Twin-to-twin transfusion syndrome: current understanding of pathophysiology, in-utero therapy and impact for future development

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SUMMARY

Whereas monochorionic twins account for only 30% of twin gestations, they contribute to a disproportionate extent to the overall twin perinatal morbidity and mortality. Twin-to-twin transfusion syndrome can occur at any point in a monochorionic gestation but is associated with significant increases in both morbidity and mortality when it develops before 26 weeks of gestation. It is still not possible to predict accurately those pregnancies that will be affected. This has resulted in the practice of routine ultrasound surveillance beginning at the end of the first trimester. Our understanding of the physiology still has many gaps but there is an increased recognition of the heterogeneity that exists especially in the early stages of the disease. The role of the cardiovascular response of the recipient twin offers the potential for further refining the application of our current treatment modalities and may offer insight into future therapies. The optimal therapy at this point in time resides clearly with selective laser photocoagulation, and further refinements of techniques and patient selection may continue to improve outcomes. Finally, the in-utero responses generated by the fetuses to the physiologic stress of twin-to-twin transfusion may influence their response or ability to respond to cardiovascular stress in later life. If there is in-utero programming, then the detection and timely treatment of conditions such as twin-to-twin transfusion syndrome may have lifelong implications for both members of the twin pair.

1. Introduction

Monozygotic (MZ) twin pregnancies account for about 30% of spontaneously conceived twins. It is estimated that the occurrence of MZ twins is 0.4–0.45% of non-stimulated in-vivo conceptions.1 The incidence of monochorionic twins is rising, owing to the increase in the use of assisted reproductive technology (ART) to achieve pregnancy. The use of ART has been associated with a 2–12-fold increase in the conception of MZ twins.2 This is important because of the increased perinatal risk in twin gestations in general but in MZ twins in particular.

In all, 25–30% of MZ twins are dichorionic, diamniotic (DCDA) meaning that the embryo splits before embryonic cell differentiation. The perinatal outcome of dizygotic (DZ) twins and dichorionic MZ twins does not differ: 70–75% are monochorionic diamniotic (MCDA) where the inner cell mass divides during the preimplantation blastocyst stage. If the division takes place in the postimplantation blastocyst phase then monochorionic monoamniotic (MCMA) twins occur. Only 1–2% of MZ twins are MCMA. It is the monochorionic twins that are susceptible to additional complications because of their unique placental architecture. Both fetuses share the placental mass and virtually all monochorionic twin pregnancies have vascular anastomoses that allow the flow of blood between the fetuses. Normally this flow is balanced with equal amounts exchanged between the two fetuses. In about 15% of cases, the flow becomes unbalanced and this creates the environment for the development of twin-to-twin transfusion syndrome (TTTS). Left untreated, the perinatal mortality rate is about 90%.3

2. Pathophysiology

TTTS is not a homogeneous clinical entity and encompasses a spectrum of severities. It can develop at different gestational ages and with different degrees of clinical findings. There can be a dynamic nature to the findings from one evaluation to the next. Some cases demonstrate rapid progression whereas others follow a more indolent course. It is difficult to completely understand the reasons for the degree of clinical variations that are observed and at present it is not possible to predict whether a patient will display a stable type of TTTS or show rapid clinical progression.
Commonly MC placetas have anastomoses between pairs of arteries (AA) from the different circulations and less commonly between pairs of veins (VV). These AA and VV anastomoses lie on the surface of the placenta and mediate bidirectional flow with the net direction and volume of flow varying according to the pressure dynamics between the circulations of the two fetuses. The unbalanced transfusion of blood is mediated at least in part by arteriovenous (AV) anastomoses within the placenta. The number and size vary within each placenta but each only allows for unidirectional flow. The presence of AV anastomoses without a compensating AA anastomosis is associated with a higher risk for the development of TTTS. This underlying angio-architecture is likely further influenced by the diameter of the vessels involved and the intrinsic placental resistance.

