

Review

Research Progress on Twin Reversed Arterial Perfusion Sequence Characteristics: A Narrative Review

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Abstract

Objective: Twin Reversed Arterial Perfusion (TRAP) sequence is a rare and severe complication unique to monochorionic multiple gestations. This article systematically reviews recent research findings and incorporates previous cutting-edge studies to comprehensively analyze new developments in the diagnosis and management of TRAP, so as to provide valuable insights for optimizing clinical practice. **Mechanism:** The hallmark of TRAP sequence is that a normally functioning pump twin supplies blood to its acardiac parasitic twin through arterial-arterial anastomosis on the placental surface. Cardiac dysfunction in TRAP predominantly arises from high-output heart failure, and the acardiac twin frequently presents multi-organ developmental anomalies. Without timely intervention, persistent high-output circulatory overload significantly raises the risk of severe heart failure and even death in the pump twin. **Findings in Brief:** Advances in fetal medicine, imaging techniques, and interventional therapies have achieved substantial progress in deciphering etiological mechanisms of TRAP, enabling precise diagnosis and promoting individualized treatment strategies for this condition. **Conclusions:** Updated understanding on diagnosis and management of TRAP sequence provides important references for clinical decision-making in this rare monochorionic twin complication.

Keywords: Twin Reversed Arterial Perfusion sequence; fetal medicine; diagnosis; treatment

1. Introduction

Twin Reversed Arterial Perfusion (TRAP) sequence, also known as acardiac twin sequence, is a rare and life-threatening complication occurring exclusively in monochorionic twin pregnancies. The core pathophysiological feature of TRAP is a significant hemodynamic imbalance resulting from abnormal placental vascular anastomoses between the twins. The clinical severity of TRAP is underscored by its profound adverse impact on both fetuses and the mother. Maternal complication rates in TRAP-affected monochorionic twin pregnancies are markedly elevated compared with singleton gestations, with the preterm birth rate reaching 32% [1]. Among affected fetuses, the “pump twin” faces the greatest risk. Without timely intervention, it may develop high-output cardiac failure and hydrops fetalis, leading to intrauterine or neonatal death. Moreover, survivors have a substantial risk of long-term neurodevelopmental impairment [2]. The acardiac twin is characterized by absent or severely dysmorphic cardiac structures, and is dependent on low-oxygen arterial perfusion from the pump twin. It exhibits multiple severe structural anomalies and invariably succumbs prenatally or shortly after delivery, with 100% mortality [3]. Continued growth of the acardiac mass further exacerbates the hemodynamic strain on the pump twin, establishing a self-perpetuating vicious cycle. For the mother, TRAP signif-

icantly increases the risks of polyhydramnios, preeclampsia, preterm premature rupture of membranes (PPROM), and postpartum hemorrhage, potentially threatening maternal life.

Advances in multimodal imaging and molecular techniques—including first-trimester ultrasound screening, three-dimensional vascular reconstruction, prenatal genetic testing, and magnetic resonance imaging (MRI)—have enabled earlier detection and improved the diagnostic accuracy of TRAP. Intrauterine interventional procedures constitute the mainstay of therapeutic management, with the primary objective being selective interruption of blood flow to the acardiac twin. The most widely adopted modalities include radiofrequency ablation (RFA), microwave ablation, and bipolar cord coagulation [4,5,6]. Concurrently, integrated multidisciplinary care encompassing obstetrics, fetal medicine, neonatology, radiology, and genetic counseling has been shown to increase the perinatal survival rate of the pump twin.

Recent research has highlighted the critical importance of long-term, systematic follow-up of surviving infants, with particular emphasis on neurodevelopmental outcomes and cardiovascular function. Precise elucidation of the underlying etiopathogenic mechanisms remains challenging, although there is evolving consensus on indications for intervention and optimal strategies for severe



cases. Future progress is likely to require a better understanding of the molecular disease pathways, innovation in diagnostic technologies, and stronger multicenter collaborative research. This should ultimately lead to refinement and optimization of the diagnostic and therapeutic framework for TRAP.

Literature Search

In this review, we systematically summarize current evidence on TRAP, covering clinical features, prenatal diagnosis, management, and perinatal outcomes. Given the limited number of high-quality primary studies, we included reviews, letters, conference abstracts, and case reports—excluding only those that were clearly redundant, severely data-deficient, or off-topic. We conducted and updated a structured literature search across PubMed, Embase, Web of Science, and the Cochrane Library from database inception to March 1, 2026, using both MeSH terms and relevant free-text keywords focused on TRAP sequence and its clinical implications.

Inclusion criteria: English-language studies reporting on TRAP—its clinical features, prenatal diagnosis, management, or perinatal outcomes—including original research, reviews, letters, conference abstracts, and case reports.

Exclusion criteria: Studies unrelated to TRAP sequence, non-English publications, duplicates, or those with severe data deficiencies precluding meaningful use.

Literature screening strictly followed PRISMA 2020: Initial search yielded 298 records; after deduplication, 229 underwent title/abstract screening, of which 102 were excluded (e.g., irrelevant topic, non-English). Full texts were retrieved for the remaining 127 records; 7 were excluded due to unavailability, leaving 120 for full-text assessment. Of these, 35 were excluded for ineligible study design and 25 for unclear TRAP diagnosis or incomplete data. Ultimately, 57 studies were included. See Fig. 1.

2. Epidemiological Advances

Recent global multicenter meta-analyses have revealed a relatively low incidence of TRAP in monochorionic twin pregnancies, despite the increasing application of assisted reproductive technologies (ARTs). The prevalence of TRAP among all twin gestations is estimated to be between 1 in 35,000 and 1 in 10,000. Of note, there is approximately one case of TRAP for every 100 instances of monozygotic twins [7]. However, the prevalence of early, non-cardiac malformed single chorionic twin pregnancies has increased from 1.1% to an adjusted figure of approximately 2.6% (calculated as $1.1 / (1 - 0.58)$) [8]. Depending on the methodology employed in ART, the incidence of TRAP in all pregnancies has increased from an initial rate of 1 in 35,000 to the current range of 1 in 9500–11,000. It is noteworthy that acardiac twinning occurs in approximately 1 in 8 monochorionic placentas containing both arterial-arterial and venous-venous anastomoses [8].

In these scenarios, one fetus—referred to as the “acardiac twin”—exhibits no cardiac structure and presents with multiple malformations predominantly affecting the upper body. Tragically, the mortality rate for this condition is a staggering 100%. Conversely, the other fetus assumes the role of the “pump twin” and is frequently accompanied by polyhydramnios and heart failure. Complications associated with this condition are significantly elevated due to preterm birth and cardiac insufficiency [9]. Without timely intervention, the mortality rate for the pump twin can be as high as an alarming 55%, primarily because of congestive heart failure [7]. Nevertheless, some scholars have contested these statistics, positing that if diagnoses were made during early gestation stages, the actual incidence of TRAP would be 1 in 9500–11,000 pregnancies, with a reported incidence in monochorionic twin gestations of approximating 2.6% [10]. Moreover, in addition to occurring in monochorionic twins, TRAP could also arise in triplet or higher-order multiple gestations [11,12]. It has also been observed that TRAP leads to elevated mortality rates during the period from the early first trimester through to the early second trimester [13].

Several studies have examined the epidemiological characteristics related to risk factors and genetic susceptibility concerning placental vascular connections. A significant finding is that large-diameter (>1.5 mm), single artery-to-artery (AA) anastomoses in pump twins are associated with an increased incidence of heart failure. Whether this constitutes a critical risk factor influencing disease severity remains under investigation.

