Twin reversed arterial perfusion sequence: A review of cases in the Philippines from 2000 to 2022

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Abstract
Twin reversed arterial perfusion (TRAP) sequence, or acardiac twinning, is a congenital anomaly associated with monochorionic twin pregnancies. It occurs when the cardiac system of one twin supplies blood for both twins. This congenital anomaly has been previously reported in several case reports from the Philippines. However, there is still limited information about its local epidemiology and management. This study reviewed the previous cases of TRAP sequence and discussed the diagnosis, management, and ways to improve care for pregnant patients affected by this condition. There were five reported cases of TRAP sequence from the Philippines. Ultrasonography was used in diagnosing the disease antenatally. Preterm birth was reported in 60% of the cases, while 80% were delivered via Cesarean section. The most common type of acardiac twinning in the Philippines was the acardius acephalus. The most common placentation observed in TRAP sequence cases was monochorionic, monoamnionic placenta (75%), two of which had arterio-arterial and veno-venous anastomoses. All donor twins in the Philippines were delivered alive, with only one (20%) neonatal death due to Pseudomonas infection. Only a few centers can perform minimally invasive fetal interventions; one center has been performing fetoscopic surgery in the Philippines since 2021. Thus, cases of TRAP sequence in the Philippines have only been managed through antenatal surveillance with serial ultrasound and high-risk prenatal care until their eventual delivery.

Key words: acardiac twinning, chorangiophagus parasiticus, congenital anomaly, multifetal pregnancy, twin reversed arterial perfusion sequence

INTRODUCTION
Twin reversed arterial perfusion (TRAP) sequence, or acardiac malformation, is a rare congenital anomaly associated with monochorionic multifetal pregnancies. One of the twins lacks a complete cardiac structure (acardiac twin), while the other is morphologically normal and supports the circulation of the acardiac twin aside from supplying its own (pump twin). The current incidence is 2.6% in monochorionic twin pregnancies and 1:9500 to 11,000 in all pregnancies. The pathogenesis of TRAP sequence is not yet fully understood. However, it was proposed that the disease could be due to underlying vascular anastomoses in the monochorionic placenta. The twin with higher blood perfusion usually develops and becomes the pump twin, while the twin with decreased blood perfusion becomes the acardiac twin due to compromised morphogenesis. Another hypothesis is that primary failure of heart development in one twin, due to a chromosomal abnormality or environmental...
factors, ultimately leads to its perfusion by the pump twin through artery-artery anastomoses. A retrograde blood flow pattern through the umbilical arteries supports the unique perfusion of an acardiac fetus.\textsuperscript{1,4} The acardiac twin is often mistaken to be viable, leading to conservative management or the reluctance to interrupt its blood supply through minimally invasive surgery. While this anomalous intertwin blood supply persists, the pump twin becomes increasingly at risk of developing congestive heart failure and polyhydramnios which may give rise to the complications of preterm delivery. This results in up to 55% perinatal mortality for the pump twin.

TRAP sequence has been previously reported in the Philippines.\textsuperscript{5–7,9} However, there is still limited information regarding the local epidemiology and management of this disease. This study reviewed the previous cases of TRAP sequence in the country and discussed the diagnosis, management, and ways to improve care for pregnant patients affected by this condition. An extensive literature search in the Health Research and Development Information Network (HERDIN) database, the national health research repository of the Philippines, was conducted using the keywords: twin reversed arterial perfusion sequence, TRAP sequence, acardiac twin, acephalus twin, and chorangiophagus parasiticus. Relevant original articles and case reports in English and Filipino were included in this review.

**TRAP SEQUENCE IN THE PHILIPPINES**

The first case of monoamnionic twinning in the Philippines was reported in 1946.\textsuperscript{10} In our hospital, the Philippine General Hospital, there were 1752 delivered babies with multiple congenital anomalies from 2010 To 2022. Of these, only three were recorded as cases of acardiac twinning (0.17%). During the 21\textsuperscript{st} century, we obtained five distinct cases of TRAP sequence from the Philippines (Table 1).\textsuperscript{5–7,8} Three additional cases were reported but with notably incomplete clinical data. Hence, they were not included in this review.

