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Clinical management of twin reversed arterial perfusion cases: insights into a complex and challenging twinning

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Summary

Twin reversed arterial perfusion (TRAP) sequence occurs in approximately 1% of monozygotic pregnancies. The proposed pathogenesis is the association of paired artery-to-artery and vein-to-vein anastomoses through the placenta combined with delayed cardiac function of one of the embryos early in pregnancy. Presently the most commonly used technique for TRAP sequence is intrauterine radiofrequency ablation (RFA) of the cord of the recipient twin. This report shares the authors' experience in managing similar cases, the rationale leading to clinical decisions, the timing of the RFA procedure, the potential complications associated with TRAP, and the outcome of these two cases.

Key words: Twin reversed arterial perfusion; Radiofrequency ablation; Monozygotic twinning.

Introduction

Twin reversed arterial perfusion (TRAP) sequence occurs in about one per 35,000 pregnancies, complicating approximately1% of monozygotic pregnancies [1]. Placentation among TRAP cases has been predominantly reported to be monochorionic diamniotic and to a lesser degree monochorionic monoamniotic twins [1]. Though less commonly, this abnormality has also been reported in triplets with monochorionic triamniotic, diamniotic, and monoamniotic gestation. It results from the development of anomalous vascular anastomoses between the placental arteries and veins of monochorionic embryos early in embryogenesis [2]. The blood exchange is responsible for unique complications in monochorionic twins, such as the twin-to-twin transfusion syndrome (TTTS), the twin anemia polycythemia sequence (TAPS), the twin reversed arterial perfusion (TRAP) sequence, and monoamniotic twinning [3].

The proposed pathogenesis is the association of paired artery-to-artery and vein-to-vein anastomoses through the placenta combined with delayed cardiac function of one of the embryos early in pregnancy. This situation allows blood pumped from the healthy twin also known as the "pump twin" to perfuse retrogradely the heart of the other twin the "acardiac twin" or "parabiotic twin". Thus, flow in the artery and vein are reversed in the umbilical cord of the acardiac twin, giving rise to the acronym TRAP. Retrograde perfusion interferes with normal cardiac development, which rarely goes beyond the stage of tubular heart.

Common abnormal findings in the "parabiotic twin" include impaired or absent development of the cephalic pole, rudimentary or absent heart, abnormal or absent upper limbs, relative preservation of the lower limbs, although clubbing and abnormal toes are common, abnormal viscera, and single umbilical artery [2]. A common finding is massive edema around the upper body including the neck of the "parabiotic twin". Another common sonographic finding is the close proximity of the placental cord insertion of the two fetuses.

Left untreated, TRAP sequence results in more than 50% mortality of the normal pump twin due to high-output cardiac failure. Due to the high degree of morbidity and mortality associated with TRAP sequence, investigators have attempted to minimize complications to the pump twin by discontinuing the blood flow to the acardiac twin. Presently the most commonly used technique for TRAP sequence is intrafetal radiofrequency ablation (RFA). Radiofrequency devices induce temperature changes by high-frequency alternating current applied via electrodes placed within the tissue to cause coagulation.

The present authors have recently cared for two pregnancies complicated by TRAP sequence. In addition to the common abnormal sonographic findings found in the "parabiotic twin", these two cases exemplify the clinical dilemma of when and how to intervene as well as complications associated with RFA. More importantly the second case highlights an inherent risk of premature delivery associated with RFA treatment of the "parabiotic twin" and its potentially harmful affect on the brain of the normal twin. The goal of this report is to share the authors' clinical management, including the decision-making process that led to

