors, several authors propose expectant management with serial ultrasound (US) evaluation [7, 12, 13], while others favor an early prophylactic in utero intervention [14–16]. The aim of this survey was to determine the clinical practice patterns among the international fetal therapy community in the treatment of TRAP sequence.

## Materials and Methods

Contact was made with Maternal-Fetal Medicine (MFM) scientific federations to determine the fetal units around the world to send the survey. We contacted members of the North American Fetal Treatment Network (NAFNet), the International Fetal Medicine and Surgery Society (IFMSS), the Ibero-American Society for Fetal Diagnosis and Therapy (SIADTP), the Latin American Federation of the Association of Perinatal Medicine (FLAMP), the Perinatal Medicine committee of the Latin American Federation of Societies of Obstetrics and Gynecology (FLASOG); the members of the previous EUROFETUS consortium and the International Society for Prenatal Diagnosis (ISPD). The units were contacted between December 2020 and December 2021 with the possibility to choose between two formats, either to reply to the questions in the same email or submit the questionnaire through Google Forms. Individuals were surveyed in Spanish or English, as appropriate.

The survey was divided into two modules (online suppl. material; for all online suppl. material, see <https://doi.org/10.1159/000531791>). The first part collected data on center- and operator-related characteristics, and the second part contained questions about US surveillance and surgical indications and techniques. In total, 13 statements were evaluated, of which, four were open and the remainder were multiple choice questions (online suppl. Table 1).

Surveys were excluded if there was an incomplete answer to the questionnaire. If the survey was sent in more than once through automatically forwarding by the Google Forms platform or to the institutional e-mail address, we eliminated the second and subsequent copies of the questionnaire.

We entered the responses into a database in Excel (Microsoft® Excel® for Microsoft 365 MSO version 2110 compilation 16.0.14527.20234) and performed descriptive statistical frequency measures. The differences in practice between center- and operator-related characteristics of the different fetal therapy units

**Table 1.** Center- and operator-related characteristics of the included fetal centers

Respondent characteristics	n (%)
Geographic location	
North America	24 (31)
Europe	24 (31)
Latin America	24 (31)
Other	6 (7)
Total	78 (100)
Experience, years	
<5	5 (6.5)
5–10 s	17 (22)
>10 years	54 (71)
Health care setting	
Public	17 (22)
Private practice	8 (10.5)
Private hospital	10 (13)
University hospital	41 (54)
Average MC twin pregnancies assessed per year	
<100 cases	33 (43)
100–200 cases	33 (43)
>200 cases	10 (13)
Average acardiac twin cases assessed per year	
<5 cases	47 (62)
5–10 cases	26 (34)
>10 cases	3 (4)

were compared using Fisher’s exact test to determine the degree of association between independent categorical variables and Kruskal-Wallis analysis (for numerical variables – assuming a normal population distribution) and considering  $p < 0.05$  as significant.

## Results

We contacted 101 fetal therapy units and received 89 responses; eleven duplicate responses from the same unit were excluded, resulting in a survey response rate of 77% (78/101 centers). The value associated with each variable in Tables 1–4 corresponds to the count of fetal centers ( $n$ ) that answered affirmatively. Two centers stated they did not offer any fetal therapy for TRAP sequence, so 76 surveys were included in the final analysis.

From North America, we obtained a response rate of 75% (24/32), from Europe 82% (24/29), Latin America 82% (24/29), and 54.5% (6/11) from centers in Australia, Asia, and Africa, of which two were in Australia, and one each in India, Lebanon, Israel, and South Africa. Centers from North America, Europe, and Latin America were equally represented, whereas less than 10% were located in Australia, Asia, and Africa. Most respondents (71%)

had more than 10 years’ experience, and 80% worked in a public or university setting. About half of the units evaluated more than a hundred MC twin pregnancies a year, but only 4% evaluated more than 10 TRAP cases per year (Table 1). The ultrasound variables used in the US evaluation of TRAP sequence are represented in Table 2. The most common parameters are echocardiogram in the pump twin and umbilical artery Doppler studies in the acardiac and pump twins assessed in 90% and 80% of TRAP cases, respectively. Also, the difference in the estimated fetal weight (EFW) or abdominal circumference between the acardiac and pump twins was evaluated in most units. A variety of 23 additional US parameters were assessed in minority of units.

