



UNIVERSITÀ DI PARMA

ARCHIVIO DELLA RICERCA

University of Parma Research Repository

The use of radiofrequency in the treatment of twin reversed arterial perfusion sequence: a case series and review of the literature.

This is the peer reviewed version of the following article:

Original

The use of radiofrequency in the treatment of twin reversed arterial perfusion sequence: a case series and review of the literature / Cabassa, P.; Fichera, A.; Prefumo, F.; Taddei, F.; Gandolfi, S.; Maroldi, R.; Frusca, Tiziana. - In: EUROPEAN JOURNAL OF OBSTETRICS, GYNECOLOGY, AND REPRODUCTIVE BIOLOGY. - ISSN 0301-2115. - 166:2(2013), pp. 127-132. [10.1016/j.ejogrb2012.10.009]

Availability:

This version is available at: 11381/2681586 since: 2016-10-06T16:57:43Z

Publisher:

Published

DOI:10.1016/j.ejogrb2012.10.009

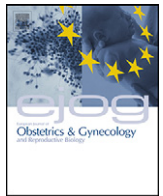
Terms of use:

Anyone can freely access the full text of works made available as "Open Access". Works made available

Publisher copyright

note finali coverpage

(Article begins on next page)



The use of radiofrequency in the treatment of twin reversed arterial perfusion sequence: a case series and review of the literature

Paolo Cabassa^a, Anna Fichera^b, Federico Prefumo^{b,*}, Fabrizio Taddei^{b,1}, Silvia Gandolfi^a, Roberto Maroldi^a, Tiziana Frusca^b

^aDepartment of Radiology, University of Brescia, Brescia, Italy

^bMaternal–Fetal Medicine Unit, Department of Obstetrics and Gynaecology, University of Brescia, Brescia, Italy

ARTICLE INFO

Article history:

Received 24 January 2012

Received in revised form 29 July 2012

Accepted 5 October 2012

Keywords:

Twin reverse arterial perfusion sequence

TRAP sequence

Acardiac fetus

Monochorionic

Radiofrequency ablation

Intrafetal ablation

ABSTRACT

Objective: To evaluate the initial experience at our centre in the treatment of monochorionic twin pregnancies complicated by twin reversed arterial perfusion sequence (TRAP), using radiofrequency ablation (RFA) with expandable needles, and to review the existing literature on the subject.

Study design: Between July 2007 and October 2010, 11 monochorionic twin pregnancies complicated by TRAP were referred to our centre. Seven patients underwent intrafetal ablation of the acardiac twin with RFA using LeVeenTM expandable needle electrodes. Data on the procedures and the obstetric outcome were reviewed, and subsequently we performed a review of the literature on the use of RFA in TRAP.

Results: Median gestational age at the intervention was 17⁺³ weeks (range 14⁺¹–23⁺¹ weeks). Technical success was obtained in all cases. Preterm premature rupture of membranes (PPROMs) occurred in 4/7 (57%) patients. Intrauterine death of the pump twin occurred in one patient at 21⁺⁵ weeks, and one patient opted for termination of pregnancy because of PPROM at 21⁺⁴ weeks. Five fetuses were delivered alive at a median gestational age of 33⁺⁰ weeks (range 31⁺⁰–39⁺⁵ weeks). All five infants (71%) were alive and had a normal examination at 6 months of age. The review identified 6 studies, for a total of 78 pregnancies (either monochorionic twins or triplets with a monochorionic component). Including our data, overall neonatal survival was 75/88 (85%).

Conclusion: RFA appears to be a relatively safe and reliable technique in the treatment of TRAP sequence pregnancies. Further research is needed to define the best timing of the procedure.

© 2012 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Acardiac malformation, also known as twin reversed arterial perfusion (TRAP) sequence, is a rare condition unique to monochorionic twin pregnancy, occurring approximately 1 in 35,000 pregnancies [1]. In this complication, one twin (“acardiac”), with a variable degree of anomalous cardiac structure, depends on the circulation of the normal (“pump”) fetus. The presence of placental superficial anastomoses allows blood flow from the “pump” fetus to the acardiac twin by means of reversed arterial flow. Possible perinatal complications for the pump twin are reported, such as cardiac failure, polyhydramnios and prematurity, leading to mortality rates as high as 55% if left untreated [2]. Several treatments have been proposed for the TRAP sequence

including symptomatic therapies (amniocentesis, inotropic agents and indomethacin), hysterotomy for selective delivery and cord occlusion of the acardiac twin [2]. More recently, several centres have gained experience in interrupting blood flow to the acardiac twin with intrafetal ablative therapies, in particular radiofrequency and interstitial laser [3–8].

