Twin to twin transfusion syndrome

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Abstract: Twin to twin transfusion syndrome (TTTS) is a common complication that typically presents in the second trimester of pregnancy in 10–15% of monochorionic twins due to net transfer of volume and hormonal substances from one twin to the other across vascular anastomoses on the placenta. Without recognition and treatment, TTTS is the greatest contributor to fetal loss prior to viability in 90–100% of advanced cases. Ultrasound diagnosis of monochorionicity is most reliable in the first trimester and sets the monitoring strategy for this type of twins. The diagnosis of TTTS is made by ultrasound with the findings of polyhydramnios due to volume overload and polyuria in one twin and oligohydramnios due to oliguria of the co-twin. Assessment of bladder filling as well as arterial and venous Doppler patterns are required for staging disease severity. Assessment of fetal cardiac function also provides additional insight into the fetal cardiovascular impacts of the disease as well as help identify fetuses that may require postnatal follow up. Fetoscopic laser ablation of the communicating vascular anastomoses between the twins is the standard treatment for TTTS. It aims to cure the condition by interrupting the link between their circulations and making them independent of one another. Contemporary outcome data after laser surgery suggests survival for both fetuses can be anticipated in up to 65% of cases and survival of a single fetus in up to 88% of cases. However, preterm birth remains a significant contributor to postnatal morbidity and mortality. Long term outcomes of TTTS survivors indicate that up to 11% of children may show signs of neurologic impairment. Strategies to minimize preterm birth after treatment and standardized reporting by laser centers are important considerations to improve overall outcomes and understand the long-term impacts of TTTS.

Keywords: Fetoscopy; placental diseases, pregnancy, twin; twin to twin transfusion syndrome (TTTS)

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Introduction

Twin to twin transfusion syndrome (TTTS) is a disease that occurs in 10–15% of monochorionic twins as a result of volume imbalance across the vascular anastomoses between the twins and is the largest contributor to previable pregnancy loss for this type of twins. Diagnosis of monochorionicity in the first trimester and adherence to international guidelines for close surveillance of these pregnancies at least every 2 weeks after 16 weeks provides the best opportunity and early diagnosis and definitive treatment with fetoscopic laser surgery. The current technique allows >70% survival of at least one twin but preterm birth is a common consequence of the intervention. This unique features of the monochorionic placenta that contribute to the TTTS, as well as diagnosis, treatment and anticipated outcomes are reviewed.

Features of the monochorionic placenta

Monozygotic twins are classically considered the result of
division of a single embryo and account for approximately 30% of all twin pairs worldwide (1,2). The timing of the split is related to the observed number of placentas and amniotic sacs, with earlier division leading to more complete separation (Figure 1) (1,3). Chorionicity refers to the number of placentas in the pregnancy. This can be determined in the first trimester by ultrasound identification of a single placental mass with a thin dividing membrane that inserts directly into the placental surface (T-sign) and absence of placental tissue extending in between the intertwin membrane (λ-sign) with a sensitivity and specificity of up to 98–100% (Figure 2) (4-7). Correct identification of monochorionicity is critical because it defines the risk profile and the range of complications that can occur. The mortality for monochorionic twins is twice that of dichorionic twins and four times that of singleton pregnancies with a highest rate of previable pregnancy loss prior to viability most commonly attributable to the unique features of the monochorionic placenta (8,9).

In a monochorionic twin placenta, the umbilical cord for each fetus can insert either centrally, at the placental edge (marginal) or into the membranes (velamentous). The fetal vessels originate from the base of the umbilical cord, branch and extend over the surface of the placenta essentially claiming their respective portion of the placenta that provides the predominant nutrient supply for fetal growth.

Figure 1 Timeline for division of the monozygotic embryo and proportion of all monozygotic twin pairs. Earlier division of the monozygotic embryo results in more complete separation of the twin pair beginning from two separate placentas and amniotic sacs in dichorionic diamniotic twins when the division occurs in the first three days to conjoined twins when the division of the embryo occurs after 13 days.