If the shift of blood flow becomes significant, the donor twin becomes hypovolemic and polyuric while the recipient twin becomes hypervolemic and polyuric. In the donor twin, the renal system, in response to the decreased circulating volume, activates the renin–angiotensin system (RAS). The effect is to increase tubular reabsorption and the production of angiotensin II, mediating vasoconstriction to maintain circulating volume. This produces hypertension within the donor. This may also have the paradoxical effect of decreasing renal and placental perfusion, further worsening oliguria and resulting in growth restriction. The observation of decreased or absent diastolic flow in the umbilical artery of the donor would implicate the effect of these endocrine products on the vascular tone of the placental bed. In the recipient twin, a variety of mediators may be involved in response to increased blood volume. The increased atrial pressure mediates an increase in cardiac atrial natriuretic peptide synthesis. This increases glomerular filtration and resulting in growth restriction. The observation of AV anastomoses without a compensating AA anastomosis is associated with a higher risk for the development of TTTS. This underlying angio-architecture is likely further influenced by the diameter of the vessels involved and the intrinsic placental resistance.

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Thus the imbalance of blood volume brought about by the presence of vascular anastomoses initiates a cascade of events in both fetuses that would be somewhat adaptive were they not confined to an intrauterine environment but instead lead to significant morbidity and mortality that is associated with untreated TTTS.

### 3. Clinical diagnosis

There is a spectrum of sonographic features that may suggest the diagnosis of TTTS. There must be evidence of monochorionicity that includes the presence of a single placenta, a thin inter-twin membrane usually measuring a thickness of <2 mm, and the absence of a twin peak sign. In any twin gestation, the establishment of chorionicity is paramount at the time of the earliest ultrasound evaluation. TTTS is defined sonographically by discrepancy in the amount of amniotic fluid. There must be polyhydramnios with a deepest vertical pocket of >8 cm in the sac of the recipient twin, and oligohydramnios with a deepest vertical pocket of <2 cm in the sac of the donor twin. In some European centers the gestational age is taken into consideration with polyhydramnios consisting of a deepest vertical pocket of >8 cm before 20 weeks of gestation and >10 cm after 20 weeks. Other sonographic features include a discordance in sizes between the co-twins of >20%, discordant fetal gender, Doppler changes within the fetal vasculature, frank hydrops or demise of one or both fetuses. Current clinical staging follows that proposed by Quintero (Table 1). This staging system has been a very useful construct to allow for comparison of treatment results and for choosing between various management strategies as it incorporates the severity of the underlying disease. It does, however, create the impression that the natural history of TTTS follows an orderly progression over time. Clinical experience has shown that this is not the case. The natural history of TTTS is variable and unpredictable. This staging system also does not incorporate elements describing the fundamental cardiovascular perturbations that are central to understanding the disease and that are present in subtle form even at the earliest stage of the disease process. Ryckie et al. have proposed the addition of a cardiovascular scoring system from the Children’s Hospital of Philadelphia (CHOP) to quantify the magnitude of cardiovascular derangement (Table 2). A more precise gradation of severity based in the physiologic underpinnings of the disease should augment and refine the clinical diagnosis and assist in the measuring of the effectiveness of various treatment modalities or possibly assist in the selection of patients for specific treatments. Significant degrees of cardiovascular abnormalities are seen even in the early Quintero staging such that a substantial number of twin pairs had a higher grade of disease severity based on the cardiovascular assessment than that designated by the Quintero stage.

Various attempts have been made to identify sonographic features that may predict or increase the likelihood of developing TTTS. The first has been the use of nuchal translucency (NT) measurements done between 11 and 13-16 weeks of gestation. Increased NT is a marker for chromosomal anomalies, cardiac defects and a range of genetic syndromes. It has also been postulated that the underlying hemodynamic changes in TTTS may be present much earlier than is apparent from our current sonographic criteria and may manifest as increased NT in the recipient fetus. One study evaluated the presence of an NT measurement >95th percentile for gestational age in MCDA twins that were structurally and chromosomally normal. The definition of severe TTTS included cases with an ultrasound diagnosis consistent with

### Table 1

<table>
<thead>
<tr>
<th>Stage</th>
<th>Findings</th>
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<tbody>
<tr>
<td>1</td>
<td>Polyhydramnios in recipient sac (MVP &gt; 8 cm) and oligohydramnions in the donor sac (MVP &lt; 2 cm)</td>
</tr>
<tr>
<td>2</td>
<td>No visible bladder in the donor twin</td>
</tr>
<tr>
<td>3</td>
<td>Doppler abnormality consisting of absent or reverse flow in the umbilical artery, reverse flow in the ductus venosus or pulsatile flow in the umbilical vein</td>
</tr>
<tr>
<td>4</td>
<td>Ascites or hydrops in either fetus</td>
</tr>
<tr>
<td>5</td>
<td>Demise of either fetus</td>
</tr>
</tbody>
</table>