In expectantly managed cases, 68% of centers ( $n = 52$ ) indicated they would assess the patient once a week; 19% ( $n = 15$ ) would see the patient every 2 weeks; 5% ( $n = 4$ ) twice a week; and 7% ( $n = 5$ ) would prefer another time interval (Table 3). There were no differences in surveillance interval according to center- or operator-specific characteristics (online suppl. Fig. 1).

Almost half of the surveyed fetal centers (43.3%,  $n = 33$ ) recommended an in utero intervention in all cases of an acardiac twin; 32.8% ( $n = 25$ ) when the EFW of acardiac:pump twin was >50%; 27.6% ( $n = 21$ ) waited until the TRAP sequence was set; 19.7% ( $n = 15$ ) used an acardiac:pump twin abdominal circumference ratio >50%; and 9.2% ( $n = 7$ ) recommended intervention when there was evidence of a low pulsatility index (PI) in the UA Doppler of the acardiac compared to the pump twin. Nineteen centers stated that they had more than one surgical indication. There were significant differences ( $p = 0.003$ ) between the geographic location of the fetal therapy center and the indications for intervention in the management of these cases, with the majority of European (54.1%,  $n = 13$ ) and Latin American (50%,  $n = 12$ ) centers recommending an in utero intervention in all cases of TRAP sequence. Alternatively, the acardiac:pump twin EFW ratio >50% was the most frequent indication for an intervention in North American centers ( $n = 14$ , 58.3%) (online suppl. Fig. 2).

### Preferred Surgical Intervention

In most centers (59%,  $n = 45$ ), interstitial laser ablation of the acardiac twin was their preferred approach. In decreasing order, other techniques included radiofrequency ablation (RFA) (38%,  $n = 29$ ), fetoscopic placental laser ablation (34%,  $n = 26$ ), bipolar ligation (28%,  $n = 21$ ), and fetoscopic bipolar ligation (22%,  $n = 17$ ). One Latin American center utilized percutaneous monopolar thermal occlusion. Eleven (14.4%) centers

**Table 2.** Ultrasound variables used in the evaluation of TRAP sequence

Ultrasound variable	<i>n</i>	%
Echocardiography		
Twin pump echocardiogram	68	89.47
TEI index	2	2.63
Fetal echocardiography in case of subjective cardiac dysfunction, Doppler alteration, or hydrops	1	1.32
Doppler assessment		
Umbilical artery Doppler in the acardiac twin and pump twin	61	80.26
Ductus venosus Doppler	16	21.05
MCA Doppler	9	11.84
Tricuspid flow Doppler	3	3.95
Color Doppler of the anastomoses	1	1.32
Umbilical vein Doppler of the twin pump	1	1.32
Umbilical artery Doppler in only the acardial twin	1	1.32
Umbilical artery Doppler in only the pump twin	1	1.32
Biometric parameters		
Weight ratio calculation of the acardiac and pump twins	34	44.74
Abdominal circumference ratio calculation between acardiac and pump twins	28	36.84
Weight of the acardiac twin	27	35.53
CRL/URL ratio	6	7.89
Volume of the acardiac twin	4	5.26
Amniotic fluid assessment	4	5.26
Prospective evaluation of the pump twin growth	2	2.63
Length of the acardiac twin	2	2.63
Femoral length of the acardiac twin	1	1.32
Cervical length	1	1.32
Diameter of the intra-abdominal umbilical vein	1	1.32
Subjective characterization		
Umbilical cord insertions	3	3.95
Evaluation of subcutaneous edema and hydrops	2	2.63
Chorionicity	2	2.63
Subjective assessment without taking biometrics	1	1.32
CNS evaluation in the twin pump	1	1.32

MCA, middle cerebral artery; CRL, crown-rump length; URL, upper pole-rump length.

**Table 3.** Intervals to follow-up protocols used in the cases of the acardiac twin – TRAP sequence of the included fetal centers

Follow-up interval	<i>n</i> (%)
Twice a week	4 (5.3)
Once a week	52 (68.4)
Once every 2 weeks	15 (19.7)
Other	5 (6.6)

indicated that they used an alternative method, including fetoscopic ligation of the acardiac twin's umbilical cord ( $n = 5$ ), cord coagulation by laser ( $n = 3$ ), microwave ablation ( $n = 2$ ), or placental laser ablation of the AA and VV anastomoses ( $n = 1$ ). Forty-three fetal centers (56.5%) use more than one technique to treat these cases

(Table 4). There were also significant differences according to the geographic location of a fetal therapy center and their preferred surgical technique for the treatment of TRAP sequence ( $p < 0.001$ ). Percutaneous RFA was the most widely used technique in North America (75%,  $n = 18$ ), whereas interstitial laser ablation was preferred in Europe (75%,  $n = 18$ ) and Latin America (70.8%,  $n = 17$ ). There were no differences in the preferred surgical intervention when comparing a fetal therapy center's years of experience, type of institution, or number of MC twin pregnancies or TRAP sequence cases seen per year (online suppl. Fig. 3).