Figure 2 First trimester ultrasound appearance of a monochorionic and dichorionic twin pregnancy. A monochorionic twin pregnancy is diagnosed when the membrane is thin and inserts directly on the placental surface (T-sign) as indicated by a thin arrow (A). A dichorionic twin pregnancy is diagnosed when the intertwin membrane is thick with intervening placental tissue at its base (λ-sign) as indicated by a thick arrow (B).
Near universally, fetal vessels from each twin meet along the border between the placental territories for each twin (10). They may connect directly creating superficial vascular anastomoses or perfuse a shared placental cotyledon with deep anastomoses of arterioles and venules. The imaginary line along the surface of the placenta that connects the anastomosis is referred to as the vascular equator. This portion of the shared placenta may account for 5–10% of the shared vascular volume for each twin and is referred to as the third circulation (Figure 3) (11).

Vascular anastomoses may be found in any number, size and arrangement between arteries and veins. Arteriovenous anastomoses occur when a shared placental cotyledon is perfused by the artery from one twin and drained by a vein from the co-twin (12). This results in a unidirectional transfer of volume, hemoglobin and substances from one fetus to the other. Artery-to-artery or vein-to-vein anastomoses directly connect to one another along the chorionic surface and allow bidirectional flow between the twins based on pressure gradients (10). In the majority of monochorionic twin pairs, the net exchange between the twins remains balanced in their shared circulation.

**Pathophysiology of twin to twin transfusion syndrome**

In 10–15% of monochorionic twins the balance becomes skewed due to volume shunting across arteriovenous vascular anastomoses resulting in TTTS (13). Placental observations in uncomplicated monochorionic twins compared to those with TTTS demonstrate that unbalanced arteriovenous anastomoses are the prerequisite to develop the condition (14,15). Surface artery to artery or vein to vein anastomoses are considered protective from TTTS by allowing redistribution of volume more efficiently across a range of vessel diameters compared to reciprocal artery to vein anastomoses (16).

This chronic net transfer of volume and vasoactive substances from one twin to the other leads to an abnormal intravascular volume status and compensatory response of both twins. Observable findings on ultrasound include discordance in amniotic fluid, bladder filling, and cardiovascular manifestations. The recipient twin experiences increased preload demonstrated by higher umbilical venous flow (17). Increased stretch on the cardiac chambers triggers release of atrial natriuretic peptide and brain natriuretic peptide, which stimulates diuresis leading to polyhydramnios (18,19). Additionally, the potent vasoconstrictor endothelin is increased contributing to recipient hypertension and consequently cardiac hypertrophy and valvular regurgitation (19,20). In contrast, the donor twin experiences hypovolemia and subsequently decreased urine production resulting in oligohydramnios and minimal or no visible bladder filling.
In response there is upregulation of the renin-angiotensin system, which passes to the hypervolemic recipient via their shared circulation amplifying recipient hypertension and cardiomyopathy that cannot be explained solely by changes in volume status (21,22).

The hemodynamic impacts of TTTS can contribute to both functional and ultimately structural cardiac disease for each fetus. Changes in recipient cardiac function may be observed prior to development of overt TTTS and may include cardiac enlargement, biventricular hypertrophy, valvular regurgitation, impaired contractility (23,24). Right ventricular hypertrophy and hypertension coupled with tricuspid regurgitation may lead to decreased flow through the pulmonary valve and right outflow tract, essentially creating a functional subvalvular right ventricular outflow obstruction in up to 9% of recipients (25-27). These findings may resolve after treatment but persistent pulmonary stenosis or functional atresia may result and require postnatal treatment (28). Structural heart disease and cardiac dysfunction are less likely to be diagnosed in donor fetuses, however decreased flow through the aortic isthmus from hypovolemia, decreased venous return and higher placental resistance may evolve into coarctation (29,30).

**Staging criteria**

The initial diagnosis of TTTS is made by ultrasound identification of both polyhydramnios for the recipient twin by a maximum vertical pocket (MVP) of amniotic fluid of >8 cm and oligohydramnios for the donor twin with a MVP <2 cm, which is well above the 95th percentile and below the 5th percentile across gestational age (31). Measurement of the MVP should be performed with the patient in the dorsal supine position and in an area free of fetal parts or the umbilical cord in order to avoid underestimation of the amniotic fluid volume. Due to oligohydramnios, the donor twin may appear “stuck” to the placenta or uterine wall. On occasion the fetus may appear suspended from the uterine wall, termed the “chandelier sign” from being wrapped in the membrane and the folded membrane may appear thicker from being folded on itself. Use of the Quintero staging criteria is widely accepted as the standard to communicate the severity of disease (32). It includes assessment of bladder filling, Doppler assessment of the umbilical artery, ductus venosus and umbilical vein, presence of hydrops or fetal demise (Table 1). Importantly, each component of the classification system is a categorical assessment. For instance, to meet criteria for critically abnormal Dopplers absent or reversed end diastolic velocity in the umbilical artery or ductus venosus a-wave is required. Increased resistance or abnormal indices are not sufficient to satisfy criteria for TTTS Stage 3 or higher but may provide important insight into the overall clinical assessment.