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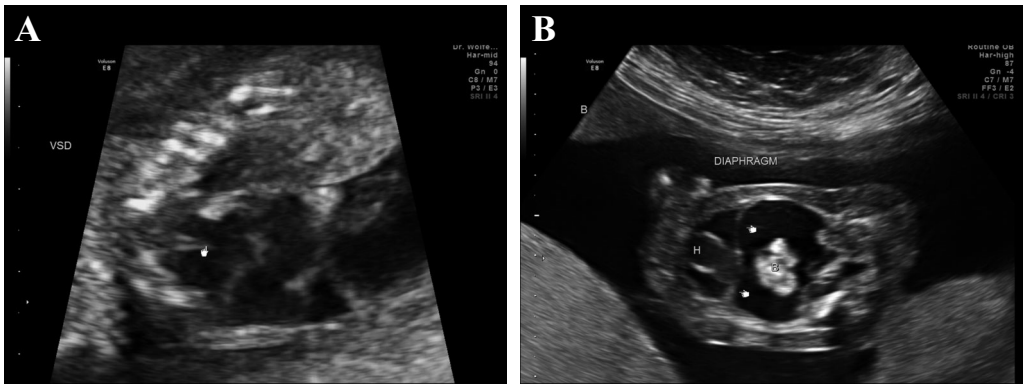

Figure 1. — A) Case 1: four chambers view of the heart of the "parabiotic twin" with a large VSD. Note the atria appear almost the same size as the ventricles. B) Case 1: free anechoic fluid is seen in the fetal chest and abdominal cavity. The diaphragm is clearly seen (hand pointing). H: heart, B: bowels.

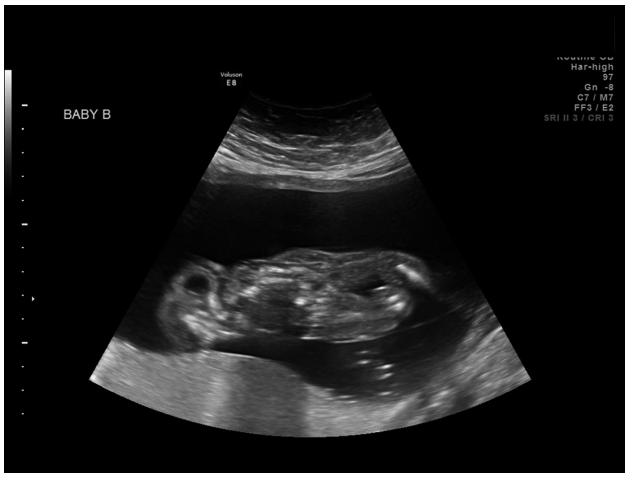

Figure 2. — Case 1: the spine is twisted and abnormally formed. The lower extremities are short with skin edema.

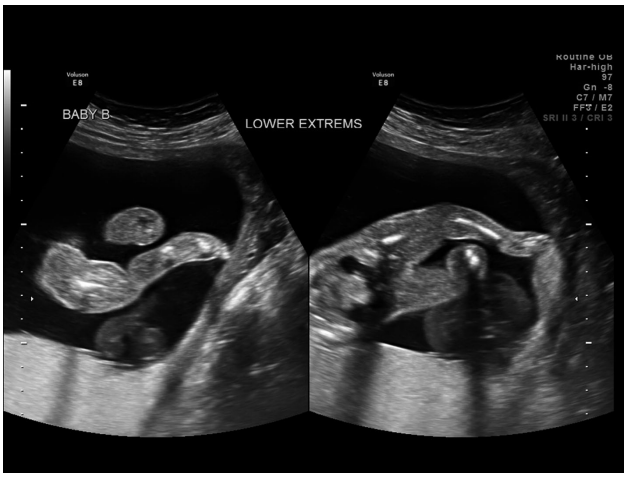

Figure 3. — Case 1: the femur tibia and fibula are short, mildly bowed, and abnormally thin.

RFA intervention, the abnormal sonographic findings and outcome, and the potential complications associated with RFA therapy.

Cases Report

Case 1

The patient was a 32-year-old G2P1001 woman, who was 21 weeks pregnant at the time she was referred from an outside facility due to the finding of monochorionic monoamniotic twins with one of the fetuses (twin B) showing multiple abnormalities. The pregnancy was otherwise uncomplicated. Prenatal screening for Down syndrome was declined. Her past obstetrical history was significant for one uncomplicated full term gestation. Her past medical history was unremarkable.