MVP, maximum vertical pocket of amniotic fluid.
Quintero stage 2 that resulted in pregnancy loss, intrauterine fetal demise (IUPD), intrauterine treatment or postmortem evidence that the cause of death was TTTS. The presence of an increased NT in at least one of the fetuses predicted the development of severe TTTS with a sensitivity of 0.32, a specificity of 0.88 and a positive likelihood ratio of 1.45. Kagan et al. evaluated the ability of discordance in the measurement of NT between 11 to 13 weeks to predict the subsequent need for endoscopic treatment of TTTS. A discordance of more than 20% was associated with a sensitivity of 0.57, a specificity of 0.77 and a positive likelihood ratio of 1.73. As a screening tool, the use of discordant NT measurements does not provide sufficient discrimination to be recommended for routine use. Combining increased NT thickness with abnormal flow in the ductus venosus (DV) has also been proposed as a screening tool for early TTTS. An abnormal NT thickness was defined as >95th percentile for gestational age with a discrepancy between the co-twins of >0.5 mm considered significant. An abnormal DV waveform was defined as reversal of the A-wave during atrial contraction. In a prospective series of 50 cases, four cases developed TTTS. An abnormal DV Doppler was seen in all four cases. An additional two cases with abnormal DV Doppler developed another complication. None of the remaining 44 cases with a normal DV Doppler developed TTTS. This results in a sensitivity of 0.66 and a specificity of 1.0.

Folding of the inter-twin membrane is an ultrasound marker that demonstrates a decrease in the amount of amniotic fluid in one sac compared to the other and has also been proposed as a screening test for MCDA twin gestations that will develop TTTS. Sebire et al. prospectively evaluated 83 MCDA pregnancies that presented for routine NT screening. Serial ultrasound evaluations were performed at 10–14, 15–17 and 19–21 weeks. Membrane folding was seen in 23 cases, 12 of which developed severe TTTS. The remaining 11 had a more ‘moderate’ syndrome with a subjective major discrepancy in the amniotic fluid volume between the two sacs. Thus 52% of those observed to have membrane folding developed severe TTTS. Only one of these was detected at the time of the initial ultrasound done at 10–14 weeks. Although this appears to be a useful marker, what is unclear is whether this provides additional information over the simple observation of discordance in the amniotic fluid volume during a routine ultrasound. A subsequent evaluation done by the same group showed a sensitivity of 0.43, a specificity of 0.98 and a positive likelihood ratio of 21.5.

The presence of AA anastomoses is considered protective for the development of TTTS. Placental mapping for the presence of AA anastomoses by color flow and spectral Doppler has technical limitations, the majority of anastomoses being detectable only after 18 weeks of gestation. Increasing gestational age, the presence of an anterior placenta and larger diameter vessels enhanced the ability to detect an AA anastomosis. The overall sensitivity and specificity measured 0.85 and 0.97 respectively. The odds ratio of developing TTTS if an AA anastomosis was not detected was 8.6. This demonstrates feasibility of detection; nevertheless, if they are not detected, is it that they are truly not present or does detection require a certain level of special skill or patience during the evaluation? Factors relying on a special level of skill or persistence will never perform as well in general use as they do with those that originate them.

Again as a screening tool, it is unclear whether any of these provides additional benefit over the observation of a discrepancy in the amniotic fluid volumes. A study of multifactorial screening confirms this impression. Evaluating a group of 202 MCDA pregnancies with multivariate regression, the only factors that significantly predicted an adverse outcome, including TTTS, were differences in the crown–rump length and discordance in the amniotic fluid volume in the first trimester. Screening strategies may be able to identify a subgroup of patients at higher risk, but it is unclear whether those cases identified at a lower risk will be subjected to different clinical care following their risk stratification.