3. Advances in the Etiology and Pathogenesis of TRAP

3.1 Deepening the Classic Vascular Anastomosis Theory

The pathological basis of TRAP is reversed arterial perfusion, a condition whose core features differ from those of twin-to-twin transfusion syndrome (TTTS). The first hypothesis posits that during the early stages of embryonic development in TRAP fetuses, abnormal formation of the placental vasculature leads to the establishment of AA vascular connections, resulting in a significant influx of hypoxic blood from the pump twin to the acardiac twin. This condition can only sustain the development of localized tissue (specifically the lower body), ultimately culminating in the evolution of an acardiac twin [14,15]. The second hypothesis suggests that one twin experiences primary cardiac malformation during early embryogenesis, resulting in an acardiac state. Consequently, to ensure continued growth and development, placental adaptations give rise to AA vascular connections necessary for maintaining blood supply to the acardiac fetus [16]. Furthermore, confirmation of TRAP pathology requires adherence to two critical criteria: the existence of substantial congenital AA anastomoses facilitating circulation between both fetuses within the placenta, and evidence of cardiac anomalies or developmental deficiencies in one of the twin pairs [17].

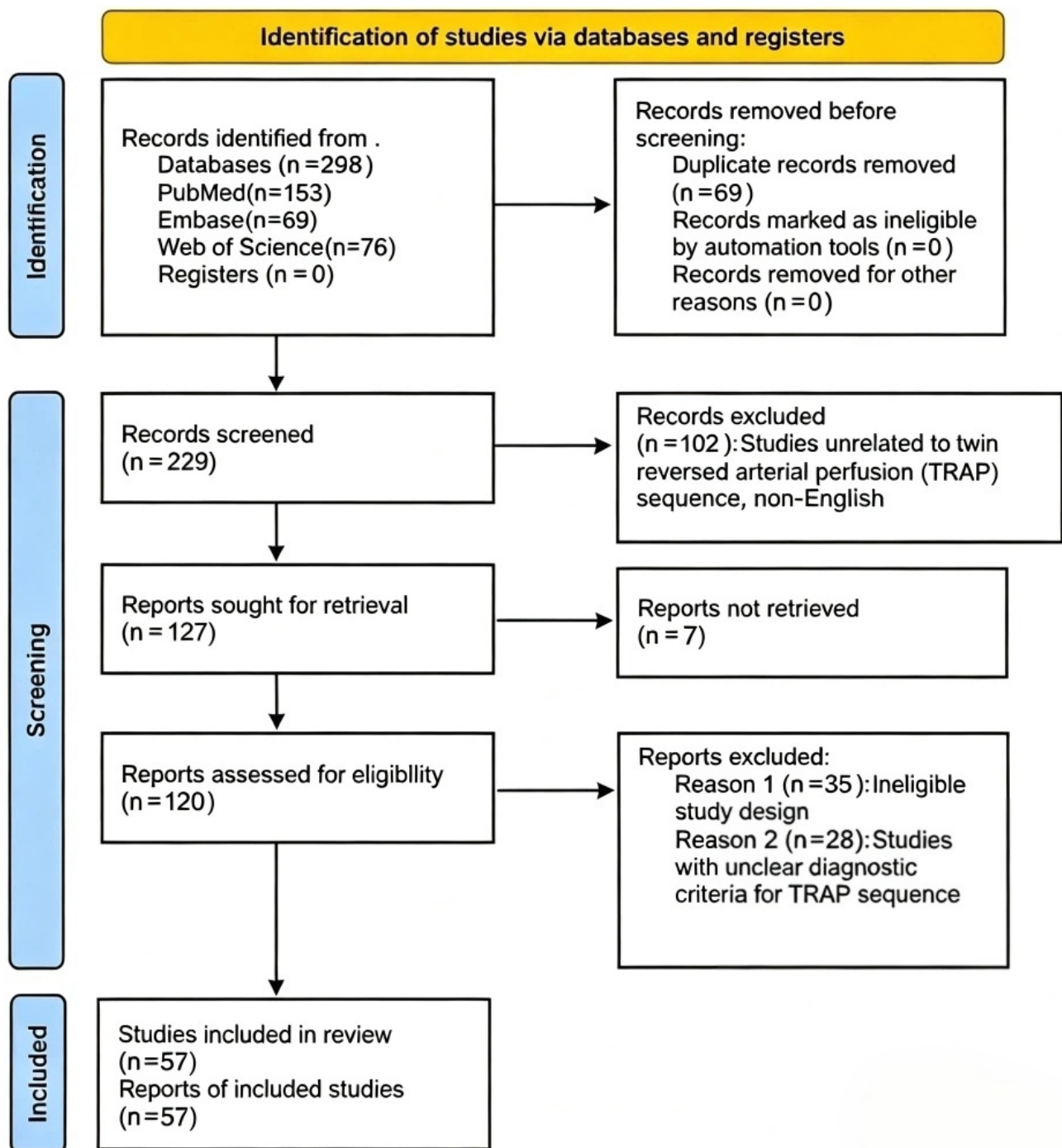


Fig. 1. Literature screening.

3.2 Unequal Cell Division (Hypothetical)

This hypothesis asserts that factors contributing to embryonic defects may be linked with imbalances that occur during early cell division among monochorionic twins. Such embryonic anomalies are deemed fatal for acardiac twins. Conversely, aberrant structures within placental vascular anastomoses appear conducive to sustaining further development of these acardiac entities [10]. Siwatch et al. [18] proposed that uneven embryonic cleavage and genetic abnormalities contribute to developmental defects in

TRAP. However, this remains speculative, with no supporting evidence from basic research, animal models, or histopathological studies. Further clinical investigation of this hypothesis is warranted (see Fig. 2).

4. Clinical Manifestations and Signs

At present, there is no clear consensus on the clinical manifestations and signs associated with TRAP. The following summary is based on several case reports [19,20].

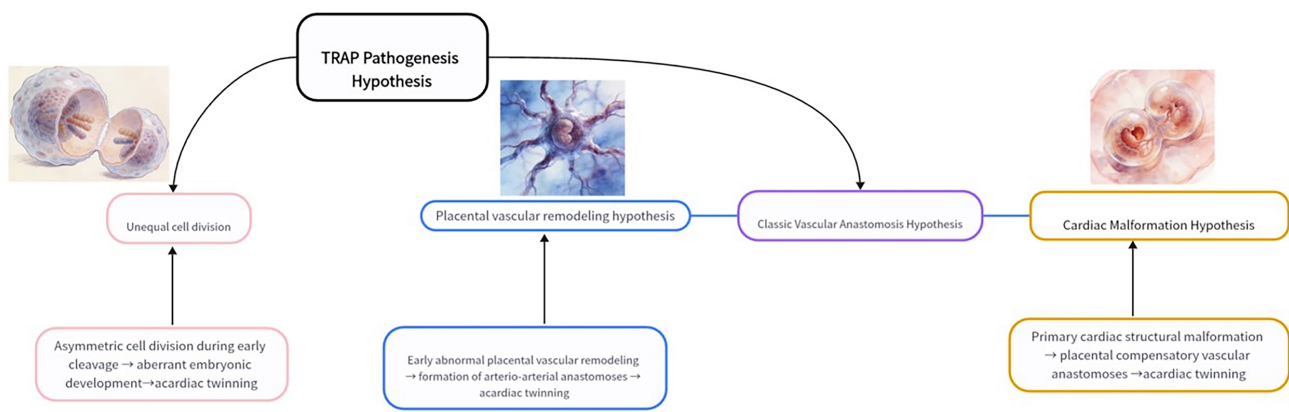


Fig. 2. Several hypotheses regarding the pathogenesis of TRAP.