Ultrasound study at 21 weeks in our ultrasound unit noted the following findings: monochorionic monoamniotic twins. Twin A ("pump twin") showed normal interval growth, mild cardiomegaly, dilation of the umbilical vein, borderline enlarged liver, borderline abnormal heart to chest circumference of 0.61, and persistent right umbilical vein. Fetal echocardiogram of twin A showed normal segmental anatomy with no structural abnormalities. The spectral Doppler pattern across all valves, venous structures, and arterial structures was within normal limits. An abnormal ratio of measured to expected femur and humeral length was noted thus increasing the risk for Down syndrome by about six-fold. No other fetal malformations or abnormal sonographic markers were identified. Doppler interrogation of the ductus venosus noted abnormal a wave suggesting increased pressure in the right atrium of the fetal heart. Normal peak systolic velocity of the middle cerebral artery (1.28 MoM) was noted.

Twin B showed the following abnormalities: absent calvaria and brain structures, rudimentary upper limbs, and small abnormally formed chest with hydrothorax, as well as short and deformed ribs. Four chambers of the heart could be identified (Figure 1A). The cardiac axis was abnormal and a large VSD was noted. The atria appeared almost the same size as the ventricles. Normal mitral and tricuspid valves motion was seen. Free anechoic fluid was seen in the abdominal cavity (Figure 1B). A small bladder was seen. The spine was noted to be twisted and abnormally formed (Figure 2). The lower extremities were short with skin edema. The femur tibia and fibula were short, mildly bowed, and abnormally thin (Figure 3). Arterial blood flow was seen in a retrograde fashion from twin A (pump twin) to twin B (recipient twin/parabiotic twin). The placental cord insertions were adjacent to each other with cord entanglement (Figure 4). The body volume of the "parabiotic twin" was about 61% of the normal twin.

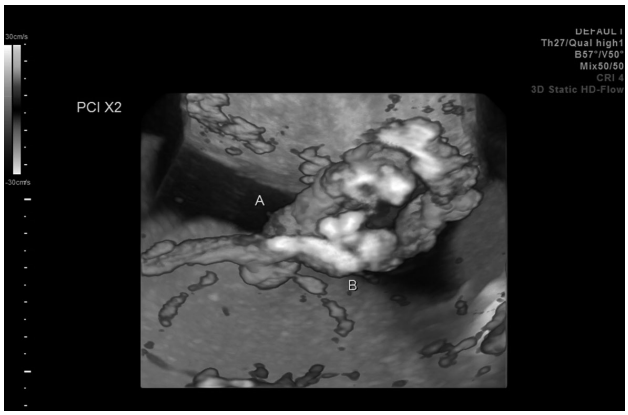

Figure 4. — Case 1: the placental cords' insertions are adjacent to each other. The umbilical cords are entangled.

Following the initial work-up, a diagnosis of TRAP sequence was made. Amniocentesis was performed due to the abnormal ratio of measured to expected femur and humeral length which was noted in twin A. The results showed normal female chromosome constitution 46,XX. In addition whole genome chromosome SNP microarray analysis was normal.

It was thought that due to the cord size of the "parabiotic twin" (about 12 mm), that minimally invasive cord coagulation/ligation would not be technically feasible by fetoscopic instruments and RFA would be the best viable option available. The patient underwent the RFA procedure under conscious sedation and in addition a local anesthetic was administered. In order to discontinue blood flow within the umbilical cord of the recipient fetus, the tip of the electrode was centered in the abdominal part of the recipient fetus close to the insertion of the umbilical cord. The procedure was deemed successful once absence of cord blood flow was demonstrated using color Doppler study. The patient was observed in the hospital for the next 24 hours and then discharged home. Prior to discharge color Doppler study again documented no blood flow in the umbilical cord of the recipient twin.