The maternal age range of TRAP sequence patients in the Philippines was 27 to 41. The most common maternal comorbidity was preeclampsia (2 out of 5). The diagnosis of TRAP sequence was made via ultrasonography. Three TRAP sequence patients were delivered preterm (60%\textsuperscript{a}) and two at term (40\textsuperscript{a}). Most were delivered via Cesarean section (80\textsuperscript{a}), and only one was via vaginal delivery (20\textsuperscript{a}). The most common type of acardiac twinning in the Philippines is the acardius acephalus type, where the fetus has a well-developed pelvis and lower limbs but no head, usually no thoracic organs, and no upper limbs. This is also the most common type worldwide.\textsuperscript{11} The birth weight range of the donor or pump twin was 1250 g to 2500 g, while the acardiac twin ranged from 500 g to 1950 g. Only four cases reported the amnionicity and chorionicity of the placentas. The most common were monochorionic, monoamnionic placentae (75%), where two patients had arterio-arterial and veno-venous anastomoses. Only one patient had monochorionic, diamnionic placenta (25%). Lastly, all donor twins in the Philippines were delivered alive, with only one (20\textsuperscript{a}) neonatal death due to *Pseudomonas* infection. This fetus was delivered alive with hydrops fetalis, cardiomegaly, and hepatomegaly.

**DIAGNOSIS OF TRAP SEQUENCE IN THE PHILIPPINES**

The prenatal diagnosis of acardiac twinning or TRAP sequence in the Philippines is commonly via ultrasonography alone. TRAP sequence can be diagnosed at the end of the first trimester, where one of the twins is found to be a hydropic fetus without cardiac activity.\textsuperscript{12,13} The acardiac twin may also present with several head, trunk, or limb malformations, as well as with subcutaneous edema or with other areas of excess fluid accumulation. Intertwin growth discrepancies in the biometrical measurements of the twins, particularly in the abdominal circumference, are also typical findings in TRAP sequence patients.\textsuperscript{11,14} Furthermore, a pathognomonic feature of reverse flow within arterio-arterial anastomoses in the umbilical arteries can be seen in Doppler studies. This is characterized by a paradoxical circulation where arterial blood flows towards the acardiac twin in a caudal to cranial pattern through the abdominal aorta.\textsuperscript{13}

It is important to establish the correct diagnosis for TRAP sequence patients. Misdiagnosis may lead to adverse outcomes for the pump twins. Differntial diagnoses for TRAP sequence that should be ruled out include choiromioma, a placental cyst or teratoma, and an early single demise in a monochorionic twin pregnancy.\textsuperscript{11}

**MANAGEMENT OF TRAP SEQUENCE IN THE PHILIPPINES**

The acardiac twin is 100% not viable.\textsuperscript{17} Hence, the management of TRAP sequence should prioritize the prevention of complications in the pump fetus and the mother and maintain the pregnancy for delivery at term. Based on the current evidence and consensus of experts, minimally invasive techniques are associated with the best prognosis with minimal maternal and fetal risks. Available interventions include ultrasound-guided and fetoscopic-guided treatments.\textsuperscript{11} Ultrasound-guided and fetoscopic-guided treatments can directly target the umbilical cord vessels of the acardiac twin. Ultrasound-guided umbilical cord occlusion techniques involve using thrombogenic steel coils, alcohol-soaked suture material, glucose, fibrin, enbucrilate gel, ligation, or electrical energy in the form of monopolar or bipolar thermocoagulation.\textsuperscript{11,18,19} These interventions are usually carried out at or after 16 weeks of gestation. However, several studies reported that
ultrasound-guided bipolar thermocoagulation resulted in higher rates of miscarriage when performed at 16–19 weeks compared to those treated after 19 weeks.\[^{20,21}\] On the other hand, fetoscopic-guided treatment may involve ligating the umbilical cord or coagulating the umbilical vessels using laser energy.\[^{22}\] A previous study showed that fetoscopic-guided umbilical cord occlusion achieved better pregnancy outcomes if performed at or before 24 weeks of gestation.\[^{21,22}\] Endoscopic laser coagulation at 26 and 28 weeks of gestation failed to arrest blood flow because the umbilical cords were very edematous.\[^{23}\]