Cardiovascular manifestations of TTTS may be evident in early stage disease (33), so additional scoring systems that incorporate fetal cardiac function can be used to complement the assessment (34,35). Recipient twins are more likely to demonstrate signs of myocardial hypertrophy, impaired diastolic function, and valvular regurgitation that ultimately leads to abnormal venous Dopplers. Fetal hydrops resulting from fetal cardiac failure is a late manifestation of the disease. Donor twins are more likely to display signs of elevated placental resistance reflected in the umbilical artery Doppler waveform and much less likely to exhibit cardiac dysfunction (20). Since the Quintero staging criteria only accounts for late reflections of cardiovascular dysfunction, this explains the discrepancy commonly observed between scoring systems (34). Although prospective evaluation of the cardiovascular score may not be predictive of ultimate pregnancy outcome (36), it allows recognition of significant cardiac dysfunction across the spectrum of disease. Therefore, fetal echocardiogram is recommended before and after laser surgery to monitor for disease resolution and identify fetuses with persistent cardiac disease that require neonatal echocardiogram and follow-up.

**Twin anemia polycythemia sequence (TAPS)**

Another condition along the spectrum of monoclonal
transfusion syndromes is TAPS. This condition occurs spontaneously in about 5% of monochorionic twins due to chronic transfusion predominantly of red blood cells via small diameter vascular anastomoses (<1 mm) from one twin to the other resulting in anemia of one and polycythemia of the co-twin (37-39). The features of TAPS are more subtle since it may occur in the absence of fluid discordance (40). Its incidence is likely underestimated since international screening protocols do not always include assessment of fetal anemia as a part routine surveillance of monochorionic twins. Fetal anemia is suspected when the velocity in the middle cerebral artery is elevated >1.5 multiples of the median (MoM) for gestational age (41). However, performance of the middle cerebral artery peak systolic velocity (MCA-PSV) to detect fetal polycythemia is unvalidated (42). Accordingly, a small prospective study demonstrated that discordance of the MCA-PSV was more strongly correlated with postnatal intertwin hemoglobin difference than the MCA-PSV MoM of the polycythemic twin (43). Another retrospective study by Tollenaar et al., demonstrated that discordance of MCA-PSV of >0.5 MoM was a better predictor of hemoglobin differences at birth than absolute cut-offs for the MCA-PSV even if both twins had normal measurements (44). Although the diagnostic and staging criteria are not standardized, a recent Delphi consensus of international experts supported use of either absolute MCA PSV cutoffs of >1.5 MoM for the donor and <1 MoM for the recipient or a discordance of >1 MoM to make the diagnosis (45).

Evaluation for TTTS

TTTS most commonly occurs between 16–26 weeks of pregnancy (13). The combination of serial ultrasound assessment beginning in the first trimester and every two weeks after 16 weeks combined with maternal education about symptoms of polyhydramnios allows for early risk stratification and timely identification of the condition (46-48). A recent meta-analysis identified first trimester intertwin discordance in the nuchal translucency or crown rump length, nuchal translucency >95th percentile, or reversed ductus venosus a-wave identify monochorionic pregnancies that are increased risk for developing TTTS (49). In the second trimester, discordance in amniotic fluid, placental cord insertions, and the abdominal circumference can be helpful to identify >70% of monochorionic pregnancies at risk for adverse pregnancy outcome but has a positive predictive value for TTTS of only 22%.

This is likely due to the fact that these factors contribute to the entire range of complications that are specific to monochorionic pregnancies (46). For this reason, there is international agreement that ultrasound surveillance of monochorionic twins should include determination of chorionicity followed by an assessment at least every two weeks after 16 weeks to evaluate for complications including TTTS (48,50,51).