The patient showed for follow up ultrasound study four days later. No cardiac motion or blood flow was seen in the umbilical cord of the "parabiotic twin" (Figure 5A). The pump twin had normal Doppler interrogation of the middle cerebral artery suggesting low risk for fetal anemia. The fetal brain appeared sonographically normal. Doppler interrogation of the fetal ductus venosus was normal. Follow up study four days later noted umbilical artery flow in the "parabiotic twin" (Figure 5B) possibly due to re-canalization of one of the umbilical arteries and the umbilical vein. The blood flow could be traced to the lower abdomen. As the body volume of the "parabiotic twin" was only about less 49% of the normal "pump twin", repeated RFA was not considered. No cardiac activity was present in the "parabiotic twin". The patient continued to be followed up weekly. No sonographic findings of cardiac decompensation in the "pump twin" were seen. Normal fetal brain structures as well as normal Doppler interrogation of the ductus venosus and the middle cerebral artery were repeatedly noted. Of note at 24 weeks the maximum vertical pocket of amniotic fluid was more than 80 mm for the first time suggesting polyhydramnios. Twenty-six days following the RFA procedure the patient experienced premature rupture of the membranes. At this point re-evaluation of the clinical situation was done. As there was no clinical or laboratory finding suggesting chorioamnionitis or fetal distress, a decision was made to continue the pregnancy. The patient was admitted to the hospital for closer observation and testing. Her vital signs and laboratory studies continued to be normal and stable. The fetus underwent daily non-stress-test study and twice weekly amniotic fluid volume assessment combined with biophysical profile, as well as Doppler studies of the middle cerebral artery and ductus venosus. During this latency period the body volume of the "parabiotic twin" was repeatedly assessed and was shown to shrink from about 61% to 37% of the "pump twin". The patient received betamethasone and latency antibiotics.

The patient and the "pump twin" continued to be stable up until 34 weeks at which point she was induced to labor as planned. She had an uneventful vaginal delivery and uncomplicated postpartum course. She was delivered of a female newborn weighing 2,120 grams (49%) with Apgar scores of 5/7/9 at one, five, and ten minutes, respectively. The newborn had an uneventful neonatal intensive care unit (NICU) stay and was discharged home on day 10 of life. Head ultrasound study following delivery and on the day of discharge was normal. The parabiotic twin's weight was 706 grams about 30% of the normal twin.

The placental pathology examination noted slightly mature monochorionic monoamniotic twin placenta weighing 550 grams. Major artery to artery anastomosis connecting placenta A ("pump twin") to placenta B ("parabiotic twin") was seen. Necrosis and thrombotic obliteration of one of the two umbilical arteries was seen while the umbilical vein and the second umbilical artery were patent in the umbilical cord of the "parabiotic twin". Focally avascular villi with trophoblast basement membrane calcification near the arterial anastomosis site was also noted.

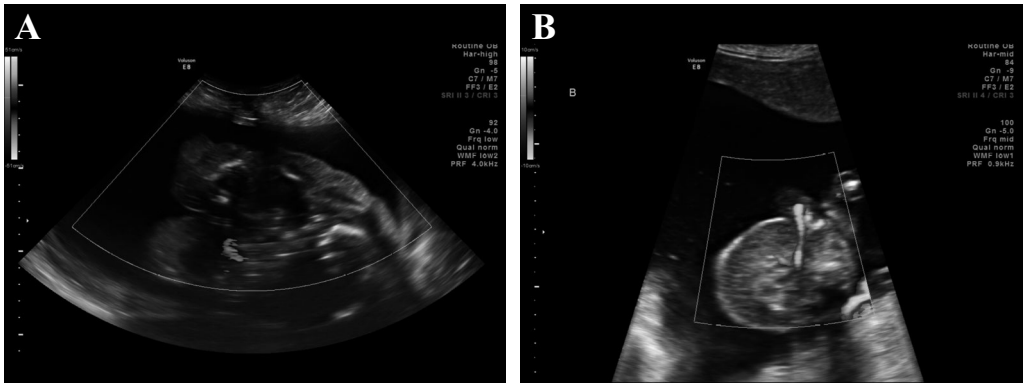

Figure 5. — A) Case 1: no cardiac motion or blood flow is seen in the umbilical cord of the "parabiotic twin". B) Case 1: follow up study documents umbilical artery flow in the "parabiotic twin" possibly due to re-canalization.