In the case of a monoamniotic TRAP sequence, most centers (57.8%,  $n = 44$ ) offered transection of the cord with fetoscopic laser. There were no differences in this recommendation regardless of the preferred surgical technique at each center, but again geographic differences

**Table 4.** Surgical technique preferences for the acardiac twin – TRAP sequence treatment of the included fetal centers

Surgical technique	n (%)
Percutaneous interstitial laser reduction	45 (59.2)
Percutaneous radiofrequency ablation	29 (38.1)
Fetoscopic placental ablation laser	26 (34.2)
Percutaneous bipolar ligation	21 (27.6)
Fetoscopic bipolar ligation	17 (22.3)
Fetoscopic ligation of the acardiac twin’s umbilical cord	5 (6.5)
Cord coagulation by laser	3 (3.9)
Microwave ablation	2 (2.6)
Placental laser ablation of the AA and VV anastomoses	1 (1.3)
Percutaneous monopolar reduction	1 (1.3)

were seen ( $p = 0.007$ ), with most North American (66.6%,  $n = 16$ ) and Latin American (75%,  $n = 18$ ) centers ideally opting to transect the umbilical cord. In comparison, most units in Europe did not opt to transect the cord (62.5%,  $n = 15$ ) (online suppl. Fig. 4).

#### Gestational Age for Intervention

The earliest GA at which a center offered an in utero intervention for TRAP sequence was 10 weeks, reported from one European center. Worldwide, the earliest GA for an intervention was 12 weeks (mode) and 14 weeks (median). According to the geographic location, European centers intervened at a significantly earlier GA ( $p = 0.001$ ), at an average of  $13 \pm 3$  weeks versus  $15 \pm 5$  weeks in North and Latin America, 15 weeks in Latin America, and 14.6 weeks in other locations; operating at a median of 12 weeks versus 16 weeks in the remainder of locations (online suppl. Fig. 5). Centers that saw >200 sets of MC twins per year intervened earlier, at an average of 12.6 weeks versus 14.2 weeks in those that saw 100–200 sets per year and 15 weeks in those that saw <100 sets per year ( $p = 0.01$ ). As for the type of institution where the fetal center was situated, the intervention was recommended at a later GA in private practice centers ( $p = 0.02$ ) at an average of 16.1 weeks (SD 2.47) versus 14.6 weeks in public hospitals, 13.5 weeks in private hospitals, and 14 weeks in university hospitals.

Three fetal centers stated that they had no upper GA limit for an intervention, five centers individualized the decision, and for the remainder, the average GA for intervention was 26.1 weeks (SD: 3.1, 28 weeks [mode] and 26 weeks [median]). There was a statistically significant geographical difference for the GA for intervention, with North American centers intervening later (median 28 weeks) than those in other geographic areas ( $p = 0.02$ ) (median 26 weeks). Also, fetal centers that have

less than 5 years of practice recommended a lower limit in the latest gestational age for intervention ( $p = 0.02$ ) (median 23 weeks) (online suppl. Fig. 5).

#### Discussion

The objective of any therapeutic fetal intervention in cases of TRAP sequence is to maximize the probability of a term birth and optimal outcome for the pump twin. In this regard, some authors prefer expectant management in the absence of poor prognostic markers for hemodynamic decompensation of the pump twin. The aim of any fetal intervention is to interrupt the blood flow to the acardiac twin [19]; however, there is lack of conclusive scientific evidence, so the optimal approach and therapeutic method have yet to be established.

Our survey documents the current management of TRAP sequence among fetal intervention centers worldwide and demonstrates a lack of uniformity regarding the ultrasound surveillance, eligibility for surgery, optimal surgical technique, and the earliest gestational age for an in utero intervention. Once the diagnosis is made, the most frequent US parameters used include an echocardiogram of the pump twin, UA Doppler in the acardiac and pump twins, and calculation of the acardiac:pump twin EFW or AC ratio.