4.1 Clinical Manifestations and Signs: Pump Twin

The pump twin is the primary focus of clinical intervention. All of their manifestations are associated with high-output heart failure: (1) fetal edema, polyhydramnios, and abnormal growth and development; (2) signs related to cardiac dysfunction, such as structural changes in the heart (primarily left atrial/ventricular enlargement, increased wall thickness, pericardial effusion), valvular dysfunction (mild to moderate mitral/tricuspid regurgitation), and hemodynamic abnormalities (abnormal umbilical artery blood flow, abnormal venous duct blood flow, abnormal middle cerebral artery blood flow).

4.2 Clinical Manifestations and Signs: Acardiac Twin

The acardiac twin exhibits developmental abnormalities due to “reverse perfusion”, while also lacking autonomous viability. They are characterized by typical malformations that are readily identified via ultrasound. (1) Core characteristic signs: absence of cardiac malformations and abnormal blood flow direction. (2) Associated presentation of partial malformations: central nervous system anomalies—anecephaly being the most common due to insufficient head perfusion—as well as spina bifida, hydrocephalus, encephalocele, etc., which may present as cranial bone defects or exposed brain tissue under ultrasound examination, or interruption of spinal continuity; limb and trunk abnormalities (shortened limbs, underdeveloped trunk); edema along with skin anomalies. (3) Abnormal growth patterns: typically manifesting as small but malformed shapes.

4.3 Clinical Manifestations and Signs: Maternal

According to existing data, most mothers with TRAP fetuses do not exhibit significant clinical manifestations or signs. However, some scholars have reported that maternal symptoms may include the following characteristics. (1) Abnormal uterine enlargement: significantly exceeding the normal range for corresponding gestational weeks; mothers may perceive a “rapid increase” in abdominal size accom-

panied by bloating or a feeling of heaviness. (2) Compression symptoms: gastrointestinal compression leading to decreased appetite, nausea, vomiting; diaphragmatic pressure causing chest tightness, shortness of breath, difficulties in breathing; bladder pressure resulting in frequent urination or urgency. (3) Symptoms related to preterm labor: irregular contractions during mid-pregnancy accompanied by minimal vaginal bleeding or cervical shortening. (4) Gestational hypertension with proteinuria due to worsening fetal edema caused by heart failure in the pump twin.

4.4 Confirmation of Diagnosis and Differential Diagnosis

The definitive diagnosis of TRAP relies primarily on ultrasound imaging. This reveals one twin without visible cardiac structures throughout its course, along with an absent fetal heartbeat, while Doppler ultrasound indicates abnormal blood flow directionality. It is important to differentiate TRAP from the following conditions. (1) Twin pregnancy with one fetus undergoing demise: although acardiac twins lack a heartbeat, they still show evidence of perfusion through detectable body blood flow signals via ultrasound, whereas demised fetuses display no such signals alongside gradual atrophy. (2) TTTS: both twins possess intact cardiac structures but demonstrate imbalanced fluid exchange—the donor twin exhibits oligohydramnios while the recipient twin experiences polyhydramnios—without the presence of acardiac deformities. (3) Selective intrauterine growth restriction (sIUGR): both twins maintain normal cardiac structures but differ in weight by >25%, lacking reverse arterial perfusion alongside any acardiac deformities.

5. Advances in Prenatal Screening, Monitoring, and Obstetric Research

5.1 Prenatal Screening

For cases diagnosed with TRAP, prenatal screening is recommended. In non-TRAP cases where early aneuploidy screening indicates a high risk, attention should be paid to ruling out the presence of TRAP.

5.2 Monitoring

5.2.1 Ultrasound Monitoring

For cases of TRAP undergoing conservative treatment, follow-up ultrasounds should be conducted every two weeks [21]. The initial assessment must include observation of the number of chorionic membranes and amniotic sacs in twin pregnancies, determination of fetal positions for both fetuses, differentiation between the pump twin and the acardiac twin, as well as evaluation of general growth parameters for both fetuses.

5.2.2 Monitoring of the Pump Twin

The following aspects should be monitored. (1) Comprehensive examination is recommended to assess potential abnormalities in various systems, including cranial structures, facial features, spine, thorax/abdomen, and limbs. (2) Ultrasound evaluation should assess whether there are signs of high-output heart failure in the pump twin while monitoring cardiothoracic ratio, ventricular size and wall thicknesses, fractional shortening percentage, overall cardiovascular scoring (CVPS), cardiac output (CO), inferior vena cava preload index; indicators such as polyhydramnios, myocardial hypertrophy, pericardial effusion, tricuspid regurgitation or mitral regurgitation which may suggest heart failure [22]; additionally monitor for abdominal fluid accumulation or fetal edema; increased systolic/diastolic flow velocity ratios in umbilical arteries; elevated middle cerebral artery flow velocities; pulsatility indices may also indicate compromised hemodynamics. (3) Number of umbilical arteries present in the fetus. (4) Placental location. (5) Fetal maturity status.

5.2.3 Monitoring of the Acardiac Twin

The following aspects should be monitored. (1) Weight discrepancy between the pump and acardiac twin. (2) Umbilical cord diameter for both twins. (3) Assessment of any reverse perfusion occurring within acardiac anomalies [23]. Additionally, observe the blood flow volume to acardiac twins, along with their size and growth rate [24], checking for any fine linear structures resembling umbilical cords between acardiac anomalies and placentas.

5.2.4 Monitoring of Post-Intrauterine Interventions

Post-operative ultrasound examinations should be performed weekly for four weeks after the intervention surgery. If no abnormalities are detected during this period, then monitoring can continue as per conservative management protocols [1]. The primary objective of post-monitoring is to evaluate treatment efficacy, while also preventing the occurrence of postoperative complications.

5.3 Antenatal Care

Given that TRAP constitutes a high-risk pregnancy condition, it is advisable to increase the frequency of antenatal visits. After mid-pregnancy, assessments should oc-

cur biweekly and focus on maternal comorbidities alongside fetal intrauterine safety concerns. Simultaneously, maternal metrics such as fundal height changes, abdominal circumference, and weight gain trends should be tracked. In the case of rapid increases, heightened vigilance should be directed towards potential heart failure symptoms manifesting within the pump twin, alongside rising levels of amniotic fluid. For pregnant women receiving intrauterine intervention, careful monitoring with regard to infection risk and coagulation function is essential.

6. Advances in Diagnostic Technology

In clinical practice, the diagnosis of TRAP primarily relies on ultrasound examination, including both two-dimensional (2D) and three-dimensional (3D) ultrasonography. Color Doppler and power Doppler ultrasound are critical for confirming the diagnosis, particularly with regard to identifying reversed arterial flow. Prenatal genetic testing and MRI serve as valuable complementary modalities [25].