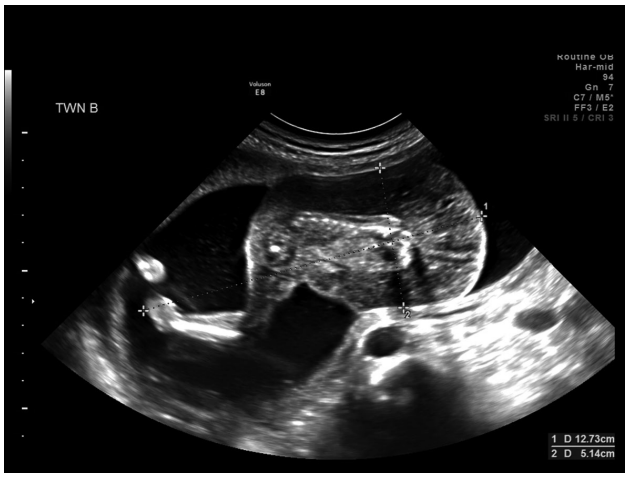

Figure 6. — Case 2: image of the "parabiotic twin" showing well developed lower extremities and spine. The remainder of the fetus is amorphous and severely edematous.

Figure 7. — Case 2: a dividing membrane can be seen following the RFA procedure.

Case 2

The patient was a 34 year-old G4P2002 woman. Her past medical history was remarkable for drainage of breast abscess and laparoscopic excision of ectopic pregnancy with right salpingectomy. She showed for routine ultrasound study to an outside facility where a preliminary diagnosis of TRAP sequence was made. Twin A appeared to be normal while twin B was noted to be acardiac and amorphous. She was than referred to the present ultrasound unit for confirmation and Maternal Fetal Medicine consultation and continued care. Up to this point no pregnancy complications were apparent. She declined first trimester screening for Down syndrome.

Ultrasound study in the present laboratory at 17 4/7 weeks confirmed TRAP sequence in what was thought at that time to be monochorionic monoamniotic gestation. Detailed and comprehensive study of twin A the "pump twin" was unremarkable. Fetal echocardiogram showed normal segmental anatomy with no structural abnormalities. The spectral Doppler pattern across all valves, venous structures, and arterial structures was within normal limits. Doppler interrogation of the ductus venosus and the middle cerebral artery were both normal. Twin B was confirmed to be a "parabiotic twin" (Figure 6). The lower extremities were well developed and the fetal spine was seen. The remainder of the fetus was amorphous and severely edematous. Increased amniotic fluid volume was noted as the maximum vertical pocket of fluid was 92 mm. The patient was offered the option of amniocentesis but declined.

Following Maternal Fetal Medicine consultation, it was decided to postpone RFA of the "parabiotic twin" as its weight was calculated to be about 30% of twin A and there were no sonographic findings to suggest cardiac failure in the "pump twin". The patient continued to undergo weekly ultrasound studies to assess the overall measurement of the "parabiotic twin" in comparison to the "pump twin". In addition the studies checked for evidence of cardiac failure in the "pump twin" by checking for tricuspid regurgitation, pericardial or pleural effusion, ascites, and Doppler study of the ductus venosus. The middle cerebral artery was interrogated to rule out fetal anemia.

Over the next four weeks, the size of the "parabiotic twin" had been steadily increasing. At 22 weeks repeated fetal echocardiography evaluation showed mild tricuspid regurgitation and right ventricular thickening of the pump twin. In addition, the "parabiotic twin" was noted to measure about 70% that of the "pump twin". There was no sonographic suspicion for pericardial or pleural effusion as well as fetal ascites. Doppler study of the ductus venosus and the peak systolic flow of the middle cerebral artery continued to be normal. At this point in time a decision was made to perform RFA. The procedure was successful and the patient was discharged home.

Four days following the RFA procedure the patient showed for a planned follow up study. This time a dividing membrane could be clearly seen separating the two gestational sacs (Figure 7). Thus a diagnosis of monochorionic diamniotic twining was confirmed. No blood flow to or inside the acardiac twin was seen. There was no sonographic suspicion for pericardial or pleural effusion, and ascites in the "pump twin". Doppler study of the ductus venosus and the peak systolic flow of the middle cerebral artery were normal. The "pump twin" demonstrated active movement and normal amniotic fluid volume. The patient continued to undergo weekly assessments of fetal well being through biophysical profile and Doppler studies until 28 weeks at which time the interval between assessments was increased to three weeks. The sonographic evaluations showed normal interval growth of the "pump twin", normal Doppler studies of the ductus venosus and the middle cerebral artery, and continued decrease in the "parabiotic twin" volume. Repeated images of the brain structures of the "pump twin" were normal (Figure 8).