The fact that none of the above sonographic screening tools functions well individually or collectively underscores that the best method for early diagnosis is likely the regular ultrasound evaluation of ‘at risk’ monochorionic pregnancies. This strategy too is not presently supported by strong research findings. A small case series evaluated the ability to make a timely diagnosis of TTTS with a program of biweekly ultrasound combined with patient reporting of symptoms suggestive of TTTS. Although only four of 23 patients developed TTTS, the authors concluded that sonography combined with maternal symptom monitoring allowed the diagnosis and management of all cases before the onset of severe complications.

### 4. Treatment

Since the publication of the Eurofetus randomized trial comparing amnioreduction with selective laser photocoagulation, there has been no question that laser therapy is currently the optimal therapy for TTTS that develops before 26 weeks of gestation. Of all the available therapies, it is the one that seeks to interrupt the vascular connections on the chorionic plate that are responsible for the development of the syndrome. The group that underwent laser therapy had a significantly higher mean gestational age at delivery (33 vs 29 weeks) along with higher survival of at least one fetus to 28 days of age (76% vs 56%). Postnatal follow-up was only to 6 months’ duration but demonstrated improved neurologic outcomes with decreased risk of periventricular leukomalacia in the laser group (6% vs 14%) and a higher likelihood of being free of neurologic complications at 6 months of age (52% vs 31%). The Eurofetus trial confirmed the many prior studies of lesser epidemiologic rigor. A recent meta-analysis of ten of these studies supported the superiority of laser therapy over amnioreduction.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Children’s Hospital of Philadelphia (CHOP) Cardiovascular Score.</th>
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<tbody>
<tr>
<td>Recipient twin</td>
<td>Dilatation</td>
</tr>
<tr>
<td>Ventricular characteristics</td>
<td>None</td>
</tr>
<tr>
<td>Valve function</td>
<td>None</td>
</tr>
<tr>
<td>Venous Doppler characteristics</td>
<td>None</td>
</tr>
<tr>
<td>Great vessel analysis</td>
<td>Mild</td>
</tr>
<tr>
<td>Donor twin UA Doppler</td>
<td>Normal</td>
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</tbody>
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PA, pulmonary artery; Ao, aorta; AEDF, absent end diastolic flow; REDF, reverse end diastolic flow; UA, umbilical artery.
The technique for laser therapy has undergone some changes since it was first proposed by De Lia. A laparotomy is no longer performed with the procedure now performed percutaneously. The use of general anaesthesia has given way to the use of conscious sedation or local anaesthetic. The method for ablation of the vessels crossing the inter-twin membrane has changed from a non-selective approach, in which all vessels crossing the inter-twin membrane were photocoagulated, to a selective approach involving precise identification of the anastomotic vessels. This change resulted in an improved survival of at least one fetus from 61% in the non-selective group to 83.1% in the selected group largely as a result of less dual intraterine demise in the selected laser group.

Further refinements in laser technique have been explored. Quintero et al. have proposed a sequential selective laser photocoagulation of the communicating vessels. The rationale for photocoagulation of the AV anastomoses from the donor to the recipient first is that this could improve the hemodynamic status of the donor and result in less demise of the donor twin. Although they do report a lower rate of IUFD among donors in the sequential technique (21.4% vs 7.3%), this was a non-randomized study and the groups were severely unbalanced in terms of size. Also, there was no difference between the groups in overall stage – the sequential group had twice as many stage 1 patients as did the select group. Adoption of this technique awaits further evaluation.

The finding of residual anastomoses following laser surgery is of great clinical concern. Depending on the number, size, direction and vessels involved they can result in persistent TTTS, reversal of TTTS, twin anemia polycythemia sequence (TAPS), intrauterine demise of both twins, or hypotensive sequelea in a surviving twin. These residual connections can represent anastomoses that were missed at the time of laser ablation or revascularization of previously ablated vessels. In one study that evaluated 50 placentas postpartum from MCDA twins that had undergone laser ablation, residual surface anastomoses that should have been treated with laser ablation were found in 32%. The pregnancies with residual anastomoses were more frequently associated with adverse outcomes such as double fetal demise or evidence of anemia in one twin requiring intrauterine transfusion. Case reports have been published that use treatment of fetal anemia through intrauterine transfusion to determine the rate of blood flow through the residual AV anastomosis. Advanced mathematical modeling of twin-to-twin transfusion has led to the development of equations that can be used in similar situations. A more recent study found a similar frequency of residual surface anastomoses but noted that most measure <1 mm in diameter and are more commonly located near the placental margins. The presence of deeper anastomoses within the placenta that cannot be photocoagulated by laser therapy have also been identified. Their contribution to the post-laser complication rate from ongoing exchange of blood would appear to be unimportant in producing hematological or hemodynamic changes of clinical significance.