In the past decade radiofrequency ablation (RFA) has gained a primary role in the treatment of liver neoplasms. The scope of the applicability of RFA is not, however, limited to liver neoplasms, and several reports discuss its applicability for the necrosis of lung, renal, bone and other extra hepatic neoplasms [9]. The purpose of this study was to illustrate the initial experience of the treatment of this rare condition at our centre using RFA with expandable needles, and to perform a review of the literature on this subject.

2. Materials and methods

2.1. Patients

Between July 2007 and October 2010, 11 women were referred to our centre because of a suspicion of TRAP sequence or the

* Corresponding author at: Maternal–Fetal Medicine Unit, Department of Obstetrics and Gynaecology, University of Brescia Piazzale Spedali Civili, 1, 25123 Brescia, Italy. Tel.: +39 030 3995340; fax: +39 030 3995034.

E-mail address: federico.prefumo@gmail.com (F. Prefumo).

¹ Current address: Department of Obstetrics and Gynaecology, Carlo Poma Hospital, Mantova, and Asola Hospital, Italy.

Table 1

Patient data and outcome of selective reduction of acardiac fetus by RFA.

| Case | Gestational age at procedure (weeks) | Gestational age at delivery (weeks) | Outcome of the pump twin |
|------|--------------------------------------|-------------------------------------|-----------------------------------------------------------------------------------|
| 1 | 21 ⁺⁶ | 39 ⁺⁵ | Alive |
| 2 | 23 ⁺¹ | 33 ⁺⁰ | Premature rupture of membranes (31 weeks); alive |
| 3 | 14 ⁺¹ | 35 ⁺³ | Fetal growth restriction; alive |
| 4 | 17 ⁺⁰ | 31 ⁺⁰ | Premature rupture of membranes (29 weeks); alive |
| 5 | 17 ⁺² | – | Intrauterine death (21 ⁺⁵ weeks) |
| 6 | 17 ⁺³ | – | Premature rupture of membranes (21 ⁺⁴ weeks); termination of pregnancy |
| 7 | 18 ⁺³ | 31 ⁺² | Premature rupture of membranes (27 weeks); alive |

presence of an anomalous “growing” twin with apparently no heartbeat. A detailed ultrasound examination was performed in all cases, including the search for blood flow in the umbilical cord and within the mass of the acardiac twin. The abdominal circumference of both twins was measured. One patient was managed expectantly, amnioreduction was performed in one case, interstitial laser was chosen as ablative therapy in two cases and seven women were treated with RFA. Eligibility for RFA included the following criteria: a monochorionic placentation; the presence of

an acardiac twin with documented blood flow (both in the umbilical cord and within the fetal mass) at Doppler examination; demonstration of continued growth of the acardiac fetus over at least 1 week; and a structurally normal “pump” twin [2]. Patients were counselled in detail about the possible complications for the pump twin, and expectant management or RFA were offered as treatment options. All patients gave their written informed consent to be treated. The study was conducted in accordance with the principles of the Helsinki Declaration.