At 31 5/7 weeks the patient experienced rupture the membranes and went into spontaneous labor. She vaginally delivered an appropriate for gestational age female newborn weighing 1,740 grams with Apgar scores of 7 and 9 at one and five minutes, respectively. Ultrasound study of the newborn's brain on the day of delivery noted periventricular leukomalacia, normal lateral ventricles size without intraventricular hemorrhage, and focal infarct in the right occipital lobe. The head ultrasound study was repeated on day 8 of life and showed the same findings. The newborn was discharged home in stable condition on day 16 of life. During the entire NICU stay she did not experience seizures. MRI of the brain at two months of age showed minimally dilated lateral ventricles with no evidence of hydrocephalus. Periventricular leukomalacia and small amount of bilateral intraventricular hemorrhage, as well as blood products in the right medial occipital lobe were noted

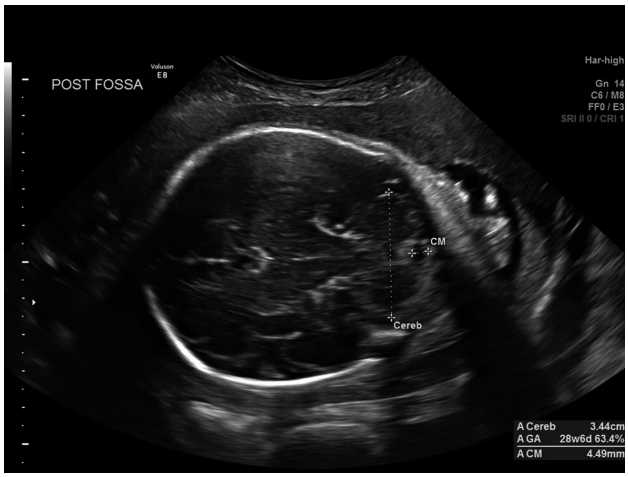

Figure 8. — Case 2: normal image of the brain structures of the "pump twin" following the RFA procedure in case 2.

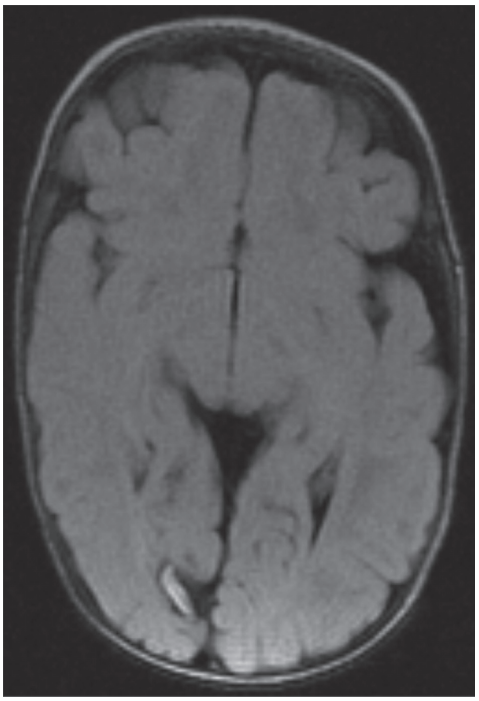

Figure 9. — Case 2: MRI of the brain at two months of age showing minimally dilated lateral ventricles with no evidence of hydrocephalus, as well as blood products in the right medial occipital lobe.

(Figure 9). In addition asymmetry of the CSF spaces surrounding the cerebral hemispheres, with relatively more prominent CSF around the left hemisphere was seen.

The placental pathology examination noted slightly immature monochorionic diamniotic twin fused placentas weighing 428 grams (less than 10th percentile for the gestational age). Acute chorioamnionitis with fetal inflammatory response in the chorionic plate and umbilical vessels is seen. Major artery to artery anastomosis connecting the placenta of the "pump twin" to placenta of the "parabiotic twin" was seen. On cut section, the cord of the normal twin had three vessels. The umbilical cord of the acardiac twin was poorly formed with distal atresia. On cut section, the cord had three vessels. The acardiac twin was markedly autolyzed, with nearly fully developed bilateral lower body and extremities, a partially developed spinal column, and one partially developed hand. No brain, heart and other upper body organs developed. The acardiac twin weighed 74.5 grams, and measured 15×5.0×2.0 cm.