Natural history of TTTS

Untreated TTTS has a very poor prognosis. Although stage I disease may remain stable or regress in up to 30% of expectantly managed cases, progression, fetal demise, or previable birth may occur (52,53). Advanced TTTS results in 90–100% mortality from either single or double twin demise or pregnancy loss from preterm labor due to overdistention of the uterus from polyhydramnios especially when it occurs at <28 weeks gestation (54-56). When TTTS presents in the third trimester, outcomes are more favorable since delivery may be considered. Acute TTTS occurs rarely in labor but may contribute to abnormal fetal heart rate patterns before birth or significant discrepancies in fetal hemoglobin or even hypovolemic shock in the donor (57).

Management of TTTS/TAPS

Fetoscopic laser ablation of placental vessels is the only intervention that aims to cure TTTS by closing the interconnecting vascular communications between the twins giving each fetus a chance for survival (58-60). The procedure is typically performed between 16–26 weeks gestation using local anesthesia with intravenous sedation as needed, epidural or occasionally with general anesthesia (61,62). Preoperative ultrasound mapping of the placental cord insertions, intertwin membrane and consideration of fetal size discordance is used to estimate the location and orientation of the vascular equator (63). Using ultrasound guidance, the sac of the recipient fetus is entered with a fetoscope that has an outer trocar diameter of <4 mm. The intertwin membrane and vascular equator are identified under direct visualization. A 400–600 μm laser fiber is advanced through the operative channel of the fetoscope and the vessels are coagulated at the site of the anastomosis. The chorionic plate is also coagulated between each vascular anastomosis along the vascular equator (Figure 2). This is termed the “Solomon technique” and leads to the highest reported rates of double twin survival of
Selective fetal reduction is typically performed for cases as a temporizing measure particularly if late in gestation. Amnioreduction is a consideration for amnioreduction, selective fetal reduction, or pregnancy between parents and physicians after counseling. Fetal status after viability require shared decision making amnioreduction (81), but thresholds for intervention for delivery with decreased neurologic morbidity compared to delivery with laser affords the potential to avoid a very preterm or delivery timing observed (79,80). Definitive treatment with no differences in duration of surgery, complication rate or delivery timing observed (73). Although several interventions for cervical shortening have been utilized perioperatively including cerclage, progesterone, and pessary, optimal management of a short cervix remains elusive (74-76).

Maternal complications are less common but are estimated to occur in >5% of cases and include intraperitoneal amniotic fluid or bleeding, placental abruption, mirror syndrome, pulmonary edema and occasionally need for intensive care. Underreporting of maternal complications is assumed since many minor complications are self-limited and not universally reported outcomes (77,78). TTTS presenting after 26 weeks requires additional considerations. The procedure may be technically more challenging due to increased amniotic fluid turbidity and larger vessel diameter. However, outcomes for TTTS cases treated before and after 26 weeks appear to be comparable with no differences in duration of surgery, complication rate or delivery timing observed (79,80). Definitive treatment with laser affords the potential to avoid a very preterm delivery with decreased neurologic morbidity compared to amnioreduction (81), but thresholds for intervention for fetal status after viability require shared decision making between parents and physicians after counseling.

Alternative management options for TTTS include amnioreduction, selective fetal reduction, or pregnancy termination. Amnioreduction is a consideration for situations where referral to a laser center is not feasible or as a temporizing measure particularly if late in gestation. Selective fetal reduction is typically performed for cases with associated fetal anomalies of one twin or where survival is unlikely after treatment for TTTS (82). Some parents may also choose previable pregnancy termination if the perioperative risks and potential outcomes are not acceptable to the family (51).

For cases of TTTS Stage V with a single fetal demise, there is about a 15% risk of death to the surviving co-twin and up to 30% risk for neurologic impairment due to sudden reversed perfusion from the surviving fetus to the demise fetus at the time of death (83,84). No interventions have been shown to alleviate these risks including rescue transfusion of the surviving twin (85). When a single fetal demise is identified in a monochorionic pair, evidence of cerebral injury may not be evident for several weeks by ultrasound or magnetic resonance imaging. The findings are typically consistent with hypoxic-ischemic injuries resulting in periventricular leukomalacia, encephalomalacia, ventriculomegaly, intraventricular hemorrhage, and infarction (86,87).