6.1 Precision of Ultrasound Diagnosis and Early Pregnancy Applications

Ultrasound is the core diagnostic tool for TRAP, and recent technological optimizations have facilitated early pregnancy diagnosis and risk stratification. (1) Ultrasound diagnosis of TRAP during early pregnancy (<10 weeks) can be challenging, often presenting as “singleton pregnancy”, a normal fetal heartbeat with a cystic structure, or as a normal fetal heartbeat alongside an atypical embryo with cardiac activity. During early pregnancy screening (11–13 + 6 weeks), nuchal translucency (NT) examination and transvaginal ultrasound can be utilized to observe the cardiac structures and umbilical artery blood flow of twin fetuses [26]. Characteristics of TRAP include the following features. (1) One fetus exhibits absent cardiac activity or severe heart failure, while the other shows increased NT and abnormal venous duct blood flow (retrograde flow during atrial contraction). Additionally, when the crown-rump length (CRL) measures between 45–84 mm, chorionic villus sampling and amniocentesis can be performed for further identification [27]. (2) Three-dimensional power Doppler ultrasound provides clear visualization of the number, type, diameter, and course of placental vascular anastomoses with an accuracy of >90%, surpassing that of two-dimensional ultrasound. This vascular reconstruction technology allows quantification of blood flow velocity through these connections [28]. (3) Pulsed Doppler ultrasound enables measurement of parameters related to blood flow in the umbilical arteries, middle cerebral arteries, and venous ducts of the pump twin. Elevated pulsatility index (PI) in the umbilical artery in combination with decreased PI in the middle cerebral artery indicates brain protective effects, while a retrograde A-wave in the venous duct suggests compromised heart function in the pump twin. These quantita-

tive hemodynamic assessments serve as supplementary indicators for monitoring disease progression and prognosis.

6.2 Supplementary Value of Prenatal Genetics

Prenatal genetic testing can provide etiological evidence in complex cases where ultrasound diagnosis is difficult or in cases accompanied by other structural anomalies. Research indicates that chromosomal abnormalities occur in approximately 9% of twin pregnancies. Prenatal genetic testing for TRAP cases is essential as it may reveal additional known hereditary conditions that could inform prognostic considerations for affected pump twins.

6.3 Auxiliary Role of MRI Diagnosis

MRI offers superior spatial resolution, enabling comprehensive evaluation of fetal anatomy and its associated structures, as well as clear visualization of their spatial relationships with surrounding maternal and fetal tissues. Multiple studies have investigated the application of MRI in the prenatal diagnosis of the TRAP sequence. In a retrospective analysis of 35 TRAP cases, Guimaraes et al. [29] reported that MRI provides distinct advantages in delineating fetal cardiac and cerebral structures, and can detect subtle pathological changes such as potential cerebral ischemia. However, MRI has inherent limitations, most notably its inability to capture real-time hemodynamic information. Consequently, the integration of MRI with ultrasound—a complementary modality capable of dynamic flow assessment—allows for a more comprehensive and objective characterization of both structural and functional alterations in TRAP, thereby providing robust evidence to guide intrauterine management. As a supplementary imaging modality to routine prenatal ultrasound, MRI is particularly valuable when sonographic visualization is suboptimal (e.g., due to acoustic shadowing from fetal skeletal structures, maternal obesity, or oligo-/polyhydramnios). Because MRI is unaffected by these confounding factors, it yields consistent, high-fidelity anatomical images.

6.4 AI-Assisted Screening

AI-assisted screening for TRAP sequence leverages deep learning models to automatically identify characteristic features of the acardiac twin, abnormal Doppler flow patterns, and cardiac functional alterations in the pump twin on ultrasound images—thereby improving early detection rates, reducing diagnostic omissions, and mitigating inter-observer variability among clinicians. Although several limitations must be addressed prior to the routine clinical implementation of AI models, artificial intelligence has already demonstrated promising performance in fetal cardiac diagnosis [30].

6.5 Four-Dimensional Blood Flow Ultrasound Technology

Emerging four-dimensional blood flow ultrasonography quantitatively analyzes vector fields associated with

placental vascular anastomoses, while clearly depicting spatial distribution characteristics indicative of “retrograde perfusion”. This advanced imaging technique facilitates comprehensive evaluations not only with regard to cardiovascular aspects, but also other organs such as placenta and cords alongside twin-related anomalies [31].

7. Clinical Classification and Staging Progression

7.1 Clinical Classification

The classification of TRAP is based on the development of the head, face, and upper limbs in acardiac fetuses [32]. (1) Acardiac Anencephalic Type: characterized by the absence of development above the chest in acardiac fetuses, with no head, chest, lungs, or heart; various underdeveloped organs may be present within the abdominal cavity, along with poorly developed lower limbs. This is the most common type of TRAP, accounting for approximately 60%–70% of cases. (2) Acardiac Cephalic Type: characterized by fetal head development only connected to the placenta, or via a neck attachment to the umbilical cord. This type accounts for about 5% of cases. (3) Amorphous Acardiac Type: primarily characterized by indistinguishable structures in the upper body of the fetus, appearing as an irregular mass without identifiable internal organ structures on ultrasound. Some acardiac fetuses may display certain visceral echoes such as liver or intestinal echoes. Umbilical cord attachment occurs at a surface location on this mass. This type accounts for approximately 25% of cases. (4) Partial Cephalic Acardiac Type: features partial cranial bones and incomplete facial development, which may include conditions like anophthalmia, microphthalmia, or cyclopia. There may also be some degree of trunk and limb development accompanied by severe edema and cystic hygroma formation, but no cardiac structure is observable. (5) Some studies have expanded the amorphous acephalic subtype by introducing a “limb-only acephalic” subtype [33,34]. As an important variant of the TRAP-associated amorphous acephalic subtype, this subtype is characterized by an amorphous, non-structured mass combined with one or more hypoplastic limbs. The heart is completely absent and non-functional, and there is hemodynamic dependence on retrograde arterial perfusion from the pump twin. First described in 1925 by Simonds and Gowen, this subtype was explicitly defined by its core triad of “limbs only, no heart, and no intact fetal body”, a conceptual framework that laid the foundation for subsequent classification [35]. After summarizing case reports by Tonni et al. [33], the limb manifestations of this subtype are described below. ① Limb number: one or two limbs are most common—predominantly lower limbs; isolated unilateral upper limbs are less frequent; three or more residual limbs occur rarely; symmetrical limb development is consistently absent. ② Limb morphology: limbs exhibit severe structural hypoplasia, typically showing only echogenic long bones (e.g., fe-

mur or humerus) without discernible joints or hand/foot differentiation. Some cases display shortening and angulation deformities; limb length is markedly reduced compared with that of the pump twin, typically ranging from one-third to one-half. © Mass characteristics: limbs are attached to an irregular, heterogeneous mass with ill-defined margins. No thoracic or abdominal organ echoes are identifiable within the mass. Occasionally, small cystic structures are observed—most commonly lymphatic hygromas or accumulations of interstitial fluid.

7.2 Clinical Staging

The clinical staging [36,37] of TRAP is determined according to the ratio of the abdominal circumference between the acardiac and pump fetuses, as well as symptoms exhibited by the pump twin:

Ia Stage: ratio <50%, with no symptoms observed in the pump twin;

Ib Stage: ratio <50%, with symptoms present in the pump twin;

IIa Stage: ratio ≥50%, with no symptoms observed in the pump twin;

IIb Stage: ratio ≥50%, with symptoms present in the pump twin.

8. Advances in Treatment Strategies

8.1 Conservative Treatment

Currently, the general indication for conservative treatment is when the acardiac fetus exhibits relatively small development, with ultrasound showing no signs of heart failure or only minimal changes in Doppler blood flow. Additionally, the weight of the acardiac fetus should be less than half the weight of the pump twin [7,38,39]. Sullivan et al. [40] suggest that conservative management is often the best initial approach, as inter-fetal blood flow may cease spontaneously. However, their study reported that 40% of cases were associated with a very low postnatal weight ratio between the acardiac and pump twins (APTW) of <3%.