Discussion

TRAP sequence is a rare anomaly, thus series reported from single centers are limited by small sizes. Rare anomalies such as TRAP are therefore excellent candidates for multicenter collaborative efforts to pool data. The North American Fetal Therapy Network (NAFTNet) is an association of medical centers in the United States and Canada that have established expertise in fetal therapy. In 2013 NAFTNet reported its registry data on the outcomes of RFA to treat TRAP between 1998 and 2008, on a total of 98 women from 12 centers who underwent RFA of the "parabiotic twin" for TRAP sequence [4]. The present authors have used this report and other smaller volume reports to compare their cases with published data.

The two herein reported TRAP cases represent some of the clinical challenges and potential complications associated with this type of twining. The nature of placentation differed between the cases. Monochorionic monoamniotic and monochorionic diamniotic, in the first and second case, respectively. Due to the complexity associated with TTTS the second case resulting in polyhydramnios in one sac and oligohydramnios in the other, the nature of placentation could only be confirmed following the RFA procedure once new vascular equilibrium has been achieved between the two fetuses and a dividing membrane was seen. In the NAFTNet report survival was significantly higher in the monochorionic/diamniotic twins than in the monochorionic /monoamniotic twins. Unfortunately there was no mention weather this fact leads to different clinical management based on the nature of placentation.

Regardless of the severity of morphologic anomalies, the parabiotic twin is nonviable. In contrast to the striking anomalies of the parabiotic twin, the pump twin is usually morphologically normal; however, the increased perfusional demands places the pump twin at risk of high output cardiac failure and hydrops. This risk to the pump twin increases as the size of the parabiotic twin increases [5]. The rate of perinatal mortality in the pump twin has been reported to be between 35% and 55% [5-7]. Additional risks to the pump twin, including preterm labor, are observed as the size of the parabiotic twin increases. The reported rates of preterm delivery range from 35% to 79% [5-7]. Another potential risk for the pump twin is growth restriction from chronic ischemia which may also occur as the parabiotic

twin further deoxygenates the already oxygen depleted blood it receives from the pump twin [8]. However, neither case did not show growth restriction.

As parabiotic twin size seems to be the most reliable prognostic indicator of the pregnancy outcome, various methods have been put forth to help predict for which pregnancies intervention is appropriate. These methods have focused on the relative size of the parabiotic twin compared to the pump twin. In their evaluation of postpartum TRAP twin pairs, Moore *et al.* reported that the risks of preterm labor, high cardiac output failure, and polyhydramnios were significantly higher when the parabiotic twin weight exceeded 70% of the pump twin's weight [5]. By contrast, the authors reported that the prognosis was considerably better when the parabiotic/pump twin weight ratio was less than 50%. Based on this report a decision was made not to reattempt RFA in case 1 following recanalization of one umbilical artery and the vein. In retrospect, this has been a well justified decision. In case 2 the decision to proceed with RFA was based on the observation of the "parabiotic twin's" volume reaching 70% of the pump twin and concomitant concerns related to the cardiac performance of the pump twin.

An interesting aspect of the parabiotic twin morphologic features in case 1 pertains to the presence of a heart with associated cardiac activity. The heart rate of the pump twin was 149 beats per minute and that of the "parabiotic twin" 131 beats per minute. This finding of two distinct heart rates is in line with a study by Oliver *et al.* who have reported their findings of the cardiac rate observed in "parabiotic twins" with rudimentary hearts [1]. Cardiac activity was identified in 14 of the 15 "parabiotic twins" with rudimentary hearts, and in nine of these cases, the cardiac rate was documented within a range of 100 to 180 beats per minute and distinct from that of the pump twin. As the "parabiotic twin" had reversed arterial flow, it is conceivable that the presence of "parabiotic twin" cardiac activity could increase the vascular resistance against which the pump twin must work; however, the extent to which this factor contributes to pump twin compromise, if any, is unknown.