The occurrence of demonstrated residual anastomoses has led to several procedural changes. It is incumbent on those who perform laser therapy to be exceedingly vigilant when mapping the placenta. This may involve multiple runs over the vascular equator to look for residual small anastomoses that may have been missed initially and to ensure that all laser sites are adequately photo- coagulated. A modification of the selective technique has been proposed that involves performing an initial selective laser ablation and then using the laser to connect the ablation sites. This essentially photocoagulates the vascular equator in what is known as the ‘Solomon’ technique. There is currently a randomized trial underway to determine whether application of this technique is able to reduce the frequency of TAPS or recurrent TTTS. The second is the recommendation for serial weekly surveillance of middle cerebral artery Doppler velocities after laser therapy to detect developing anemia (TAPS) that is amenable to treatment with intrauterine transfusion or to detect signs of persistence of TTTS or reversal of TTTS.

Amnioreduction is no longer the mainstay of therapy for TTTS. It may, however, still have a role to play in the management of TTTS under certain conditions. It may be a useful procedure to allow a patient to be transported to a center where more definitive therapy may be offered. It may be useful to decompress the uterus in cases where there is evidence of cervical shortening or proximal funneling to allow a cervical cerclage to be placed before laser therapy. It can be used in managing symptomatic polyhydramnios when TTTS develops outside of the gestational age where laser therapy can be performed or where laser therapy is technically not possible. Finally it may be a useful therapy in the management of stage 1 TTTS.

Since the initial clinical staging was proposed by Quintero, it has been realized that a number of early stage TTTS cases do not progress and remain at stage 1 or may even regress. Several studies have evaluated this. Taylor et al. reported a progression rate of 31% in a cohort of 22 stage 1 patients. Dickinson and Evans found a progression rate of 45.5% in their cohort of 22 patients. Finally in a cohort of 46 patients with stage 1 disease, O’Donoghue et al. found a 30.4% rate of progression. Our own study of 42 patients with stage 1 TTTS revealed a progression rate of only 10%. Though studies have found that amnioreduction did not alter the rate of progression or regression, it can still be useful for symptomatic relief from polyhydramnios. In a similar way, selective termination of one fetus by bipolar cord coagulation or radiofrequency ablation is only selectively used in the management of TTTS. Cases where there are discordant anomalies, pre-existing injury or imminent demise of one twin would be considered situations where selective termination could be offered as a means of protecting the co-twin from the risks of a spontaneous intrauterine demise.

The treatment of stage 1 TTTS is controversial; whether the best therapy is simple observation, amnioreduction or laser photocoagulation has not yet been determined. Other therapies such as selective termination via bipolar cord coagulation or radiofrequency ablation or termination of the pregnancy are not usually considered at this early stage. There are few studies that report outcomes for laser treatment specifically for stage 1 disease. Middeldorp et al. reported on the outcomes of 100 pregnancies managed by laser surgery. From that series there were 10 cases of stage 1 TTTS treated with laser with a 95% survival at birth. They do not breakdown their postnatal mortality events by stage and so it is impossible to determine the survival to discharge from hospital for the subgroup of stage 1 cases. The Eurofetus trial included 11 pregnancies with stage 1 TTTS, six in the laser group and five in the amnioreduction group. They reported that the survival rate was higher in the laser group compared to the amnioreduction group for all stages, but they only reported a comparison between the therapies for stages 1 and 2 combined, showing 86% survival at 6 months for the laser group and 58% survival for the amnioreduction group. As such, the results for the 11 stage 1 patients are grouped with the results from the much larger stage 2 group of 62 patients, so it is difficult to draw definite conclusions on outcomes in this smaller group. If the rate of progression in stage 1 TTTS is low and outcomes are good for those that do not progress, then is it appropriate to expose these pregnancies to the risks of laser therapy? In the absence of an ability to predict those cases that are likely to progress, it is difficult to select those cases of stage 1 disease that may benefit from treatment before they progress. There are discussions currently underway to develop a randomized trial for the management of stage 1 TTTS.
5. Long-term outcomes