8.2 Intrauterine Treatment

The currently recognized intrauterine treatment method is selective reduction surgery. This is primarily aimed at blocking the blood supply from the pump twin to the non-viable twin. Some researchers recommend that conservative treatment should be prioritized as a first-line option [41,42]. However, if signs of fetal distress arise (such as polyhydramnios, abdominal circumference of the acardiac equal to or greater than that of the donor, abnormal blood flow in the donor), consideration may be given to transitioning to intrauterine therapy to obstruct reverse perfusion. When the non-viable twin is smaller, and few cardiovascular dysfunctions are noted in the pump twin, they recommend continuous ultrasound monitoring for disease progression. For larger non-viable twins or those

exhibiting rapid tissue growth patterns, an internationally accepted therapeutic protocol is advised. In their latest review article, Brock and Johnson [43] suggested weekly assessments focusing on: (1) the growth trends of both fetuses; (2) Doppler velocities within umbilical arteries and middle cerebral arteries alongside venous duct flows for pump twins; (3) assessment via Doppler techniques for umbilical artery flows within the acardiac twin; (4) cardiac output measurements for the pump fetus; and (5) maximum vertical amniotic fluid pocket size, which is especially critical during monochorionic pregnancies involving pump twin membranes. If no complications arise and there are no indications suggesting organ dysfunction within the pump twin, then delivery after week 34 gestation appears reasonable [43]. The choice between conservative management versus intrauterine intervention presents complexities requiring careful consideration across three domains: (1) potential deterioration risks associated with cardiac function in the pump twin, alongside preterm labor risks due to polyhydramnios leading towards fetal demise; (2) considerations regarding fetal complications such as unexpected death among donors, or premature rupture/early birth; (3) maternal risk factors including intrauterine infection and hemorrhage/sepsis. Should intrauterine intervention become necessary, several approaches exist, as described below.

8.2.1 Ultrasound-Guided Laser Therapy

Elective laser treatment performed between 13 and 16 weeks of gestation has been reported to yield favorable outcomes [44].

8.2.2 Ultrasound-Guided RFA

This technique applies RFA procedures to specifically target complex cases involving monochorionic diamniotic pregnancies, thereby presenting a less invasive approach compared with endoscopic methods. A systematic review indicates [6] that RFA is the most technically successful therapeutic strategy, with a reported overall survival rate of approximately 83% following RFA treatment. Multicenter data reveal that the incidence of early-onset complications is significantly reduced, ranging from about 10–25% fetoscopic-laser coagulation (FLC)/RFA, and increases the survival probability of pump twins to around 70–85% [4,45]. Nevertheless, high-risk TRAP fetuses with mid-pregnancy cord occlusion show negligible differences in 30-day neonatal survival after treatment with laser technology versus RFA techniques [4]. Longitudinal epidemiological studies assessing neurodevelopmental outcomes have shown promising results. Infants surviving TRAP and treated with RFA show generally positive long-term neurological development profiles, indicating minimal adverse impacts from this intervention [46].

8.2.3 Microwave Ablation

Due to its thermal properties, microwave ablation provides an excellent energy source to facilitate vascular coagulation, thereby proving beneficial in the treatment of TRAP sequences [47].

8.2.4 Cord Ligation

Infants subjected to cord ligations exhibit perinatal survival rates of approximately 65%, surpassing the 42.9% observed without this procedure. Moreover, recent investigations utilizing cord ligations combined with laser-assisted methodologies reported a fetal survival rate of 88.9%, compared to 79.9% for the control group with no intervention. A systematic literature review suggests that modern, minimally invasive technologies applied during vessel ligation/cutting can increase the overall viability of pump twins from 79% to 89% [1].

8.2.5 Laser Ablation of Placental Anastomoses Under Fetoscopy

The fetal survival rate associated with this technique was reported to be 78.9% [44].

8.2.6 High-Intensity Focused Ultrasound

Utilizing high-intensity focused ultrasound (HIFU) under magnetic resonance (MR) guidance can effectively disrupt the fetal umbilical cord vessels, thereby facilitating selective termination of fetal development. This method offers a non-invasive treatment option for fetal abnormalities caused by TRAP [48].

8.2.7 Selective Reduction Surgery

(1) Surgical Indications: these include cases where the weight of the acardiac twin is more than half that of the pump twin, when there are Doppler changes in the blood flow of the pump twin, or when there are signs of heart failure in the pump twin. (2) Fetal Weight Calculation Formula: the weight of a non-viable fetus can be calculated using its maximum length (L), with the formula being non-viable fetal weight (g) = $1.2 \times L \text{ (cm)}^2 - [1.66 \times L \text{ (cm)}]$. However, it should be noted that even if conservative management is successful and the pump twin survives, there remains a relatively high risk of low birthweight newborns, potential long-term health development risks, as well as increased socioeconomic costs. Some studies suggest that early detection and intrauterine intervention for TRAP significantly improve neonatal survival rates. (3) Choice of Surgical Method: The primary goal of fetoscopic intervention is to obstruct the blood supply from the pump twin to the acardiac twin. Currently, RFA selective reduction surgery is considered one of the preferred treatment options. Each surgical approach has advantages and disadvantages, necessitating larger sample sizes for validation. (4) Timing of Intrauterine Treatment: considerable debate exists regarding the optimal timing of treatment, particularly for

cases classified as Stage Ib or higher, or those where the body weight ratio exceeds 70%. Most procedures are typically performed between weeks 15 and 26 of gestation. Regardless of which surgical method or timing is chosen, physicians must consider individual patient factors and remain vigilant regarding the potential risks associated with each procedure. (5) Ethical Considerations for Surgery: For selective reduction surgery related to TRAP under conditions where a diagnosis is confirmed—and specifically noting that anencephalic fetuses lack viability—the presence of a non-viable twin may continue to adversely affect normal circulatory function and pose a survival threat to the pump twin. Maternal physical and mental health considerations must also be taken into account, along with possible complications during prenatal care. Therefore, performing selective reduction on the acardiac twin aligns with obstetric ethical standards [49,50].

8.3 Applicability of Different Intervention Strategies and Their Associated Potential Risks

8.3.1 Conservative Treatment

The indications for conservative treatment are as follows. (1) APTW <0.5, with a small acardiac twin volume and slow growth. (2) Stable condition of the pump twin: absence of cardiac dysfunction, fetal hydrops, or polyhydramnios (normal amniotic fluid index); normal Doppler flow in the umbilical vein and ductus venosus. (3) Early gestational age: typically <16 weeks, with spontaneous cessation of blood flow to the acardiac twin observed or anticipated. (4) Absence of severe maternal complications: Conservative management is not automatically indicated for all MCDA pregnancies complicated by TRAP. The management strategy for TRAP should be individualized according to the cardiac status of the pump twin, the size and perfusion of the acardiac twin, as recommended by the 2025 ISUOG Practice Guidelines on twin pregnancy.

The potential risks or complications associated with conservative treatment are as follows. (1) Pump twin heart failure or intrauterine demise: without intrauterine intervention, the risk of heart failure and mortality in the pump twin may increase. (2) Preterm birth: risk of preterm delivery is elevated due to uterine overdistension. (3) Pump twin hydrops and neurologic injury: prolonged high-output cardiac failure may lead to abnormal cerebral perfusion and long-term neurodevelopmental impairment. (4) Maternal complications: increased risk of preeclampsia, PPROM, and postpartum hemorrhage.

8.3.2 Intrauterine Treatment

The indications for *in utero* fetal therapy (fulfillment of any one criterion warrants consideration) are as follows. (1) APTW ≥ 0.5 . (2) Evidence of cardiac dysfunction in the pump twin, including cardiac hypertrophy, elevated cardiac output, abnormal ductus venosus flow, pre-hydrops, or frank fetal hydrops. (3) Signs of fetal compromise: polyhy-

dramnios, acardiac twin abdominal circumference $\geq$ pump twin abdominal circumference, or abnormal Doppler flow parameters in the pump twin. (4) Clinical deterioration despite conservative management: progressive increase in APTW or worsening cardiac function.

