NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ

QUALITY IN SPORT

eISSN 2450-3118 · Open Access · Peer-reviewed

Vol. 55 (2026) · Article 70991 · Published 16 May 2026

apcz.umk.pl/QS · Nicolaus Copernicus University in Toruń

Cite as: Mikusek W, Patelski M, Czapla M, Surma M, Molenda J, Kuczma M, Kotlarz W, Kamińska M, Klimczak A, Pietrzak B. Twin-to-Twin Transfusion Syndrome: A Comprehensive Review of Fetal Impact and Management Strategies. Quality in Sport. 2026;55:70991. https://doi.org/10.12775/QS.2026.55.70991

ARTICLE TIMELINE

Received: 17.04.2026 **Revised:** 05.05.2026

Accepted: 05.05.2026 **Published:** 16.05.2026

INDEXING & EVALUATION

MEiN points: 20 **Unique ID:** 201398

Disciplines: Medical Sciences; Health Sciences

The journal has been awarded 20 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32553). Unique Journal Identifier: 201398. Scientific disciplines: Medical Sciences; Health Sciences.

Punkty Ministerialne z 2019 – aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Nauki medyczne; Nauki o zdrowiu.

COMPREHENSIVE REVIEW

Twin-to-Twin Transfusion Syndrome: A Comprehensive Review of Fetal Impact and Management Strategies

a comprehensive review

HIGHLIGHTS

- TTTS affects 10–15% of monochorionic diamniotic twin pregnancies, caused by unbalanced AV anastomoses.
- Quintero staging (I–V) guides diagnosis and therapy based on ultrasound and Doppler findings.
- Fetoscopic laser photocoagulation (FLP) is the gold-standard treatment, significantly improving survival.

- The Solomon technique reduces residual anastomoses and complications such as TAPS and recurrent TTTS.
- Long-term neurodevelopmental and cardiac follow-up remains essential despite therapeutic advances.

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ABSTRACT

INTRODUCTION: Twin-to-Twin Transfusion Syndrome (TTTS) affects 10–15% of monochorionic diamniotic twin pregnancies and arises from unbalanced blood flow through placental vascular anastomoses. The presence of deep arteriovenous connections leads to chronic transfusion from one twin to the other, resulting in progressive hemodynamic imbalance. Without timely intervention, TTTS poses a high risk of fetal morbidity and mortality.

AIM OF THE STUDY: The aim of this review was to present an up-to-date overview of current knowledge, clinical approaches, and fetal implications related to Twin-to-Twin Transfusion Syndrome.

MATERIALS AND METHODS: A structured literature search was performed in PubMed and Google Scholar to identify studies on Twin-to-Twin Transfusion Syndrome, focusing on management and fetal outcomes. The search included relevant keywords and Medical Subject Headings (MeSH). Additional studies were identified through manual screening of reference lists.

CONCLUSION: Twin-to-Twin Transfusion Syndrome (TTTS) is a severe complication of monochorionic twin pregnancies that requires early diagnosis and active management. Fetoscopic laser photocoagulation (FLP) remains the gold standard treatment, significantly improving survival. Despite therapeutic advances, affected fetuses still face risks of neurological and cardiac complications, highlighting the importance of long-term follow-up.

KEYWORDS Twin-to-Twin Transfusion Syndrome (TTTS); fetofetal transfusion; monochorionic twins; fetoscopic laser photocoagulation (FLP); Quintero staging