The main disadvantage of the cord occlusion techniques is the technical difficulty of correctly targeting the umbilical vessels of the acardiac twin,\[^{11}\] which usually lie close to that of the pump twin. Consequently, this procedure can also damage the cord of the pump twin. Moreover, the umbilical cord of the acardiac twin is short, thin, and highly susceptible to rupturing and bleeding. To avoid these complications, ultrasound-guided intrafetal techniques were developed. Intraabdominal vessels can be easily visualized with color Doppler ultrasound allowing proper targeting of an acardiac twin's abdominal aorta or pelvic
vessels. Intrafetal ablation techniques include alcohol chemosclerosis, monopolar diathermy, laser coagulation, and radiofrequency ablation.24–26 These techniques are performed between 16 weeks of gestation to as long as 30 weeks of gestation, although some centers have reported that elective treatment with intrafetal laser therapy between 13 and 16 weeks’ gestation decreased adverse outcomes for pregnancies with TRAP sequence.27 Another study showed that prophylactic intervention by intrafetal laser from 12 weeks onward was associated with lower rates of preterm birth and preterm premature rupture of membranes. It was also associated with higher gestational age and birthweight than the expectant approach until 19 weeks’ gestation with subsequent radiofrequency ablation.28

Until this article was written, there have been no known reported attempts of minimally invasive treatment to address cases of TRAP sequence in the Philippines. As of 2022, there were 247 licensed Maternal Fetal Medicine (MFM) specialists in the country, most of whom maintained their practices in highly urbanized or metropolitan areas.29 Currently, only a few centers can perform minimally invasive fetal interventions, and only one center has been performing fetoscopic surgery since 2021. Thus, cases of TRAP sequence in the Philippines have only been managed through antenatal surveillance with serial ultrasound coupled with high-risk prenatal care until their eventual delivery.

CONCLUSIONS AND PERSPECTIVES

This review listed the five reported cases of TRAP sequence in the Philippines during the 21st century. The low sample size of cases of TRAP sequence is a major limitation of this review. However, based on the available information, we discussed the diagnosis and available management of this disease in the Philippines. Ultrasonography remains the standard method in diagnosing TRAP sequence in the country, while minimally invasive umbilical cord and intrafetal vessel occlusion techniques have yet to be attempted. There is still a significant need for research and development in the clinical management of TRAP sequence and most other fetal interventions locally.

One of the gaps in clinical practice is the low number of MFM specialists trained in diagnosing and caring for patients with TRAP sequence in the Philippines. Most of these specialists are concentrated only in major cities. Looking at the bigger picture, this maldistribution of specialists has contributed to socioeconomic and geographical disparities in available antenatal care and birth outcomes.30–32 For instance, only 68.5% of women residing in the Autonomous Region of Muslim Mindanao have been reported to receive antenatal care during pregnancy. This contrasts with 98% of antenatal care coverage among women in the Eastern Visayan Region. Moreover, there are still regions in the Philippines where many pregnant women deliver outside a health facility.33 Therefore, many cases of TRAP sequence and other complications of multifetal pregnancies may fail to be diagnosed and result in poor maternal and neonatal outcomes.

There is also insufficient research on TRAP sequence and other complications of multifetal pregnancy in the Philippines. Moreover, there is limited epidemiologic data on TRAP sequence due to several reasons: (1) low funding opportunities and priority allocation for antenatal health research on rare conditions; (2) lack of a national registry of multiple congenital anomalies with emphasis on prenatal diagnosis; and (3) few physicians publishing cases of TRAP sequence. There is a need for more studies on TRAP sequence and other complications of multifetal pregnancies to determine the actual burden of the disease in the Philippines. We encourage Filipino physicians to publish their cases of TRAP sequence, and for Obstetrics and Gynecology or MFM specialty societies to develop a national registry of multiple congenital anomalies incorporating both prenatal and postnatal data. This registry can help gather epidemiologic data from all regions of the Philippines and be utilized as supporting evidence to prioritize research funding for the study of perinatal conditions to improve overall clinical management strategies in the population.

DECLARATIONS

Author contributions
Tantengco OAG: Conceptualization, Methodology, Investigation, Writing—Original draft preparation. Velayo CL: Conceptualization, Writing—Reviewing and Editing.

Conflict of interests
None declared.

REFERENCES