Potential risks and complications associated with the procedure are as follows. (1) Procedure-related complications: iatrogenic injury (e.g., PPROM, maternal intra-abdominal organ injury), infection (e.g., chorioamnionitis), and hemorrhage (e.g., bleeding at placental or umbilical cord puncture sites, maternal intra-abdominal hemorrhage). (2) Fetal complications: intrauterine demise of the pump twin, preterm birth (secondary to PPROM or uterine irritability). (3) Long-term fetal complications: preterm-associated respiratory distress syndrome, intracranial hemorrhage, and neurodevelopmental delay; long-term maternal complications: postoperative abdominal pain, sequelae of infection, or retained placental tissue.

Based on the foregoing content and the systematic review and meta-analysis published by Stelson et al. [6], this section provides a systematic comparison of commonly employed intrauterine interventions for TRAP (Table 1).

9. Progress in Multidisciplinary Management and Follow-Up Studies

Multidisciplinary Management and Follow-up: The core therapeutic objective of TRAP is to ensure the survival and well-being of the pump twin. Therefore, the treatment of TRAP requires collaboration among multiple disciplines, including obstetrics, fetal medicine, neonatology, and cardiology. (1) Preoperative Management: following diagnosis, weekly monitoring of the pump fetus's cardiac function (such as echocardiographic assessment of ventricular wall thickness and ejection fraction), fetal growth development, and amniotic fluid index should be conducted. (2) Postoperative Management: After intrauterine treatment, close monitoring of the recovery status of the pump fetus's cardiac function is essential. Attention must be paid to potential complications such as postoperative anastomosis reopening and placental abruption. If severe heart failure or signs of preterm labor occur, timely termination of pregnancy is warranted. (3) Neonatal Management: surviving neonates require comprehensive physical examinations with a particular focus on assessing cardiovascular system health and neurological development. Regular follow-ups should continue until school age.

10. Correlation of Recurrent Pregnancy With TRAP

The incidence of chromosomal abnormalities in pump fetuses associated with TRAP may be up to 9%. Currently, no correlation has been found between TRAP and recurrent pregnancies. Furthermore, there is no evidence linking TRAP to ART [51].

11. Advances in Prognostic Assessment

Currently, there is no universally accepted standard for predicting adverse pregnancy outcomes in cases of TRAP. However, several indicators have been proposed for assessing the prognosis of this condition.

11.1 Weight Ratio

Research by Moore et al. [52] suggests the weight ratio between twins is a significant prognostic factor for TRAP [53]. A study conducted at the Children's Hospital of Philadelphia involving 13 cases of TRAP [54] found that edema and heart failure are unlikely to occur in the pump twin when the weight of the acardiac twin is $<40\%$ of that of the pump twin. Moore et al. [52] proposed a correlation between the prognosis of the pump twin and the size of the acardiac twin, providing a quadratic regression equation to estimate the weight of the acardiac twin: $\text{acardiac twin weight (g)} = 1.2 L^2 - 1.7 L$, where L represents the maximum length of the acardiac twin's body segment. According to their findings, if the APTW exceeds 0.7, the rates of preterm birth, polyhydramnios, and heart failure in pump twins are approximately 90%, 40%, and 30%, respectively. Conversely, when APTW falls below this threshold, these rates decrease to approximately 75%, 30%, and 10%, respectively.

11.2 The CRL of Twins and the Upper-Pole-To-Rump Length (URL) of Anencephalic Fetuses

Tang et al. [55] demonstrated that when $(\text{CRL} - \text{URL}) / \text{CRL}$ is >0.43 , or URL / CRL is <0.57 , it can effectively identify surviving pump twins.

11.3 Vascular Separation Between Twins

Studies have confirmed that vascular connections between twins may spontaneously interrupt. Notably, when the volume remains consistently smaller in the acardiac twin compared to the pump twin, this results in improved prognosis for the latter [54].

11.4 Energy Doppler Ultrasound Data

Indices such as the umbilical artery resistance index and middle cerebral artery pulsatility index from Doppler ultrasound may serve as important prognostic indicators for assessing TRAP beyond 20 weeks of gestation [56].

11.5 Hierarchical Prioritization of the Aforementioned Indicators

$\text{APTW} > \text{CRL} / \text{URL length ratio} > \text{vascular separation status} > \text{energy Doppler flow metrics}$.

11.5.1 The Core Primary Indicator is APTW

A relatively robust evidence chain supports APTW as the core primary indicator [14]. This indicator demonstrates high feasibility of acquisition, strong clinical utility, and excellent reproducibility. As the foundational core metric for

Table 1. Systematic comparison of common intrauterine treatment for TRAP.

Interventional procedure	Key operational points	Optimal gestational age	Survival rate of pump twin	Complications
Ultrasound-guided laser therapy	Percutaneous Ultrasound-Guided Laser Coagulation of Umbilical Vessels in Acardiac Twin	Weeks 13–16	Data is limited.	PPROM, hemorrhage, and infection; no fetoscopy-related complications
RFA	Transabdominal puncture; RF electrode placed at the base of the acardiac twin's umbilical cord to thermocoagulate and occlude blood flow.	Weeks 16–24	83%	PPROM (14%), placental abruption (3%), and chorioamnionitis (2%); fetal endoscopy-related complications are exceedingly rare.
Microwave ablation	Transabdominal microwave energy is applied to the umbilical vessels to induce thermal coagulation and thereby occlude blood flow.	Weeks 16–24	Data are limited; early studies are promising.	Thermal injury-associated PPRM and placental injury; insufficient long-term data
Cord ligation	Fetoscopic umbilical cord ligation for acardiac twin—complete flow occlusion; technically challenging.	Weeks 18–24	65%–88%	PPROM (28%), severe intraoperative hemorrhage (7%), ligation failure, chorioamnionitis
Laser ablation of placental anastomoses under fetoscopy	Fetoscopic localization of placental anastomotic vessels and laser coagulation to interrupt retrograde perfusion	Weeks 16–24	76%–79%	PPROM (23%), chorioamnionitis (6%), laser thermal injury, amniotic leak
HIFU	Non-invasive MR-guided HIFU ablation of umbilical vessels	Weeks 16–24	Data is limited.	Low procedural risk; risk of maternal thermal injury; insufficient long-term neurodevelopmental data
Fetal bipolar cord coagulation	Fetoscope inserted into amniotic cavity; bipolar forceps used under direct vision to coagulate and occlude the acardiac twin's umbilical cord.	Weeks 18–26	80%	PPROM (21%), chorioamnionitis (5%), intraoperative hemorrhage (4%), preterm birth

TRAP, Twin Reversed Arterial Perfusion; RFA, radiofrequency ablation; RF, radiofrequency; HIFU, high-intensity focused ultrasound; MR, magnetic resonance; PPRM, preterm premature rupture of membranes.

the prognostic assessment of TRAP, APTW should preferably be calculated during both the initial evaluation and subsequent follow-up visits. It serves as the primary basis for determining disease severity and guiding the timing of clinical intervention.

11.5.2 The Primary Auxiliary Indicator Is the Ratio of CRL

This ratio exhibits distinct advantages in the first trimester. While fetal weight estimation during early gestation is associated with substantial measurement error, CRL and URL measurements are technically simpler and yield lower inter-observer variability, thereby compensating for the limitations of weight-based ratios in this gestational window.