GRAPHICAL ABSTRACT

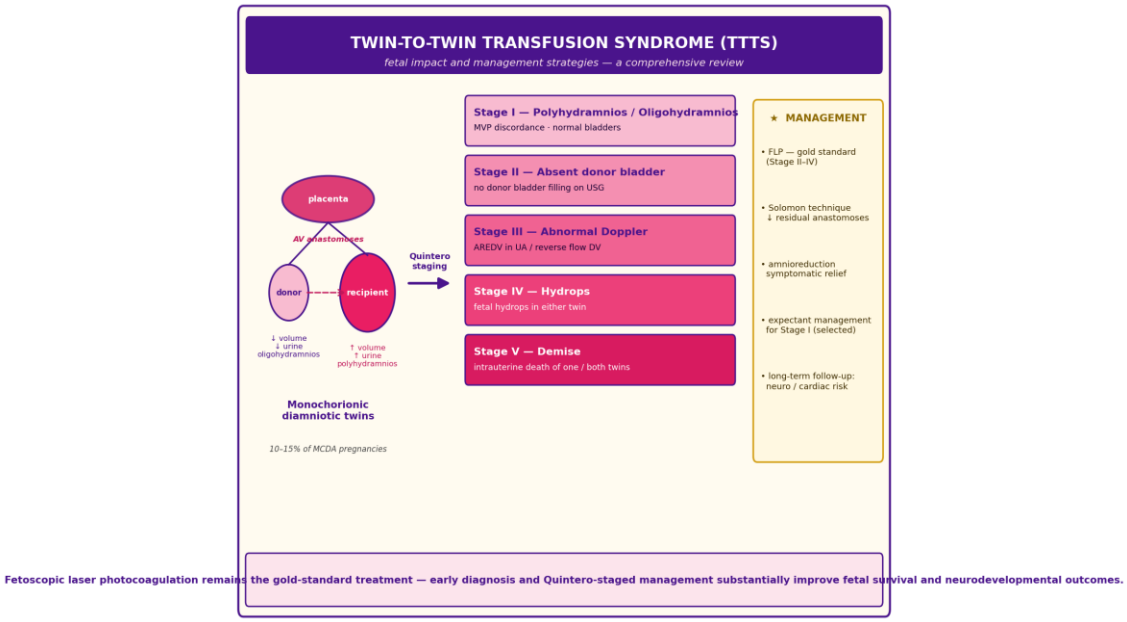

Figure 1. *Graphical overview of Twin-to-Twin Transfusion Syndrome — pathophysiology in monochorionic diamniotic twins via arteriovenous placental anastomoses (donor/recipient imbalance), the Quintero staging system (I–V), and management strategies (fetoscopic laser photocoagulation, Solomon technique, amnioreduction, expectant management).*

PLAIN LANGUAGE SUMMARY

Twin-to-Twin Transfusion Syndrome (TTTS) is a serious complication that can occur in identical-twin pregnancies sharing one placenta. Blood vessels in the placenta connect the two babies in an unbalanced way, so one twin (the donor) gradually passes too much blood to the other (the recipient). The donor twin produces less urine and has too little amniotic fluid, while the recipient twin produces too much. Without treatment, both babies are at high risk of severe complications or death. Doctors use a five-stage Quintero classification, based on ultrasound, to decide on treatment. The most effective therapy is fetoscopic laser surgery (FLP), in which a thin camera is inserted into the womb to seal the abnormal blood vessels with a laser. This greatly improves the chances of survival for both babies. Even after successful treatment,

affected children may need long-term follow-up for heart or neurological problems, which is why early diagnosis and specialised care are essential.

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1. INTRODUCTION

Twin-to-Twin Transfusion Syndrome (TTTS) is a serious complication that affects approximately 10–15% of monochorionic diamniotic (MCDA) twin pregnancies. It arises from unbalanced blood flow between twins through placental vascular anastomoses, resulting in progressive hemodynamic discordance and posing significant risks for both fetuses. In recent years, advances in prenatal imaging and the development of fetoscopic laser photocoagulation have significantly improved the prognosis in affected pregnancies. However, TTTS continues to be a major contributor to perinatal morbidity and mortality in twin gestations, particularly in cases with late diagnosis or limited access to specialized treatment [1].

Given its pathophysiological complexity, TTTS demands a multidisciplinary approach encompassing accurate early diagnosis, timely therapeutic intervention, and postnatal surveillance. Determining chorionicity in the first trimester is essential, as the condition occurs exclusively in MCDA pregnancies. Likewise, frequent sonographic monitoring during the second trimester enables early recognition of disease onset and appropriate stratification using the Quintero staging system [2].