Survival of one or both fetuses is only one aspect of the outcomes in TTTS. The mean gestational age at delivery even in successfully treated cases is still less than that seen in MCDA twin gestations without TTTS. Thus complications of prematurity still factor into the long-term outcomes. The Eurofetus trial provided information on neurologic outcomes at 6 months of age, with 52% of surviving infants from the laser group being free of major neurologic sequelae compared to 31% of surviving infants in the amnioreduction group. Reliable assessment of neurologic abnormalities requires a longer follow-up period than 6 months although the occurrence of periventricular leukomalacia is a strong predictor of the subsequent development of cerebral palsy. The frequency of longer-term neurologic sequelae has been documented in many case series of varying size and duration of follow-up. The largest involves 145 infants from pregnancies undergoing laser therapy before 26 weeks of gestation. These infants were followed to a mean age of just over 3 years. Children were categorized as having normal physical and neurologic development, minor neurologic deficiency with the prospect to normalization or minor neurologic abnormality leading to permanent disability based on standardized testing. This showed 86.8% of children with normal development, 7.2% with minor neurologic abnormality and 6% with major neurologic abnormality.

With the dramatic effects on cardiac physiology that are seen in the recipient twin in TTTS, the long-term outcome of the cardiovascular system has also come into question. The CHOP Cardiovascular Score, which is a broad, multifactor representation of cardiac function primarily in the recipient, shows a significant reduction post laser therapy. It has also been demonstrated that there is improvement in both the right and left ventricular myocardial performance index post laser when compared to preoperative assessment. Serial postoperative evaluations show continued improvement over time. The development of right ventricular tract outflow obstruction in some recipient twins is seen to improve following laser therapy but may not resolve completely, resulting in acquired congenital heart disease that requires evaluation postnatally. Postnatal studies with long-term cardiac follow-up are few. One study of 89 survivors of MCDA pregnancies treated for TTTS with laser showed that in 87% of survivors, postnatal echocardiography was normal at a median age of 21.5 months. The prevalence of congenital heart disease and particularly pulmonary stenosis in the recipient twin was increased compared to the general population (11.2% vs 0.3%).

There is a need for longer-term follow-up to assess the impact of the altered in-utero environment on the development of other forms of cardiovascular disease.

6. Conclusions

Great strides have been made in the understanding and treatment of TTTS over the last decade but much work remains. Laser photocoagulation therapy has improved overall survival and the rate of neurologically intact survival through prolongation of gestation. It remains the one therapy that addresses the underlying pathophysiology. Efforts continue to be needed to focus attention on the risk of preterm rupture of membranes following endoscopic treatment. This remains the Achilles’ heel of fetal therapy. There is a need for discussions on how many treatment centers are needed to meet the clinical demand and a means of rationalizing those choices. Procedure related complications decrease as the number of cases performed increases. Thus it may make sense to limit the number of centers in order to optimize technical expertise. Further randomized trials are needed to address clinical questions such as the optimal treatment for stage 1 disease and this will require the cooperation and participation of multiple centers. If programming takes place within the intrauterine environment, then ongoing long-term follow-up studies that will evaluate the children into their school years and beyond are needed to understand the impact of TTTS on the development of diseases in later life.

Practice points

- Monochorionic twins are associated with a disproportionately high perinatal morbidity and mortality. The determination of chorionicity is an essential component of any ultrasound evaluation of a twin pregnancy.
- There is no reliable way to screen MCDA twins for the development of TTTS. Routine surveillance with ultrasound on a biweekly basis appears to be the most efficient tool at present.
- Clinical diagnosis of even early stage TTTS should prompt a referral to a center experienced in the evaluation and management of complex MC pregnancies including the ability to perform laser therapy.

Research directions

- Further development in the understanding of the prenatal pathophysiology of TTTS.
- Further elucidate the long-term impact of in-utero intervention.
- A randomized controlled trial is needed to determine the optimal treatment for early stage TTTS.

Conflict of interest statement

None declared.

Funding sources

None.

References