11.5.3 The Secondary Reference Indicator Is the Vascular Separation Status of the Twin Pair

Vascular separation is a passive observational parameter. It cannot be actively measured, lacks standardized quantitative criteria, and can only be assessed indirectly via ultrasound imaging. Consequently, it should not be used as an independent basis for clinical assessment.

11.5.4 The Supplementary Observational Indicator is Doppler-Derived Hemodynamic Velocity Data Obtained Using Power Doppler Ultrasound

The clinical application of this indicator is constrained by limited availability and insufficient evidentiary support. Therefore, following its comprehensive evaluation using core and auxiliary indicators, this parameter should only be considered for characterizing fetal circulatory function. It is not recommended for standalone use in the prediction of outcome.

The diagnosis and treatment process for TRAP is shown in Fig. 3, while clinical outcomes and prognosis of TRAP are presented in Fig. 4.

12. Discussion

This review systematically summarizes recent advances in epidemiology, pathophysiology, prenatal diagnosis, and management of TRAP—a rare complication of monochorionic twins. Its core pathophysiological mechanism underpins the entire clinical pathway: it forms the theoretical basis for diagnosis; diagnosis informs treatment decisions; and treatment represents the clinical translation of both mechanism and diagnosis—establishing a coherent “basic-to-clinical” logic chain, not a collection of isolated facts.

Key recent advances fall into two areas: (1) iterative improvements in prenatal diagnostic techniques; and (2) maturation of minimally invasive intrauterine therapies—especially radiofrequency ablation—which have substantially improved pump twin survival. However, current evidence remains limited: most studies are small-scale,

retrospective, or case-based, lacking standardized diagnostic/therapeutic criteria and long-term follow-up data—leading to heavy reliance on clinical experience. In summary, existing research provides valuable evidence for TRAP management, yet overall evidence quality is low, and many critical questions remain unanswered. Key unresolved issues and future research directions are outlined below.

12.1 Remaining Challenges

Despite some research progress on TRAP, numerous issues remain unresolved [57]. (1) In terms of etiology, the specific genetic and epigenetic regulatory mechanisms have not been fully elucidated, precise diagnostic methods are still needed, and causative factors have yet to be identified. (2) There is still controversy regarding the selection of therapeutic options for early pregnancy or extremely severe cases, for example, where the pump twin develops high-output heart failure. This is compounded by a lack of large-sample, randomized controlled studies comparing the long-term efficacy of different intrauterine treatments. (3) Regarding prognosis, the lack of standardized risk stratification criteria makes it difficult to accurately predict individual outcomes.

Attention must also be directed towards the following areas. (1) The lack of effective screening and intervention methods for very early-stage TRAP. Currently, the balance between treatment risk and benefit remains unclear. (2) A preventive pharmacological strategy specifically targeting TRAP has yet to be developed. Future therapeutic approaches may focus on the vascular endothelial growth factor (VEGF) pathway, the Notch signaling pathway, placenta-specific angiogenic regulators, anti-angiogenic small molecules, and placenta-targeted nanocarrier delivery systems. Although these vascular targets and delivery strategies have been mainly investigated for TTTS, related insights may provide conceptual references for exploring preventive pharmacological strategies for TRAP, rather than being directly applicable to TRAP. Ⓞ The VEGF pathway serves as a central driver of placental angiogenesis. Its aberrant activation is a key pathogenic trigger underlying excessive formation and structural disorganization of placental vascular anastomoses in TTTS. Placenta-selective VEGF pathway modulators hold significant translational potential, as they minimize off-target effects on maternal systemic circulation and fetal organogenesis, thereby reducing drug-associated toxicity. Ⓞ The Notch signaling pathway is a phylogenetically conserved intercellular communication mechanism that orchestrates endothelial cell fate specification, vascular branching morphogenesis, and vascular homeostasis in the placenta through ligand–receptor interactions (e.g., DLL1, DLL4, Jag1 with Notch1–4). Dysregulated Notch signaling is closely associated with the pathogenesis of TTTS. Moreover, Notch components exhibit placenta-restricted

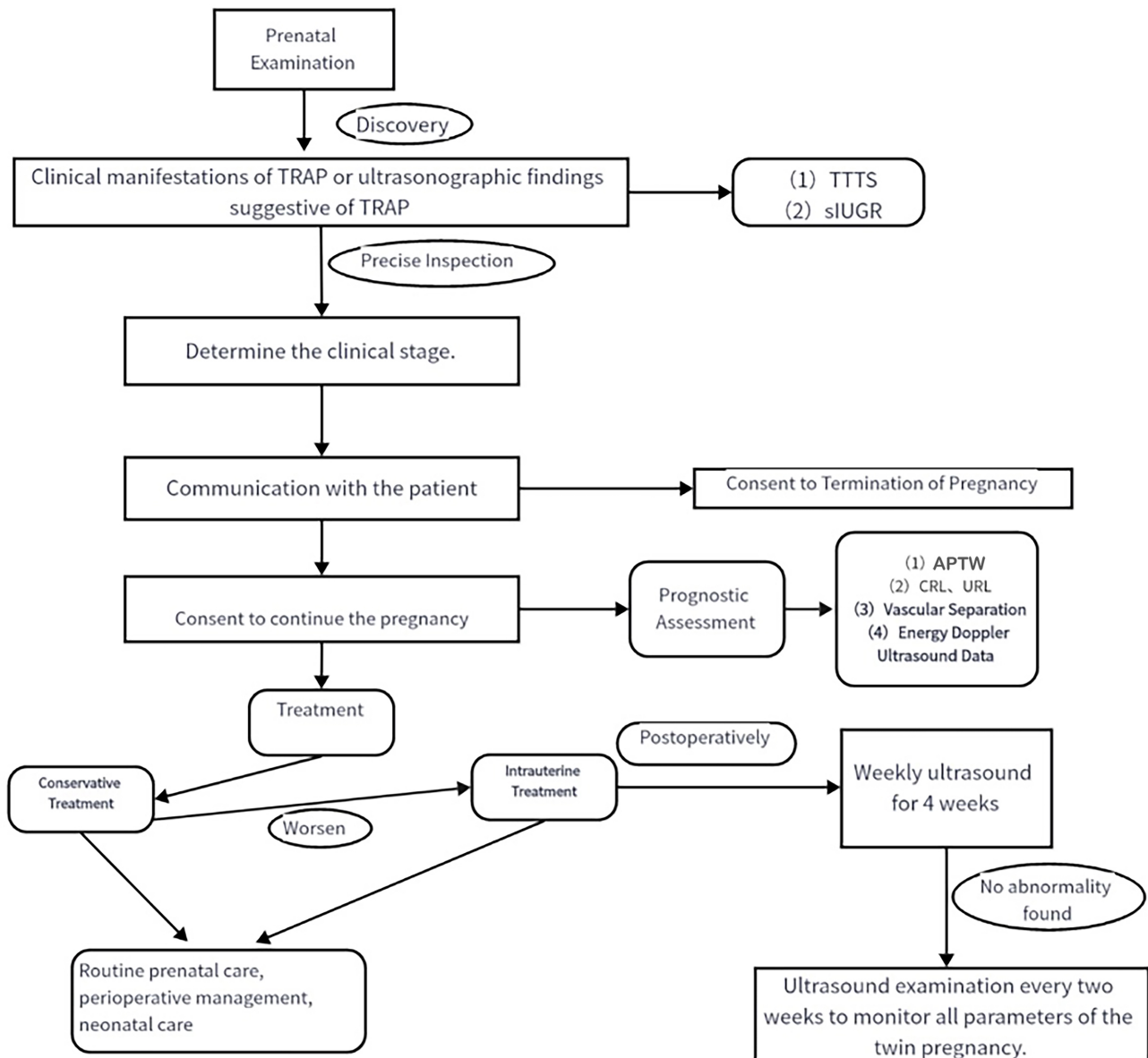


Fig. 3. The diagnosis and treatment process of TRAP. TTTS, twin-to-twin transfusion syndrome; sIUGR, selective intrauterine growth restriction; APTW, acardiac/pump twin weight ratio; CRL, crown-rump length; URL, upper-pole-rump length.