Despite therapeutic improvements, fetal complications such as neurological impairment, cardiac anomalies, and growth restrictions remain significant concerns. Therefore, a thorough understanding of the natural course, diagnostic strategies, and treatment outcomes is essential for optimizing care in pregnancies complicated by TTTS [2,3].

2. AIM OF THE STUDY

The aim of this study is to provide a comprehensive overview of Twin-to-Twin Transfusion Syndrome (TTTS), including its etiology, diagnostic methods, therapeutic strategies, and fetal outcomes. Special attention is given to evidence-based management approaches and the implications for long-term follow-up of affected twins.

3. MATERIALS AND METHODS

A structured literature search was conducted to identify relevant studies addressing Twin-to-Twin Transfusion Syndrome (TTTS), its impact on fetal outcomes, and management strategies. The electronic databases PubMed and Google Scholar were searched to ensure comprehensive coverage.

In PubMed, the search strategy incorporated both Medical Subject Headings (MeSH) and text words to maximize sensitivity. The following search string was used: “fetofetal transfusion”[MeSH Terms] OR “twin to twin transfusion syndrome”[Text Word].

In Google Scholar, a combination of relevant keywords and word variants was applied, including terms such as “twin-to-twin transfusion syndrome”, “TTTS”, “fetofetal transfusion”, “fetal outcomes”, “laser therapy”, “laser surgery”, “laser photocoagulation”, “Quintero staging”, and “prenatal management”. Boolean operators (AND, OR) were used to refine the results.

Inclusion criteria were peer-reviewed articles, in English, focusing on diagnosis, treatment options, and perinatal outcomes in TTTS. Original research articles, clinical trials, and literature reviews were included. Duplicates, conference abstracts, non-English publications, and studies not directly related to TTTS were excluded after initial title and abstract screening. Additionally, references of included studies were manually reviewed to identify further relevant publications.

4. STATE OF KNOWLEDGE

4.1. Chorionicity and Embryological Basis

The configuration of twin pregnancies—whether they are dichorionic or monochorionic, diamniotic or monoamniotic—is determined by the timing of zygotic splitting after fertilization.

Table 1. *Twin type and placental configuration based on timing of zygotic splitting [1].*

Day of split after fertilization	Resulting twin type and placental configuration
Day 1–3	Early splitting, before chorion formation, leads to dichorionic diamniotic (DCDA) twins with two placentas and two amniotic sacs
Day 4–8	Splitting occurs after the chorion but before the amnion forms, resulting in monochorionic diamniotic (MCDA) twins, which share a placenta but have separate amniotic sacs
Day 9–13	Later division leads to monochorionic monoamniotic (MCMA) twins, sharing both the placenta and the amniotic sac
After day 13	Incomplete splitting can result in conjoined twins

This process of chorionic and amniotic differentiation is clinically significant, as TTTS occurs exclusively in MCDA pregnancies, where the shared placenta enables the formation of vascular anastomoses between the twins [1].

4.2. Etiology and Pathophysiology

Twin-to-Twin Transfusion Syndrome is a condition specific to MCDA pregnancies. These pregnancies are characterized by the presence of a shared placenta and separate amniotic sacs. The hallmark of TTTS is an unbalanced blood flow through placental vascular anastomoses. The principal etiology lies in an increased number of deep arteriovenous (AV) anastomoses located within the cotyledon portion of the placenta. These allow unidirectional blood flow, facilitating chronic transfusion from the donor to the recipient twin. In contrast, superficial arterioarterial (AA) and venovenous (VV) anastomoses are bidirectional and considered protective [3,4,5].

A relative deficiency of AA anastomoses is a typical finding in TTTS pregnancies, contributing to the progressive hemodynamic imbalance. A rare, acute peripartum variant of TTTS has also been described. It is typically triggered by rapid transfusion through large anastomoses near delivery. In the majority of monochorionic twin pairs, however, the net exchange in their shared circulation remains balanced, and TTTS does not develop [1,2].