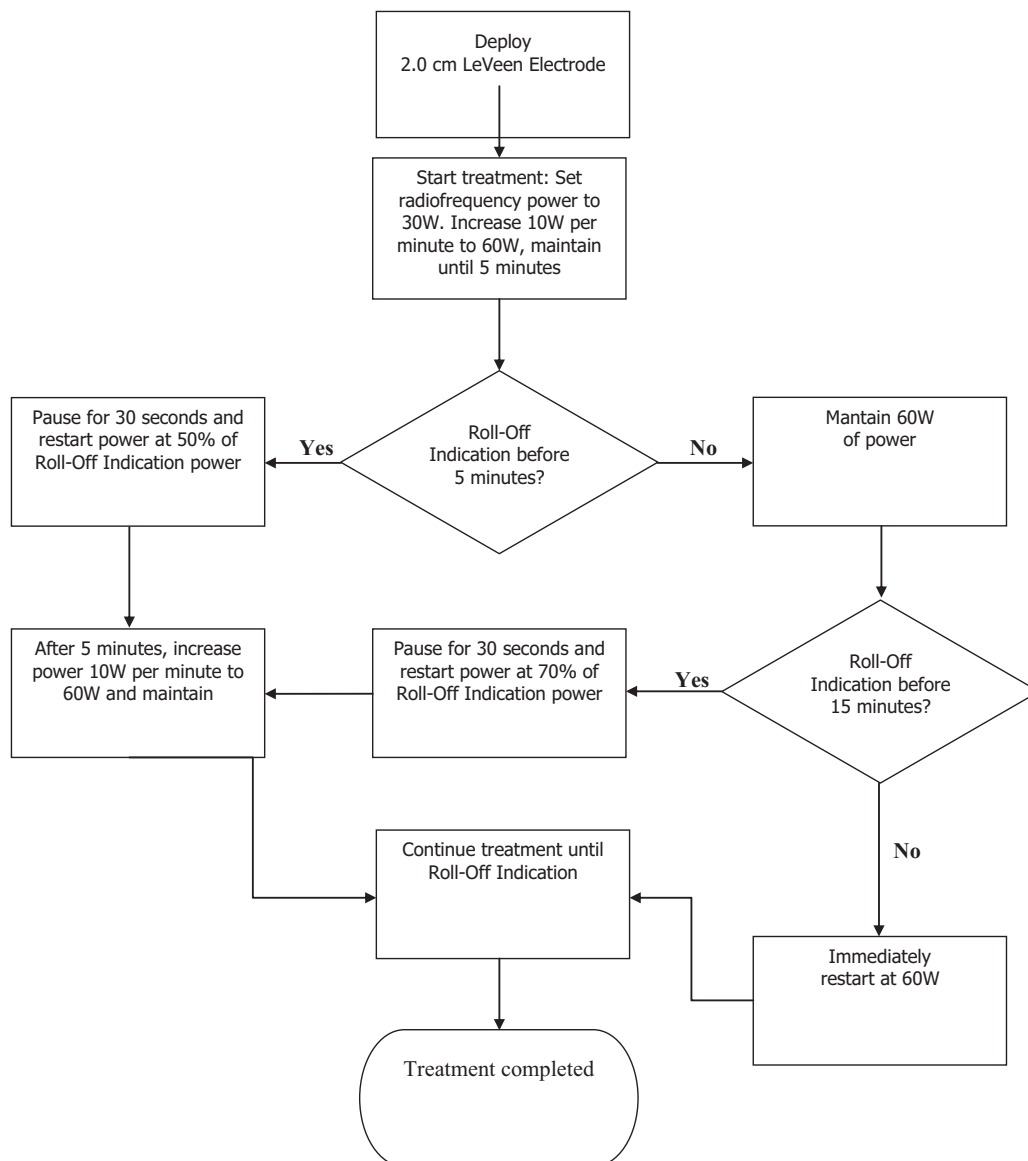
**Fig. 1.** Ablation algorithm for 2.0 cm expandable needle electrode.

Table 2
Literature review of selective reduction of acardiac fetus by radiofrequency ablation. MC, monochorionic; MCDA, monochorionic diamniotic; MCMA, monochorionic monoamniotic; PPROM, preterm premature rupture of membranes; IUFD, intrauterine fetal death.