Management options for TAPS similarly include observation, fetoscopic laser ablation, selective fetal reduction, intrauterine transfusion with or without partial exchange transfusion, termination of pregnancy or early delivery. There is an ongoing international multi-center randomized trial to investigate whether treatment with fetoscopic laser surgery improves outcomes compared to the alternative treatments (ClinicalTrials.gov Identifier: NCT04432168).

Surveillance after treatment for TTTS

After the immediate postoperative period, close ultrasound surveillance is required to monitor for resolution of the condition. In our observations, resolution of TTTS generally occurs over the first two weeks after laser surgery. Initially, weekly ultrasound surveillance is recommended with the option to extend monitoring to two-week intervals if the clinical picture is stable. Since residual anastomoses on the surface or deep to the chorionic plate may be present after laser (65,88-90), the potential for recurrent TTTS or TAPS exists until delivery (91).

The optimal strategy for antenatal surveillance in the third trimester with non-stress testing or biophysical profile is unknown, however a similar strategy for other pregnancies at high risk for fetal compromise or deterioration can be considered. Preterm delivery after laser surgery is common with a median gestational age at birth <34 weeks across several large series from experienced
laser centers. A course of betamethasone is recommended since the risk for preterm birth is elevated once TTTS is diagnosed and treated (51). The timing may be determined based on the clinical circumstances. When the postoperative course is uncomplicated and surveillance is reassuring, the pregnancy can be continued until 34–36 weeks. Mode of delivery can also be planned based on obstetric indications if fetal status is reassuring. In cases of a single survivor, delivery timing and mode can also follow recommendations for a singleton pregnancy.

**Perinatal and long-term outcomes**

Overall fetal survival has improved with experience and modification of the laser technique since its initial description. A systematic review of 34 studies including 3,868 pregnancies evaluated the outcomes treated with laser surgery over 25 years. Mean gestational age at delivery was 32.4±1.3 weeks across the time period but mean survival increased for a both fetuses from 35% to 65% and for a single fetus from 70–88% (64). After laser surgery, hemorrhagic or ischemic cerebral lesions are observed in about 2–10% of both recipient and donor fetuses on ultrasound or MRI (92,93). This risk is not affected by single fetal demise after surgery but it was higher in cases of recurrent TTTS or post-laser TAPS (93). This is important because prenatally detected severe cerebral lesions are related to neurodevelopmental outcome at age 2 years of age with an odds ratio of 34.86; (95% confidence interval, 11.83–102.75; P<0.01). A systematic review of TTTS survivors showed that 11% of children showed signs of neurologic impairment beginning in infancy (94). This may manifest as delays in cognitive, motor, or verbal skills as well as cerebral palsy but the rates are lower than those managed conservatively or with amnioreduction (95). Furthermore, prematurity has an independent impact on neurodevelopment with each gestational age week so some of these observations may be attributable to the effects of prematurity rather than TTTS (96). Longer term follow up to 6 years of age is consistent with rates of severe neurodevelopmental impairment ranging from 4–13% of children evaluated (97).

Cardiac dysfunction resulting from volume loading as well as hormonal aberrations in fetal and placental tissues have both short and potentially longer term impacts into childhood (20-22,97). Although cardiac function improves in many fetuses shortly after laser surgery (98), identifying former recipients with residual pulmonary valve stenosis or atresia may be important for delivery location and management planning in the newborn period (28,99). In the neonatal period, about 4% of former recipient twins may have persistent pulmonary hypertension of the newborn (100). Hypertension is also more common in the first year of life but normalizes through childhood with normal values observed in both recipient and donors by 10 years of age (101,102).

**Conclusion**

Although curative treatment for TTTS with laser surgery is more widely available with acceptable fetal and maternal outcomes, this condition remains a significant contributor to morbidity and mortality in monochorionic twins. Strategies to minimize ruptured membranes and preterm birth after treatment are elusive and the equipment used contemporarily has changed minimally over time. In order to further improve perinatal outcomes, accurate diagnosis (103) and referral of TTTS cases to a laser center (51) combined with effective treatments to reduce preterm birth particularly in the setting of short cervix are necessary advancements. Standardization for reporting of core outcomes measures are important steps for treatment centers to adopt in order to improve the framework for comparison studies and long-term outcome monitoring (104).

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