This vascular imbalance leads to distinct physiological consequences in each fetus. The donor experiences hypovolemia, reduced renal perfusion, renin-angiotensin-aldosterone system (RAAS) activation, oliguria, and oligohydramnios. The recipient develops hypervolemia, polyuria, polyhydramnios, and is prone to

cardiovascular strain, which can result in myocardial hypertrophy, valvular regurgitation, and even pulmonary outflow obstruction [5,6,7].

4.3. Epidemiology

TTTS develops in approximately 10–15% of MCDA pregnancies. While its incidence is low relative to all twin gestations, TTTS remains a leading cause of fetal morbidity and mortality in monochorionic twins [8].

Clinically, TTTS most often presents during the second trimester, emphasizing the importance of early identification of chorionicity via first-trimester ultrasound. If left untreated, the condition can progress rapidly, leading to fetal demise, neurological injury, or cardiac failure, particularly in the recipient twin [1].

4.4. Diagnosis of TTTS

Chorionicity Determination

Accurate determination of chorionicity is the cornerstone of early twin pregnancy assessment, as the risk of complications such as TTTS is restricted to monochorionic diamniotic pregnancies. Therefore, all twin pregnancies should undergo chorionicity assessment in the first trimester, ideally between 11 and 14 weeks of gestation [9].

Chorionicity can be reliably assessed via transabdominal ultrasound, focusing on specific criteria at the intertwin membrane insertion site. The lambda (λ) sign or twin peak sign indicates a triangular projection of chorion between the layers of the intertwin membrane, indicating dichorionic diamniotic pregnancy. The T-sign describes a thin membrane meeting the placenta at a perpendicular angle without chorionic tissue in between, characteristic of monochorionic diamniotic pregnancies [10]. Other supporting features include the number of placentas, the thickness of the intertwin membrane, and fetal sex discordance, which rules out monochorionicity.

Early and accurate classification has been shown to significantly improve pregnancy outcomes by enabling appropriate surveillance schedules and timely intervention in monochorionic pregnancies [11,12,13].

Screening and Timing of Surveillance

In monochorionic twin pregnancies, regular surveillance is essential for the early identification of complications unique to shared placentation, particularly Twin-to-Twin Transfusion Syndrome. Screening for TTTS should commence at 16 weeks of gestation. Ultrasound examinations should then be repeated at 2-week intervals until delivery or until TTTS is diagnosed or ruled out. Fortnightly monitoring has been shown to detect over 90% of TTTS cases before complications such as fetal demise or membrane rupture occur [9,14,15].

Routine sonographic monitoring includes assessment of amniotic fluid volume for each fetus, visualization of fetal bladders, and Doppler evaluation of umbilical and venous flow. While attempts have been made to identify first-trimester predictors of TTTS development, no reliable early biomarkers have yet been established. Therefore, serial second-trimester assessments remain the cornerstone of early detection [9,16].

Diagnostic Criteria for TTTS

TTTS is diagnosed when there is a significant imbalance in amniotic fluid volume between the two fetuses in a monochorionic diamniotic pregnancy. This is defined by a deepest vertical pocket (DVP) of ≤2 cm in the donor twin (oligohydramnios) and ≥8 cm in the recipient twin (polyhydramnios). In Europe, this threshold is ≥8 cm before 20 weeks and ≥10 cm after 20 weeks. Some clinicians propose using a lower cutoff of ≥6 cm for polyhydramnios before 16 weeks, though this is not universally accepted. Amniotic fluid discordance alone, when not meeting these specific DVP thresholds, does not constitute a TTTS diagnosis but still warrants

increased surveillance due to the risk of progression. Importantly, size discordance between the twins, although frequently present, is not a diagnostic requirement [9,16,17].