| | N | Type of twins | Neonatal survival | Gestation at procedure | Gestation at delivery | Fetal complications | Needle | Anesthesia | Maternal complications |
|----------------------------------|----|------------------------------------|-------------------|-----------------------------------------|-----------------------------------------|------------------------------------------------------------------------------------------------|--------------------------|------------------------------------------------------------------------|------------------------------------------------|
| Lee et al. (2007) [5] | 29 | 26 MCDA 2 MCMA 1 triplets | 26/30 | Not reported | Median 38 weeks (range 24–40 weeks) | n = 10 preterm delivery <37 weeks (5 PPROM; 4 preterm delivery; 1 induction of labor) | 14 or 17G, multi-tine | General (n = 14)/ locoregional (n = 15) | Thermal injury at grounding pads (n = 2) |
| Livingston et al. (2007) [4] | 13 | 12 MC, amnionicity not reported | 12/13 | Average 21 weeks (range 17–24 weeks) | Average 37 weeks (range 26–39 weeks) | n = 1 IUFD n = 10 preterm delivery <32 weeks (PPROM) | 19G, multi-tine | Local + intravenous sedation | None |
| Jelin et al. (2010) [10] | 7 | 7 MCDA | 7/7 | Not reported | Average 36 weeks | None | 14 or 17G, multi-tine | General (n = 14)/ locoregional (n = 15) | None |
| Paramasivam et al. (2010) [7] | 5 | 5 MCDA | 4/5 | Median 18 weeks (range 15–21 weeks) | Median 36 weeks (range 24–41 weeks) | n = 1 IUFD | 17G, multi-tine | Local | None |
| Roman et al. (2010) [11] | 6 | 2 Triplets | 7/8 | Not detailed | Not detailed | None | 17G, multi-tine | Local + intravenous sedation | None |
| Bebbington et al. (2012) [12] | 18 | Not detailed | 14/18 | Not detailed | Not detailed | Not detailed | 17G, multi-tine | Locoregional until 2005, local + intravenous sedation after 2005 | None |
| This study | 7 | 6 MCDA 1 MCMA | 5/7 | Median 17 weeks (range 14–23 weeks) | Median 35 weeks (range 31–39 weeks) | n = 1 IUFD n = 4 PPROM <32 weeks (one terminated) | 17G, multi-tine | Local + intravenous sedation | None |
| Total | 85 | | 75/88 (85%) | | | | | | |

2.2. Radiofrequency ablation

Patients were admitted to the hospital in the early morning on the day of treatment. They fasted for at least 6 h prior to the procedure. All procedures were performed by the combination of one maternal–fetal medicine specialist and one interventional radiologist in the interventional room of the obstetric department. Conscious sedation (delorazepam, 5 mg intravenously) was administered during the ablation procedure, monitoring maternal vital signs. In addition to the conscious sedation provided, a local anaesthetic was administered along the planned puncture line using 10 mL of 2% lidocaine hydrochloride.

All patients in the series were treated using the RF3000™ Radiofrequency Ablation System (Boston Scientific, Natick, MA). This monopolar system consists of a 200 W radiofrequency generator to which LeVeen™ Needle Electrodes (Boston Scientific, Natick, MA) are connected. Additionally, the generator requires the use of four patient grounding pads placed on the patient's thighs to complete the electrical circuit. The LeVeen™ needle electrodes consist of a 15–17G cannula with lengths of 12, 15 or 25 cm and a 2.0, 3.0 or 3.5 cm diameter umbrella can be chosen. The 2.0 cm, 15 cm length, 17G needle was used for all the procedures. This device has eight individual tines to form the umbrella.

All the procedures were performed percutaneously by three different operators (with more than 10 years' experience in interventional procedures) under ultrasonographic guidance with an ultrasonography unit (Antares; Siemens, Erlangen, Germany) and with a convex multifrequency probe. The baseline power output of the generator was set at 10 W and the recommended protocol as per the directions for use was used (Fig. 1). The RF3000™ generator monitors the system impedance and this impedance level determines the extent of tissue necrosis. Impedance 'roll-off' signifies treatment completion. The principles of physics which govern the operation of the generator dictate that the impedance rise measured is that which corresponds to the ablation of the mass site only. Treatment continued for 15 min or until "roll-off" occurred. The roll-off indicates a precipitous drop in power output as tissue impedance increases markedly as a result of tissue necrosis, which prohibits the passage of electrical current. After a 30 s pause, power was reapplied at 70% of the maximum power achieved for 10 min with an increase of 10 W every minute or until roll-off occurred again.

The purpose of ablation was to stop flow within the umbilical cord. For this purpose the tip of the electrode was centred in the abdominal part of the acardiac mass close to the insertion of the umbilical cord. This was monitored with colour Doppler sonography during the procedure and at the end of ablation. The procedure was stopped when absence of cord flow was demonstrated. Post-procedure protocols required a maternal blood count and a Doppler evaluation of the fetuses within 12–24 h, prior to discharge, in order to: confirm the pump twin's viability, and exclude signs of failure to stop blood flow towards the acardiac mass (cord flow, flow within the mass). This is due to the fact that Doppler artefacts generated by tissue heating may sometimes interfere with Doppler assessment during the procedure.