There is little agreement on the indication for fetal intervention, with centers in Europe and Latin America mainly proposing to intervene in all cases, whereas in North America, most centers use an acardiac:pump twin EFW ratio >50% as their threshold for fetal intervention. As for technique, centers outside of North America preferentially used interstitial laser ablation, compared to North America, where RFA was preferred. More than half of centers have access to more than one technique, and most centers offered umbilical cord transection in

monoamniotic cases. The earliest GA for intervention was at a median of 14 weeks and the latest was 26 weeks, with European centers and those that evaluated >200 cases of MC twin pregnancies per year usually intervening earlier.

The expectant management proposed by some authors is based in part on the spontaneous cessation of blood flow that may occur in up to 21% of acardiac twins [14]. Nevertheless, others have documented perinatal mortality of up to 55% in conservatively managed pump twins, a consequence of their high rate of high-output cardiac failure and very preterm birth [15, 20]. Given the advances in minimally invasive fetal therapy options, some authors propose that intervention should be moved into the first trimester, where small single-center reports have reported postoperative pump twin survival rates of 70–90%, [16, 21]. Others prefer to delay an intervention until 16–18 weeks, with the premise that the risk of pregnancy loss may be lower after spontaneous obliteration of the celomic cavity [19, 22], accepting a risk of pump demise twin in up to 33% of cases during the period from diagnosis in the first trimester until an intervention in the second trimester [14]. To try to determine when an intervention should optimally be undertaken, a multicenter international randomized controlled trial is underway to assess whether an early fetal intervention (at 12–14 weeks) can improve the outcome of TRAP sequence, compared to a later intervention (at 16–19 weeks), the TRAPis Trial (<https://clinicaltrials.gov/ct2/show/NCT02621645?cond=Twin+Reversal+Arterial+Perfusion+Syndrome&draw=2&rank=1>).

There are multiple options for a fetal intervention. Historically, the goal of the first interventions was symptomatic relief of polyhydramnios using indomethacin [23] and/or amnioreduction to prevent preterm delivery [24] and digoxin for its inotropic effect on cardiac failure in the pump twin [25]. With the expanded knowledge of the pathophysiology of this entity, techniques have been developed aimed at interrupting the shared vascular flow to the acardiac twin. Historically, this was achieved using thrombogenic intravascular coils or absolute alcohol for vascular sclerosis [25, 26] [37–40]; however, due to the high failure rate, these techniques have largely been abandoned. Minimally invasive techniques have been subsequently developed using US- and fetoscopically directed vascular occlusion, including cord ligation [26]; monopolar or bipolar flow thermocoagulation of the umbilical cord [27–30]; interstitial laser ablation [31, 32]; and RFA [33].

We recognize the limitations of our survey since it was not possible to contact all fetal centers worldwide, es-

pecially those that have emerged more recently. As such, less than 10% of fetal medicine centers in our series were located in Australia, Asia, or Africa. However, most well-established international centers were approached. This is the first descriptive study of such magnitude on this subject, and we achieved a high of response to the survey (77%), from 5 continents and 29 countries, allowing a broad comparison of responses.

In conclusion, there is currently little agreement regarding the optimal approach to TRAP sequence, including indication, technique, and GA at which to perform any fetal intervention. Nevertheless, the majority of centers agree that once the diagnosis has been established, antenatal evaluation should include an echocardiographic evaluation of the pump twin, along with the UA Doppler waveform measurement in both the acardiac and pump twins and calculation of the acardiac:pump twin EFW or AC ratio to indicate the need for an in utero intervention. The most frequently used interventions were interstitial laser ablation or RFA at a median GA between 14 and 26 weeks.

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## Statements of Ethics

This study protocol was reviewed and approved by the Research and Ethics Committee of Hospital San José in Bogotá, Colombia, by expedited approval number (SIDI) 7194. This Ethics Committee, under Resolution No. 008430 of 1993 of the Colombian Ministry of Health, indicated that it is an investigation without risk since it includes “studies that use retrospective documentary research techniques and methods and

those in which no intentional intervention or modification of the biological, physiological, psychological, or social variables of individuals”; for this reason, it omits the need for written informed consent and the fetal surgery units to whom the invitation to participate could decide whether or not to include them by answering the survey sent.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

S.M. conceived the presented idea. S.M., N.T., A.J., and L.L. designed the survey model. N.T. performed the reception of the data and the computations. S.M., A.J., and L.L. verified the analytical methods. S.M. and N.T. wrote the manuscript in consultation with A.J., L.L., G.R., and W.S.

## Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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