4.5. Staging: The Quintero Classification

TTTS severity is traditionally assessed using the Quintero staging system, which remains the most widely adopted framework despite certain limitations. The five stages are defined as follows [16]:

Table 2. *The Quintero Staging System for TTTS [2].*

Stage	Ultrasound Findings	Description
I	Polyhydramnios in recipient + oligohydramnios in donor	DVP ≥8 cm in recipient, ≤2 cm in donor; donor bladder still visible on ultrasound
II	Donor bladder not visible	Donor twin's bladder no longer visible on ultrasound
III	Abnormal Doppler waveforms	Absent or reversed end-diastolic flow in the umbilical artery (AREDV), reversed flow in the ductus venosus, or pulsatile umbilical venous flow in either twin
IV	Fetal hydrops	Presence of hydrops fetalis in one or both twins
V	Fetal demise	Intrauterine demise of one or both twins

Although this system allows for standardized classification, it has notable limitations. For example, Stage I is not necessarily associated with better outcomes, as recipient twins may already show early signs of cardiac dysfunction. Moreover, disease progression does not always follow a linear sequence, and survival rates do not consistently correlate with Quintero stage. Despite these criticisms, Quintero staging remains the basis for both clinical communication and decision-making, especially regarding eligibility for fetoscopic laser photocoagulation therapy. Supplementary parameters, such as fetal echocardiography, are increasingly used to provide additional prognostic insight, particularly in early stages of the disease [9,18,19].

4.6. Treatment of TTTS

Fetoscopic Laser Ablation

Fetoscopic laser photocoagulation (FLP) remains the gold standard for treating Twin-to-Twin Transfusion Syndrome (TTTS), particularly in pregnancies diagnosed at Quintero Stages II–IV. This minimally invasive procedure targets and coagulates placental vascular anastomoses, effectively interrupting the unbalanced blood flow between twins. Evidence from multiple studies supports its superiority over other modalities, showing improved survival and neurological outcomes, especially when performed before 26 weeks of gestation. Laser therapy is indicated even in early (<16 weeks) or late (>26 weeks) gestations, although

outcomes vary. Procedures performed before 16 weeks are associated with an increased risk of PPROM. In contrast, interventions after 26 weeks may be complicated by involvement of larger placental vascular anastomoses, which can increase the risk of bleeding and contribute to disturbances in hemostasis. The Solomon technique, which involves coagulating the entire vascular equator, has been shown to reduce the risk of recurrence, compared to the selective technique. However, it may be associated with a slightly increased risk of placental abruption and earlier delivery [9,20,21,22,32].

Management of Quintero Stage I TTTS

Management of Stage I TTTS remains controversial. While FLP is the treatment of choice for advanced stages, conservative management is often considered for asymptomatic patients with Stage I disease and a cervical length >15 mm. A recent meta-analysis comparing expectant management, amnioreduction, and laser therapy in Stage I TTTS found similar survival rates across strategies. However, approximately 60% of conservatively managed cases ultimately progressed to higher stages, necessitating rescue intervention [23,24,25].

Alternative Treatments

When FLP is not available or is contraindicated, serial amnioreduction may be used to relieve polyhydramnios and delay preterm labor. This approach is more commonly employed after 26 weeks' gestation. However, studies have consistently shown that it is associated with higher recurrence rates, lower neurological outcomes, and increased perinatal mortality compared to laser therapy. Another therapeutic option is selective reduction, typically reserved for severe cases with a poor prognosis for one twin. Techniques include bipolar cord coagulation, radiofrequency ablation (RFA), or intrafetal laser, and aim to protect the healthier twin from the adverse effects of disease progression [9,26].

Post-treatment Follow-up and Delivery

Postoperative monitoring following FLP should include weekly ultrasound for the first two weeks to assess amniotic fluid normalization and fetal well-being, then biweekly thereafter. Surveillance should focus on amniotic fluid volumes, fetal biometry, and Doppler assessments of the umbilical artery (UA), ductus venosus (DV), and middle cerebral artery (MCA).

Although no firm consensus exists on delivery timing, the common practice is delivery at 34 weeks of gestation, unless complications necessitate earlier intervention. In cases with complete resolution of TTTS, delivery may be postponed until 37 weeks [1,9,27].

4.7. Fetal Complications and Long-Term Outcomes

Despite advances in the diagnosis and treatment of Twin-to-Twin Transfusion Syndrome, monochorionic twin pregnancies remain at increased risk of a variety of perinatal and long-term complications. These complications can affect either twin differently, reflecting the distinct hemodynamic burden carried by donor and recipient fetuses [28].