Follow-up was organised locally or at the referring Institutions. Pregnancy and neonatal outcome data were obtained from the clinical notes or from the referring physicians.

2.3. Literature review

Data sources were identified using a search of Medline and EMBASE databases up to 2012, and a manual search of the citation lists of the relevant publications and reviews. Keywords for the search were "TRAP sequence" or "acardiac" and "radiofrequency".

Exclusion criteria were case reports, non-English language publications, data reported in graphs, review articles and personal communications. In cases of data duplication, only the most recent and complete report was included. Discordance was resolved with consensus. An effort to contact the corresponding author from the original publication was performed in an attempt to obtain unpublished data.

3. Results

Seven consecutive twin monochorionic pregnancies with selective reduction by RFA are reported (Table 1). Mean maternal age was 29 ± 5 years and five out of seven patients (71%) were nulliparous. Median gestational age at referral was 17^{+3} weeks (range 14^{+1} – 23^{+1}).

None of the pump twins had sonographic evidence of hydrops at presentation or evidence of cardiac failure. Mild polyhydramnios in the sac of the pump twin was found in only one case (case 5). Six out of seven pregnancies were diamniotic, and only one (case 3) was monoamniotic. In all cases, the abdominal circumference of the acardiac twin was $>50\%$ of the abdominal circumference of the pump twin. At the time of intervention, the median gestational age was 17^{+3} weeks (range, 14^{+1} – 23^{+1} weeks). Technical success, as demonstrated by complete and persistent absence of blood flow to the acardiac twin at colour Doppler examination, was obtained in all cases. No major immediate complications were noted. Preterm premature rupture of membranes occurred in four cases at a median gestational age of 28 weeks (range 21^{+4} –31 weeks). Intrauterine death of the pump twin occurred in one patient at 21^{+5} weeks (case 5), 4 weeks after radiofrequency ablation. One patient opted for termination of pregnancy because of preterm rupture of membranes at 21^{+4} weeks (case 6). All other fetuses were delivered alive. Median gestational age at delivery was 33^{+0} weeks (range 31^{+0} – 39^{+5} weeks). Four out five infants were delivered preterm at 31^{+0} , 31^{+2} , 33^{+0} and 35^{+3} weeks (cases 4, 7, 2 and 3 respectively); in three cases because of preterm premature rupture of membranes, and in one case because of fetal growth restriction. Postnatally, no complications related to the use of radiofrequency devices (skin burns), were noted. All liveborn infants were alive and had a normal examination at 6 months of age.

We identified in the literature six reports involving 78 pregnancies complicated with TRAP sequence treated by RFA [4,5,7,10–12]. Of these pregnancies, three were triplet pregnancies with a monochorionic component. The total number of potential survivors was therefore 81. In Table 2, we show the available data on population, procedure details and outcomes from the literature review, together with results from the present study. The overall neonatal survival was 75/88 (85%).

4. Comment

During recent years thermal ablation has been widely used in neoplasm treatment. Interest in percutaneous ablation will likely continue to grow as long as robust data continue to validate the efficacy of this technique in the near future. In the past, symptomatic therapies or extremely invasive options such as hysterotomy for selective delivery have been proposed for the management of TRAP [2]. Alternatively, several minimally invasive techniques have been developed during the last few years in order to interrupt the vascularisation of the acardiac twin: ultrasound-guided fetal cord ligation or compression, bipolar coagulation, laser coagulation, transection with harmonic ultrasound scalpel, thermocoagulation, interstitial laser and radiofrequency ablation [13].

RFA has shown excellent results, although the number of patients treated worldwide remains low [3–7]. The lack of major complications reported in the literature tends to make radiofrequency preferable to other thermal treatments such as interstitial laser ablation [14]. Our results indicate that RFA with expandable electrodes is a relatively safe and effective procedure. We obtained complete ablation in all the procedures, and five women out of seven (71%) delivered an apparently healthy baby. Furthermore, our review of the literature indicates that neonatal survival is achieved in 85% of cases with this technique. The rate of maternal complications was very low, with only two cases of thermal injury at grounding pads in one of the early series [5]. There are, however, no long-term follow-up studies available in infants surviving a pregnancy treated with RFA.