expression patterns, particularly in trophoblasts. Therefore, targeted modulation offers enhanced tissue specificity, mitigating adverse effects on maternal non-placental tissues and improving both safety and clinical translatability. ③ Beyond VEGF and Notch, dysregulated expression of multiple placenta-specific angiogenic regulators also contributes to TTTS pathophysiology. These factors represent promising complementary therapeutic targets for the development of multi-target, synergistic intervention strategies, thus expanding the repertoire of viable preventive approaches for TTTS. ④ Compared with large-molecule biologics (e.g., monoclonal antibodies), small-molecule anti-angiogenic agents offer distinct pharmacokinetic advantages, including low molecular weight, high tissue permeability, and oral bioavailability. This makes them partic-

ularly suitable for early, long-term prophylaxis in TTTS (i.e., initiation in the first trimester and sustained administration until placental vascular maturation). Such properties can increase patient adherence and confer higher clinical translatability. Research efforts should prioritize the development of placenta-selective, small-molecule modulators to circumvent systemic anti-angiogenic toxicities, such as hypertension and proteinuria. ⑤ Nanoparticle-based delivery systems are characterized by tunable small particle size, favorable biocompatibility, and high target specificity. They represent a highly promising strategy to overcome the “off-target” distribution of conventional therapeutics in TTTS prevention. By enabling selective drug accumulation within placental tissue, these systems can improve therapeutic efficacy while minimizing systemic exposure and as-

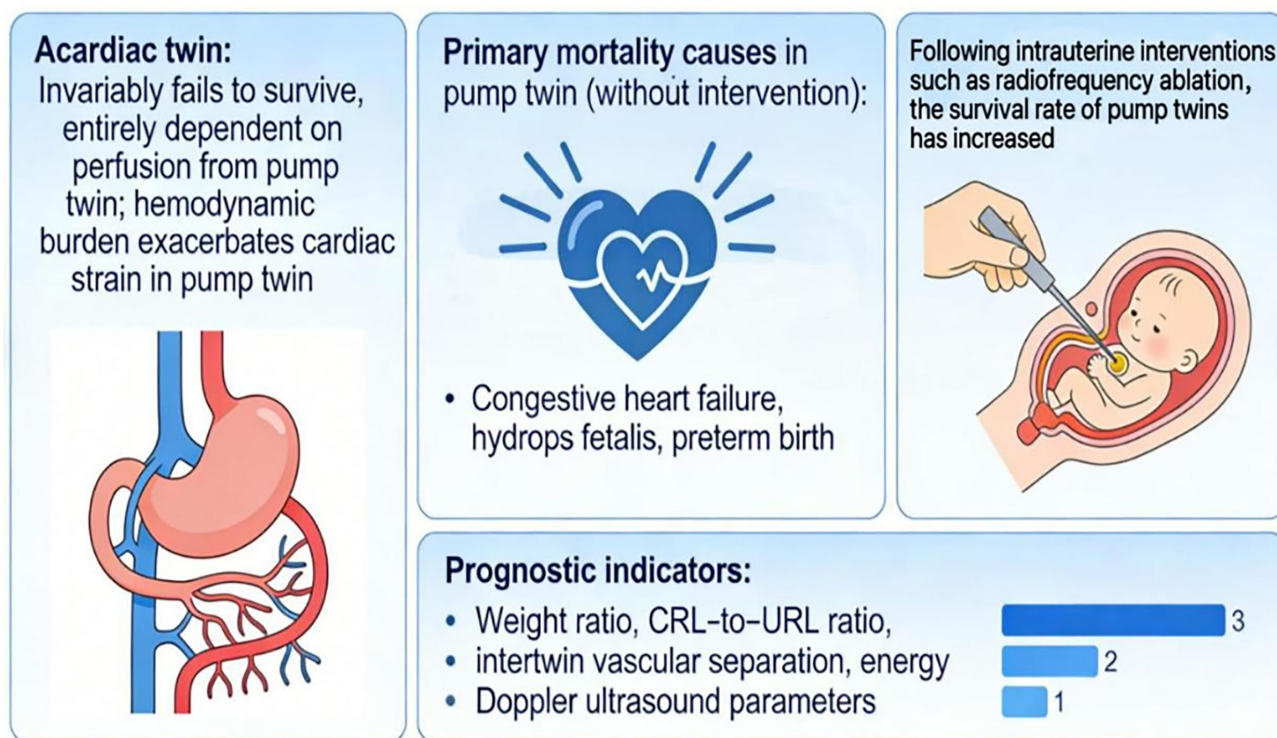


Fig. 4. Clinical outcomes of TRAP.

sociated adverse effects. Consequently, placenta-targeted nanocarriers constitute one of the most clinically translatable and precision-oriented research directions currently under investigation. (3) Research into the correlation between subsequent pregnancies or ARTs and the occurrence of TRAP has yet to provide definitive conclusions. (4) Although current mainstream opinion suggests that blocking of abnormal perfusion may be an appropriate strategy, questions persist regarding whether to retain the acardiac twin in rare cases where it exhibits no significant structural abnormalities while maintaining normal cardiac function.

12.2 Future Prospects

Future research directions should focus on the following areas. (1) Investigating molecular mechanisms through single-cell sequencing and analysis of epigenetic regulatory networks to reveal precise etiologies associated with TRAP, leading to the development of targeted preventive strategies. (2) Innovating diagnostic technologies by optimizing non-invasive screening methods during early pregnancy to increase the rate of early diagnosis. (3) Improving therapeutic techniques by exploring minimally invasive and precision-based intrauterine interventions aimed at reducing complication risks. (4) Promoting multi-center collaborations to establish a global database for TRAP cases and facilitate large-sample prospective studies, while formulating standardized clinical guidelines and prognostic assessment systems. (5) Developing relevant pathways with potential maternal administration aimed at improving placental

vascular anomalies as part of primary disease prevention efforts. (6) Planning global research collaborations that compare long-term efficacy across various intrauterine treatment modalities, while also establishing the first globally unified clinical practice guidelines. (7) Exploring placenta-derived mesenchymal stem cell transplantation as a novel therapeutic approach aimed at enhancing placental vascular remodeling.

Author Contributions

RS conceived and designed the review and drafted the original manuscript; XY participated in the conception of the review outline and literature screening, and critically revised the manuscript for important intellectual content. XH performed literature retrieval and screened eligible references, and critically revised the manuscript for important intellectual content. YT extracted and synthesized evidence from included studies, and critically revised the manuscript for important intellectual content. YW assisted in review framework design and quality assessment of included literature, and critically revised the manuscript for important intellectual content. NS conducted literature sorting and evidence summarization, and critically revised the manuscript for important intellectual content. SX participated in literature screening and assisted in constructing the discussion section, and critically revised the manuscript for important intellectual content. WH managed references and collated relevant clinical evidence, and critically revised the manuscript for important intellectual content. LW con-

ceived the overall review framework and secured funding, critically revised the full-text manuscript and supervised the whole project. All authors contributed to the editing of the manuscript. All authors read and approved the final version. All authors were fully involved in the work and agree to take responsibility for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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