Neurological Outcomes

Even following successful fetoscopic laser photocoagulation, prenatal brain abnormalities can still occur, although their incidence appears relatively low. The most commonly reported lesions are ischemic in nature, followed by destructive and hemorrhagic injuries. Both donor and recipient twins may be affected [29].

Long-term neurodevelopmental sequelae remain a concern, particularly in cases managed conservatively or those complicated by intrauterine fetal demise (IUFD) of one twin. The incidence of cerebral palsy appears notably higher in such scenarios. Donor twins, particularly when born after IUFD of their cotwin, are especially vulnerable to neurological injury. Longitudinal follow-up has shown that a considerable proportion of surviving children experience developmental delay [30].

Cardiac Complications

Cardiac abnormalities, particularly right ventricular outflow tract anomalies (RVOTAs), such as pulmonary stenosis and atresia, have been described in TTTS pregnancies. These anomalies may persist postnatally even after fetoscopic laser surgery. A majority of affected infants present with congenital heart disease at follow-up, with a significant proportion requiring postnatal intervention. These findings underline the need for targeted postnatal cardiological assessment, particularly in cases where prenatal signs of RVOTAs were observed [31].

Need for Long-Term Surveillance

Children born from pregnancies complicated by Twin-to-Twin Transfusion Syndrome — whether treated or not with fetoscopic laser surgery — require long-term clinical and developmental follow-up. Even after successful intervention, risks such as neurodevelopmental delay, cerebral injury, and cardiac anomalies persist.

Outcomes tend to be more favorable following laser treatment; however, data on twins managed without this intervention remain limited. Retrospective analyses suggest a higher incidence of neonatal complications in conservatively managed cases, though conclusive evidence is lacking due to small study sizes and incomplete data. Further large-scale research is needed to clarify risk factors and optimize follow-up in these pregnancies [28].

5. CONCLUSIONS

Twin-to-Twin Transfusion Syndrome remains one of the most significant complications in monochorionic twin pregnancies, requiring early and accurate diagnosis, regular surveillance, and multidisciplinary management. Early determination of chorionicity and systematic ultrasound monitoring are essential for the timely detection and treatment of TTTS, which can develop rapidly and lead to severe fetal outcomes if left unrecognized.

Fetoscopic laser photocoagulation is considered the gold standard treatment for TTTS, offering the most favorable outcomes in terms of survival and neurological development. Its use has significantly improved perinatal prognosis and reduced the need for alternative, less effective interventions.

Despite substantial progress in diagnostic and therapeutic strategies, fetuses affected by TTTS remain at increased risk for complications, including neurological impairment and cardiac anomalies. These findings underscore the need for long-term follow-up of affected children and continued research into optimizing management and improving neurodevelopmental outcomes.

6. DISCLOSURE

6.1. Author Contributions

Conceptualization: Wiktoria Mikusek, Barbara Pietrzak. Methodology: Mikołaj Patelski. Software: Mikołaj Patelski. Formal analysis: Barbara Pietrzak. Investigation: Marta Kamińska. Resources: Wiktoria Kotlarz, Adrianna Klimczak. Writing – rough preparation: Maciej Czapla, Mateusz Surma. Writing – review and editing: Jakub Molenda, Matylda Kuczma. Visualization: Wiktoria Kotlarz, Wiktoria Mikusek. Supervision: Wiktoria Mikusek. Project administration: Marta Kamińska. All authors have read and agreed with the published version of the manuscript.

6.2. Funding Statement

Study did not receive special funding.

6.3. Institutional Review Board Statement

Not applicable.

6.4. Informed Consent Statement

Not applicable.

6.5. Conflict of Interest Statement

The authors of the paper report no conflicts of interest.

6.6. Data Availability Statement

Not applicable.

6.7. Acknowledgements

Not applicable.

6.8. Declaration of Generative AI Use

In preparing this work, the authors used ChatGPT (chatGPT.com) as a tool for translation support in preparing this work. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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