In case 1, despite successful ablation of the cord within days following the procedure, color Doppler study noted continued blood flow in the umbilical cord of the parabiotic twin. In the NAFTNet report, two cases required reoperation when postoperative ultrasound imaging indicated persistence of blood flow to the acardiac twin due to either incomplete ablation or recanalization of the vessels. Unfortunately the report does not specify the clinical findings leading to the decision to repeat RFA. In the present case, a decision was made not to re-perform RFA as the calculated mass of the parabiotic twin was well below 70% of the pump twin. The pathology report of case 1 clearly suggests recanalization of one of the umbilical arteries of the parabiotic twin. Of note is the fact that despite the recanalization and continued blood flow, the rudimentary heart of the parabiotic was not "revived".

Both cases have resulted in PPROM following the RFA procedure 26 days and 52 days for case 1 and 2, respectively. In the NAFTNet report the incidence of PPROM was 17%. The time from procedure to PPROM was ≤ 10 weeks for most of the 17 cases. Of the 17 cases involving PPROM, eight neonates survived to 30 days with a mean gestational age at delivery of 26.1 ± 5.1 weeks. The four neonatal deaths that occurred were all associated with PPROM and early preterm delivery (**25.2 ± 1.1** weeks). Case 1 underwent planed induction of labor at 34 weeks, while case 2 was delivered at 31 5/7 weeks as immediately following PPROM the patient went into spontaneous labor.

A well known consequence of the shared circulation is that the well-being of one twin critically depends on that of the other. After the diagnosis of spontaneous demise of one of a monochorionic pair, the survivor has a 15% risk of death and a 25% risk of neurodevelopmental impairment because of acute exsanguination along the anastomoses into its demised cotwin [9].

The newborn in case 1 had an uneventful NICU stay and was discharged on day 10 of life. On the day of discharge head ultrasound study was normal. The outcome for the newborn in case 2 differed. Despite being born with Apgar scores of 7 and 9 at one and five minutes, respectively, ultrasound study of the newborn's brain on the day of delivery noted periventricular leukomalacia, normal lateral ventricles size without intraventricular hemorrhage, and focal infarct in the right occipital lobe. The head ultrasound study was repeated on day 8 of life and showed the same findings. The newborn was discharged home in stable condition on day 16. During the entire NICU stay the female newborn did not experienced seizures. MRI of the brain at two months of age showed minimally dilated lateral ventricles with no evidence of hydrocephalus, periventricular leukomalacia and small amount of bilateral intraventricular hemorrhage, as well as blood products in the right medial occipital lobe. In addition asymmetry of the CSF spaces surrounding the cerebral hemispheres, with relatively more prominent CSF around the left hemisphere was seen. In the NAFTNet report there is no mention of brain injury for the surviving pump twin following RFA procedure.

The fetus in case 2 suffered brain insult diagnosed on the first day of life. In the setting of monochorionic/diamniotic and monochorionic monoamniotic twinning single intrauterine fetal demise has potentially profound consequences to the co-twin, including increased risk of fetal mortality, increased risk of neurologic morbidity, and increased risk of preterm birth and its sequelae [9]. In the meta-analysis done by Hillman *et al.*, almost five-times significantly higher odds of neurodevelopmental morbidity in the surviving twin was shown in single twin demise with monochorionic compared with dichorionic placentation [9]. However, in the case of TRAP twining, this risk has not been extensively studied and reported including the NAFT-

Net report. The present authors therefore performed extensive literature search to find studies reporting intrauterine brain damage in the pump twin following RFA procedure. Unfortunately the search failed to uncover such studies. There could be many explanations for this, including lack of imaging, underreporting, inconsistency with the way abnormal imaging is reported, and lack of consistency in timing of imaging in relation to the RFA procedure. Antenatal brain damage is often detectable on prenatal ultrasound examination, but occasionally does not become apparent until several weeks after the insult. MRI may detect brain lesions earlier and with better definition [10]. Unfortunately the present report cannot clearly confirm that the fetus in case 2 has suffered brain insult as a result of the RFA procedure or alternatively, and possibly more likely, the brain insult has been the result of prematurity.

In summary the thought process, the rational leading to clinical decisions, RFA procedure, and potential complications associated with TRAP case are reported and discussed. The present authors suggest there must be consistent fetal and neonatal brain imaging, including in-utero MRI of the brain as well as meticulous neurodevelopmental follow-up to allow unbiased analysis of neurologic morbidity in TRAP cases prior to and following RFA procedure.

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