In a review, Tan and Sepulveda concluded that intrafetal ablation is superior to other umbilical cord coagulation modalities because of a lower technical failure rate (13% vs. 35%, $P = 0.03$), lower rate of premature delivery or rupture of membranes before 32 weeks (23% vs. 58%, $P = 0.003$) and higher rate of clinical success (77% vs. 50%, $P = 0.02$). [15]. RFA also seems to achieve higher survival rates of the normal twin in a recent review on selective fetocide techniques in complicated monochorionic twin pregnancies [14]. Roman et al. suggest that RFA is a technically simpler technique than umbilical cord coagulation, and also report a lower – albeit not statistically significant – rate of preterm rupture of membranes [11]. On the contrary, Bebbington et al. suggest that, despite the smaller size of the instrument, RFA is not associated with a decrease in the overall complication rate when compared to cord coagulation [12].

Preterm premature rupture of membranes is the commonest postprocedural complication: its overall incidence in the literature is at least 22% (19/85 pregnancies in Table 2, but not all studies reported details on PPRM in TRAP), and in our series it occurred in four patients out of seven (57%). This percentage is still high compared to other case series, but probably definitive conclusions on this risk cannot be drawn due to the small number of our patients.

One of our cases was complicated by intrauterine death of the pump twin 4 weeks after RFA, diagnosed on the occasion of a planned follow-up scan after normal interval scans. The clinical presentation and the postmortem examination did not allow us to identify a cause for the intrauterine death. It is therefore uncertain whether or not the fetal demise was related to the RFA procedure. Bebbington et al. [12], who observed a higher rate of intrauterine death before 28 weeks in RFA compared to cord occlusion, hypothesise that in RFA the interval to obtain complete cessation of cord flow might be longer than in cord occlusion. During this time, the surviving co-twin (the pump twin in the case of TRAP sequence) might be exposed to altered blood flow dynamics, which might increase the risk of intrauterine death. Due to technical reasons (electromagnetic and temperature artefacts) it is impossible to determine the exact timing of cessation of blood flow during a RFA procedure [16] and this might also be affected by needle geometry and generator settings [12].

There is no consensus on the use of defined sonographic criteria to choose which are the best candidates for this procedure. We used two of the criteria suggested by Wong and Sepulveda [2] for patient selection: persistent blood flow reaching the acardiac twin, and continuing growth of the acardiac twin. Although this was not a prespecified criterion, in all of our cases the abdominal circumference of the acardiac twin was always >50% of the abdominal circumference of the pump twin. The policy about TRAP

sequence has gradually shifted from intervention only in cases with impending cardiac decompensation towards a more aggressive policy, although the optimal gestational age at the procedure is still controversial. Recently Lewi et al. [17] described their experience with different techniques on 24 twins with TRAP sequence after 13⁺6 weeks. They reported a high rate of spontaneous demise of the pump twin within 18 weeks (33% of cases), thus questioning the policy followed by the majority of centres, of a prophylactic intervention at 16–18 weeks in order to reduce the risk of PPRM. They suggested that a policy of prophylactic intervention at 12 weeks should be investigated. On the other hand, Jelin et al. [10] suggested that invasive treatment can be safely withheld when the weight of the acardiac twin is less than half the weight of the pump twin.

Finally, there is no consensus on some technical aspects of RFA of TRAP sequence. Besides the 8-tine needle used in our series and by other groups, a 3-tine needle or a single needle without tines have also been used [4,5,7,10–12]. We used an 8-tine needle as we thought that it would make energy delivery less dependent on tissue dishomogeneity (bone, vessels or charred tissue). For this design, the 17G needle was the smallest diameter employable with our system.

In conclusion, radiofrequency ablation with expandable needle electrodes is a reliable technique in the treatment of acardiac twin pregnancies. With the advent of technical improvements and standardised therapies, radiofrequency ablation deserves a primary role in the treatment of TRAP sequence. However, its advantages or disadvantages compared to other treatment techniques, as well as long term development of treated infants, need further evaluation.

Conflict of interest

The authors have no conflict of interest to disclose.

Role of the funding source

There was no funding for this research.

References

- [1] Moore TR, Gale S, Benirschke K. Perinatal outcome of forty-nine pregnancies complicated by acardiac twinning. *American Journal of Obstetrics and Gynecology* 1990;163:907–12.
- [2] Wong AE, Sepulveda W. Acardiac anomaly: current issues in prenatal assessment and treatment. *Prenatal Diagnosis* 2005;25:796–806.
- [3] Tsao K, Feldstein VA, Albanese CT, et al. Selective reduction of acardiac twin by radiofrequency ablation. *American Journal of Obstetrics and Gynecology* 2002;187:635–40.
- [4] Livingston JC, Lim F-Y, Polzin W, Mason J, Crombleholme TM. Intrafetal radiofrequency ablation for twin reversed arterial perfusion (TRAP): a single-center experience. *American Journal of Obstetrics and Gynecology* 2007;197:399.e1–e3.
- [5] Lee H, Wagner AJ, Sy E, et al. Efficacy of radiofrequency ablation for twin-reversed arterial perfusion sequence. *American Journal of Obstetrics and Gynecology* 2007;196:459.e1–e4.
- [6] Moise Jr KJ, Johnson A, Moise KY, Nicleleit V. Radiofrequency ablation for selective reduction in the complicated monochorionic gestation. *American Journal of Obstetrics and Gynecology* 2008;198:198.e1–e5.
- [7] Paramasivam G, Wimalasundera R, Wiechec M, Zhang E, Saeed F, Kumar S. Radiofrequency ablation for selective reduction in complex monochorionic pregnancies. *BJOG An International Journal of Obstetrics and Gynaecology* 2010;117:1294–8.
- [8] Jolly M, Taylor M, Rose G, Govender L, Fisk NM. Interstitial laser: a new surgical technique for twin reversed arterial perfusion sequence in early pregnancy. *BJOG An International Journal of Obstetrics and Gynaecology* 2001;108:1098–102.
- [9] Brown DB. Thermal ablation 2010: unprecedented growth and promise. *Journal of Vascular and Interventional Radiology* 2010;21:S177.

- [10] Jelin E, Hirose S, Rand L, et al. Perinatal outcome of conservative management versus fetal intervention for twin reversed arterial perfusion sequence with a small acardiac twin. *Fetal Diagnosis and Therapy* 2010;27:138–41.
- [11] Roman A, Papanna R, Johnson A, et al. Selective reduction in complicated monochorionic pregnancies: radiofrequency ablation vs. bipolar cord coagulation. *Ultrasound in Obstetrics and Gynecology* 2010;36:37–41.
- [12] Bebbington MW, Danzer E, Moldenhauer J, Khalek N, Johnson MP. Radio frequency ablation vs. bipolar umbilical cord coagulation in the management of complicated monochorionic pregnancies. *Ultrasound in Obstetrics and Gynecology* 2012;40:319–24.
- [13] Chalouhi GE, Stirnemann JJ, Salomon L, Essaoui M, Quibel T, Ville Y. Specific complications of monochorionic twin pregnancies: twin twin transfusion and twin reversed arterial perfusion sequence. *Seminars in Fetal & Neonatal Medicine* 2010;15:349–56.
- [14] O'Donoghue K, Barigye O, Pasquini L, Chappell L, Wimalasundera RC, Fisk NM. Interstitial laser therapy for fetal reduction in monochorionic multiple pregnancy: loss rate and association with aplasia cutis congenita. *Prenatal Diagnosis* 2008;28:535–43.
- [15] Tan TY, Sepulveda W. Acardiac twin: a systematic review of minimally invasive treatment modalities. *Ultrasound in Obstetrics and Gynecology* 2003;22:409–19.
- [16] Morel O, Malartic C, Barranger E. Radiofrequency ablation for twin-reversed arterial perfusion sequence: the unknown cord occlusion delay calls for long term neonatal follow-up of the surviving twins. *American Journal of Obstetrics and Gynecology* 2007;197:557–8.
- [17] Lewi L, Valencia C, Gonzalez E, Deprest J, Nicolaides KH. The outcome of twin reversed arterial perfusion sequence diagnosed in the first trimester. *American Journal of Obstetrics and Gynecology* 2010;203:213.e1–e4.